

Opioid maintenance treatment of pregnant women in the Scandinavian countries

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Abstract

Background: WHO guidelines emphasise the need for descriptions of clinical practice and observational studies on risk and benefits of pharmacotherapies in pregnancy. The aims of the present study were to: (1) Describe opioid maintenance treatment (OMT) in the Scandinavian countries in general, and specifically for pregnant women, (2) Describe a project which utilises a new approach using registry-linkage data to examine associations between prenatal exposure to OMT and child outcomes: a Scandinavian cohort study of pregnant women in OMT during pregnancy (ScopeOMT). **Data:** Guidelines describing the treatment of persons with opioid use

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disorders in general, and specifically for pregnant women. Scandinavian registry-linkage data from ScopeOMT. **Results:** Registry data show that approximately 800 pregnant women received OMT during pregnancy in the period of the ScopeOMT study. Similarities across the Scandinavian countries include access to free healthcare and treatment; multidisciplinary teams trained to support pregnant women in OMT; buprenorphine as the recommended drug when initiating therapy; and a holistic focus on the patients' lives. An important difference is that Norwegian women who use illegal substances that may harm the foetus may be admitted – voluntarily, or against their will – for parts of, or the remainder of the pregnancy to inpatient treatment at specialised clinics. **Conclusion:** Many similarities in the treatment provided to opioid-dependent persons in the Scandinavian countries place this area in an excellent position to combine the efforts and carry out observational studies concerning the safety of OMT during pregnancy.

Keywords

buprenorphine, child, Denmark, foetus, guidelines, methadone, Norway, opioid maintenance treatment, pregnancy, Sweden

More than 50% of high-risk opioid users receive opioid maintenance treatment (OMT) – though with considerable variation between countries (The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2016). Both among high-risk opioid users and patients receiving OMT, about 20% are women, the majority being of childbearing age (Gyarmathy et al., 2009; The EMCDDA, 2016). Opioid use and the lifestyle associated with opioid dependence reduce the probability of getting pregnant (Brennan, 2013; Schmittner, Schroeder, Epstein, & Preston, 2005). Clinical data report that the menstrual cycle begins to normalise when an opioid-dependent woman initiates OMT, which will increase her probability of getting pregnant (Schmittner et al., 2005). Opioid-dependent women who receive OMT have improved obstetrical care compliance, and their foetuses are less exposed to illegal drugs compared to those born to women with opioid dependence who are not in OMT (Jones, Friedman, Starer, Terplan, & Gitlow, 2014; Jones, O'Grady, Malfi, & Tuten, 2008). Researchers have not fully explored the full range of risks that OMT exposure may have for the foetus; the focus has mostly been limited to neonatal outcomes. The World Health Organization (WHO) guidelines for the identification and management

of substance use and substance use disorders in pregnancy even labelled the quality of existing evidence as very low (WHO, 2014). The WHO still recommends OMT to pregnant opioid-dependent women because of the high rate of relapse following detoxification of opioid-dependent patients, with the severe consequences for the foetus.

The WHO guidelines emphasise the need for descriptions of current clinical practice and observational studies on the risks and benefits of pharmacotherapies in pregnancy (WHO, 2014). In the Scandinavian countries, a tax-funded national insurance system covers all inhabitants, and all inhabitants have equal access to free healthcare and education. Further, the Scandinavian countries have nationwide health registries, which offer a unique setting for observational studies. While the Scandinavian countries are, in general, similar concerning equal access to healthcare and education, there are some differences in the follow-up of women in OMT during pregnancy and after their children are born. The aims of this overview were to describe the clinical practice of OMT for pregnant women in three Scandinavian countries (Norway, Sweden, and Denmark) and how the families are followed up after childbirth. Further, we aimed to describe

Table 1. Opioid Maintenance Treatment drugs available in the Scandinavian countries.

Country	ATC code	Drug	Indication
Norway Sweden Denmark	N07BC01	Buprenorphine	Substitution treatment for opioid dependence as part of OMT
Norway Sweden Denmark	N07BC02	Methadone	Substitution treatment for opioid dependence as part of OMT Pain
Norway Sweden Denmark	N07BC051	Buprenorphine, combinations	Substitution treatment for opioid dependence as part of OMT
Norway	N07BC05	Levomethadone ^a	Substitution treatment for opioid dependence as part of OMT
Denmark	N02AA09	Diacetylmorfin	Substitution treatment for opioid dependence as part of OMT

ATC code: Anatomical Therapeutic Chemical code. OMT: opioid maintenance treatment.

^awith exemption from registration

a Scandinavian registry study of pregnant women in OMT as an example of the unique setting and the methodological strengths that the Scandinavian setting provides.

OMT drugs

Methadone and buprenorphine are long-acting opioids, which makes it possible to administer the drugs once a day while keeping the serum concentration relatively stable to avoid withdrawal. Methadone is a full mu-opioid agonist, and buprenorphine is a partial mu-opioid agonist and a kappa-opioid receptor antagonist (Wildner & Winhusen, 2015). Buprenorphine can be administered alone (Subutex[®]) or in combination with naloxone (Suboxone[®]). Naloxone is an opioid antagonist, but when administered sublingually the bioavailability is too low to cause withdrawal symptoms (Soyka, 2015). Both methadone and buprenorphine cross the placenta and enter the bloodstream of the foetus (Nanovskaya, Deshmukh, Brooks, & Ahmed, 2002; Nekhayeva et al., 2005). The WHO currently recommends use of methadone above buprenorphine, but buprenorphine may also be used (WHO, 2014). If buprenorphine is to be used, the mono-drug without naloxone should be chosen since the safety profile of naloxone is not known. Table 1

shows the OMT drugs available in Scandinavian countries.

Treatment of patients with opioid dependence in the Scandinavian countries

Specific features in Norway

History of OMT. An increase in HIV among injection drug users contributed to a debate about making substitution treatment for opioid-dependent patients more available as a treatment option, and in 1998 OMT was made available nationwide (Helsedirektoratet, 2010).

The original Norwegian OMT system was restrictive, allowing into the system only individuals with at least five years of opioid dependence who had failed medication-free treatment alternatives. Intake of OMT medicine was always supervised at the start of treatment and observed urinary controls twice a week were included. Recurring illegal drug use could result in treatment termination and individuals who missed their appointment to receive OMT medicine four days in a row could be expelled from the programme (Waal, 2007). After an evaluation of the OMT programme in 2004 (Waal, 2007), the national guidelines for opioid maintenance treatment were issued in 2010. The result of a re-evaluation of the programme

Table 2. Guidelines for pregnant women in opioid maintenance treatment (OMT) in the Scandinavian countries.

	Title	Year published
WHO	Guidelines for identification and management of substance use and substance use disorders in pregnancy	2014
Norway	National guidelines for pregnant women in opioid maintenance treatment (OMT) and follow-up of their families until the children reach school age [Nasjonal retningslinje for gravide i legemiddelasstert rehabilitering (LAR) og oppfølging av familiene frem til barnet når skolealder]	2011
Sweden	Information from the Swedish Medicines Agency, "Prescription drugs in opiate addiction" [Information från Läkemedelsverket. Hearing om läkemedelsassisterad behandling vid opiatberoende]	2010
	Drug-assisted treatment in opioid dependence. Knowledge support – in healthcare and social services. Draft for comment [Läkemedelsassisterad behandling vid opioidberoende. Kunskapsstöd – i hälso- och sjukvård och socialtjänst. Remissversion]	2019
Denmark	Vejledning til læger, der behandler opioidafhængige patienter med substitutionsmedicin [Guidance for physicians treating opioid-dependent patients with substitution medication]	2017
	Omsorg for gravide og småbørnsfamilier med rusmiddelproblemer [Caring for pregnant and toddler families with substance abuse problems]	2010

was that from 2004 OMT became less restrictive, so when a patient was stabilised on OMT and abstained from illegal drugs, he/she did not have to attend OMT centres for daily intake but could collect the OMT medication at a local pharmacy. Opioid maintenance treatment was now regarded as a long-term, interdisciplinary, holistic specialist treatment. For many patients it would last for the rest of their lives. In OMT, patients should receive individualised follow-up and treatment for somatic and mental health problems, help with housing and support to pursue an education, find work, or other meaningful activities.

OMT for pregnant opioid-dependent women. A national treatment guideline for pregnant women in OMT was published in 2011 (Bakstad & Welle-Strand, 2011) (Table 2). An opioid-dependent woman who becomes pregnant had, on average, been in OMT for two years, and had an established support team around her (Bakstad & Welle-Strand, 2011; Welle-Strand et al., 2013) that typically consisted of representatives from social services, the general practitioner (GP) and

an OMT consultant. Depending on the patient's situation, the team might also include representatives from the mental health services (Bakstad & Welle-Strand, 2011). While the woman is pregnant, the support team typically also includes a midwife and a representative from child protective services.

OMT drugs. The guidelines recommend that the woman should continue using the OMT drug that she used before becoming pregnant (Bakstad & Welle-Strand, 2011). For new patients, buprenorphine without naloxone is recommended as the first drug of choice (Helsedirektoratet, 2010). The pregnant woman should have a consultation with a medical doctor with expertise in interdisciplinary specialised treatment of substance abuse disorders at least 1–3 times during pregnancy regarding her OMT medication (Bakstad & Welle-Strand, 2011). Part of the guideline concerning pregnant women in OMT was recently revised (Helsedirektoratet, 2019). Notable revisions include ensuring that every woman who starts OMT also receives information about contraception.

If the woman wishes to become pregnant there is also an increased focus on pregnancy planning in the updated guideline, and the woman should receive information about different treatment alternatives during pregnancy and their consequences. The guidelines specifically mentioned the following alternatives: inpatient treatment, tapering down before pregnancy, or continuation of the same treatment as before pregnancy. The revision comes as a result of a long process with a consensus panel that had a strong focus on the precautionary principle (Konsensuspanelet, 2017).

Obstetric care. The growth of the foetus is monitored closely; four ultrasounds throughout pregnancy are recommended for these high-risk pregnancies (week 12, 18, 24 and 32) (Bakstad & Welle-Strand, 2011). Pregnant women and their partners should be offered training and preparation on becoming parents, according to their prerequisites (Bakstad & Welle-Strand, 2011). Some parents may benefit from a stay at an inpatient interdisciplinary drug treatment clinic, to receive guidance and training to better understand the child's needs and how to respond to these.

Control measures. Pregnant women in OMT regularly provide urine samples to show that they are not using illegal drugs. The frequency of urine tests should be based on how the woman manages her OMT and, in the absence of drug use, monthly urine samples can be considered sufficient (Bakstad & Welle-Strand, 2011). Repeated illegal drug use/non-prescribed intake of prescription drugs will result in follow-up treatment and possible control measures to prevent harm to the foetus. This may include detention in treatment clinics working with pregnant women with substance use problems, for parts of or the remainder of the pregnancy – with or without consent (Lovdata, 2011). If pregnant women are unable to stop using illegal drugs, healthcare providers are obliged by law to report this (Lovdata, 2011).

Follow-up after birth. If the mother needs additional follow-up after she is discharged from the

hospital, she and her child should be offered a place at an institution or receive help at home. For this to happen, the local child protective services should be informed as early as possible (Bakstad & Welle-Strand, 2011). A support group should be established for the follow-up of the child before the child is discharged from the hospital (Bakstad & Welle-Strand, 2011). The group should include the parents, the coordinator of the mother's support group, her GP, and a nurse or medical doctor (MD) at the well-baby clinic where the child receives regular follow-up. In many cases, child protective services should also be included, and contact with these services should optimally already have been established when the woman is pregnant. They can provide help with, e.g., day care, visiting homes, respite care, and parental guidance.

Well-baby clinic staff should visit the family at home in the first and second weeks after they are discharged from the hospital (Bakstad & Welle-Strand, 2011). From then on, monthly appointments for the first eight months, and then every second month until the child is one year old, should be at the well-baby clinic. Thereafter, the children will receive the same type of follow-up from health services as other children.

The guidelines recommend that an interdisciplinary team in specialist healthcare consisting of a paediatrician, a child psychologist, and a representative from the interdisciplinary specialist addiction treatment services, and others if relevant, is established to follow up the child (Bakstad & Welle-Strand, 2011). The parents should bring the child for examination at 6 and 12 months and then annually until school age.

There should be a low threshold for referring to other services such as child protective services, the pedagogical psychological services, child and adolescent psychiatric outpatient clinics etc. (Bakstad & Welle-Strand, 2011).

Specific features in Sweden

History of OMT. The maintenance programme with methadone in Sweden started as early as 1966. In 1999 buprenorphine (Subutex®) was

introduced, and in 2006 the combination of buprenorphine and naloxone was used in the maintenance programme under the brand name Suboxone® (Wikner et al., 2014). The combination product is now the recommended drug for patients other than pregnant women in OMT (Läkemedelsverket, 2010). The number of opioid maintenance treatment units increased from one in 1966 to six units in 2004 and has now increased further. From 2005 the programme became more generous regarding the maximum number of patients that could be included in the programme. Also, two years of drug dependency were now enough to enter the programme. These changes in treatment policy were stipulated to increase the availability of OMT (Romelsjö et al., 2010). The proportion of women in the programme is about one-third, many being of childbearing age (Wikner et al., 2014). The main aim of the OMT programme in Sweden is rehabilitation (Socialstyrelsen, 2012).

OMT for pregnant opioid-dependent women. In Sweden, there have been no written national guidelines, but there is a draft in preparation at the National Board of Health and Welfare, including a section on pregnancy, to be finalised by the end of 2019 (Socialstyrelsen, 2019) (Table 2). Based on clinical practice, women of childbearing age should be referred to a midwife to receive contraceptive advice in connection with the start of their OMT treatment. Pregnancy is not advised against during OMT treatment, but it is of great importance that the patient does not abuse drugs during the pregnancy.

In Sweden, there is no law protecting the foetus of an opioid-dependent woman, but there is a possibility to get support from teams specialised in helping pregnant opioid-dependent women.

OMT drugs. The drug recommended for OMT during pregnancy for new patients in Sweden is buprenorphine without naloxone, but if buprenorphine cannot be used, methadone is the drug

of choice. Methadone is also used when a woman is already being treated with methadone when she becomes pregnant. When a pregnant woman not already in the OMT programme needs treatment for acute abstinence from heroin, buprenorphine is recommended. If buprenorphine should be avoided due to, e.g., liver damage, methadone is recommended.

Obstetric care. When opioid substitution is used during pregnancy, the pregnancy is closely monitored and, in particular, the growth of the foetus. Almost all pregnant women attend routine antenatal care, which is free of charge. Collaboration between midwives at the antenatal unit with particular interest in these specific patients, the maternity and delivery unit and paediatricians at the neonatal unit, increases the possibility of optimal treatment of the new-born.

Control measures. The special care units, which provide different kinds of support for pregnant women during pregnancy, use AUDIT (alcohol use disorders identification test), DUDIT (drug use disorders identification test) and TLFB (timeline following back). Urine samples are regularly collected during pregnancy for women in OMT to monitor relapse to illegal drug use. The frequency of sampling is individually decided. Also, samples for biomarkers for ethanol are provided when needed.

Follow-up after birth. When the mother and the neonate are discharged from the hospital, the child is followed up at child healthcare centres until the age of five to six years. Families with additional needs can get help from social services and the child welfare service. Children with special needs can also get extra help.

Specific features in Denmark

OMT for opioid-dependent patients. Denmark introduced OMT for opioid-dependent individuals in 1970 (The EMCDDA, 2014). The general treatment approach involved prescription medication, methadone, and psychosocial

treatment interventions (Dole, Nyswander, & Kreek, 1966). From the 1970s, drug use treatment was framed as a social problem rather than a medical problem and moved from the national healthcare system to the social welfare system (Houborg, 2006). The public drug treatment system that was developed focused on inpatient treatment. This was supported politically; the intention was that methadone should be used only for short-term detoxification (Frank, Bjerge, & Houborg, 2013). At the same time, some GPs began to prescribe methadone to opioid-dependent persons on a long-term, maintenance basis. The GPs' treatment approach often did not involve any other treatment or support than the prescription itself (Skretting & Rosenqvist, 2010).

In the mid-nineties, the prevalence of overdoses and lack of control of OMT led the government to implement new guidelines. Only public treatment centres were authorised to provide OMT (Skretting & Rosenqvist, 2010). Still, the medical treatment of drug use was perceived as being liberal and very diverse between centres. The National Board of Health launched new medical guidelines in 2008 (Sundhedsstyrelsen, 2008) to secure a consistent and acceptable level of medical treatment. However, Denmark continued to focus on achieving a high treatment coverage by leading a prescription strategy that was less restrictive than in other European countries (The European Commission, 1996; The EMCDDA, 2014). The Danish OMT strategy may be considered "liberal", e.g., in regard to supervised intake, doses prescribed, and take-home doses (Skretting & Rosenqvist, 2010; Tjagvad et al., 2016).

Today, the municipalities, as part of the available welfare services, offer OMT. In addition to OMT with long-acting opioids, heroin-assisted treatment has been available in Denmark since 2009 (Sundhedsstyrelsen, 2013). From 2004 and onwards, individuals who need OMT have been guaranteed access to psychosocial treatment, and since 2015 also consultation with an MD within 14 days after

the initial contact with the treatment centre (Socialministeriet, 2002; Sundheds- og Ældreministeriet, 2014). Although two different sets of policies still govern OMT – health regulations and social service regulations (the Ministry of Health and the Ministry of Social Services) – practitioners consider OMT as an integrated treatment, including both healthcare and psychosocial services. The aim of OMT in Denmark is supporting the patient towards having a meaningful and satisfying life in a way that is defined and controlled by the patient themselves (Sundhedsstyrelsen, 2017). This may also include a lifelong involvement in OMT.

OMT for pregnant opioid-dependent women. The national treatment guidelines from 2017, covering all OMT in Denmark include a section describing treatment specifically for pregnant women (Sundhedsstyrelsen, 2017; Table 2). Guidelines covering treatment for pregnant women with problematic use of potentially addictive medication, alcohol or other substances were issued in 2015 (Dansk Selskab for Obstetrik og Gynækologi, 2015; Table 2).

The OMT clinics in the municipalities may provide a variety of services to opioid-dependent women, e.g., treatment and consultations provided by MDs, nurses and healthcare assistants; and psychosocial treatment provided by psychologists and social workers. The OMT clinic coordinates the treatment with the patient's GP and, if indicated, the mental health services. While the woman is pregnant, the coordinating group is extended to include the family outpatient clinic at the hospital and the child protective services in the municipality. The team at the family outpatient clinic includes MDs, psychologists, social counsellors and midwives (Sundhedsstyrelsen, 2010). The family outpatient clinic is responsible for the coordination within the group.

During the pregnancy, the OMT clinics can continue the provision of drug use treatment, including OMT, in cooperation with the family outpatient clinics (Sundhedsstyrelsen, 2017).

OMT drugs. It is recommended that the woman should continue with the OMT medication that she used before becoming pregnant and maintain the medication during pregnancy (Sundhedsstyrelsen, 2017). Until the national OMT guidelines were revised in 2017, methadone was recommended as the first-line treatment for new OMT patients (Sundhedsstyrelsen, 2008). In the revised OMT guidelines, buprenorphine without naloxone is recommended as the first-line treatment for new patients (Sundhedsstyrelsen, 2017). Careful tapering to a low dose or no medication is generally not recommended but can be tried if the woman wishes it, and she is well informed about the safety aspects associated with tapering. Changes in OMT medication, including dose, should only be conducted after consulting the family outpatient clinic.

Obstetric care. It is important as early as possible to secure a speedy, possibly acute, contact between a pregnant woman and a family outpatient clinic that can assess the need for treatment, including inpatient treatment, and follow-up (Sundhedsstyrelsen, 2008). A pregnant woman can contact an obstetric hospital department without a referral, and this includes acute and anonymous contacts. The aim is that there is no waiting list for the family outpatient clinic for this patient group.

Pregnant women who are stabilised on OMT are usually seen for obstetric control as needed during the pregnancy (Sundhedsstyrelsen, 2008). Pregnant women who have not yet been stabilised on OMT should be referred to an obstetric department or an inpatient drug-treatment clinic for pregnant women.

Control measures. To perform urine screening in case of anamnesis or clinical signs of drug use, informed consent is required (Dansk Selskab for Obstetrik og Gynækologi, 2015). However, if a woman with a history of drug use refuses to perform a urine screening, the urine screening should be considered as positive (Dansk Selskab for Obstetrik og Gynækologi, 2015). In these situations, the foetus is considered to have

been exposed to drugs, and observation for abstinence and follow-up by the neonatal team should be considered. The social authorities will also be informed.

Pregnant drug-using women who receive institutional treatment should be informed about the possibility of entering into a contract on treatment involving the possibility of detainment (Socialministeriet, 2017). The woman herself makes the choice, and women who decide not to enter into a contract will still have complete access to all existing services, including inpatient drug treatment clinic care. Women who decide to enter into a contract may revoke the contract at any time – when detainment is not indicated.

Detainment may only be practiced when there is a reason to assume that the pregnant drug user is going to cancel the agreed treatment, and it would be unjustifiable not to detain the person in question. If the prospect of ceasing drug use or a decisive improvement of the condition is considerably weakened, or the woman exposes herself or others to imminent danger, detainment is possible. Detainment may only occur if less intrusive measures are insufficient. Detainment must cease when the above conditions no longer apply (Sundhedsstyrelsen, 2017).

Follow-up after birth. The length of the admission at the obstetric department after birth depends on which substances/medications that the foetus was exposed to during the three weeks before birth and also to the condition of the child (Sundhedsstyrelsen, 2010). If the mother had consumed methadone, the child should be observed for three weeks. If the mother had consumed other opioids than methadone, the child should be observed for one week (Rigshospitalet, n.d.).

During admission, close cooperation will be (re-)established between relevant services, such as the obstetric department, child welfare services, the OMT clinic, alcohol abuse clinics, and mental health services (Sundhedsstyrelsen, 2010). The focus is on exchange of information

and planning relevant support measures for the child and parents after discharge. Contact with child welfare services should optimally have already been established when the woman is pregnant. Follow-up from the child welfare services after birth can consist of help with day care, visiting homes, respite care, and parental guidance.

The parents should bring their child for a doctor examination one month after discharge from the hospital, followed by a doctor and psychologist examination at three, six, nine, and 12 months after birth and then annually until school age (Sundhedsstyrelsen, 2010).

Common features in OMT for pregnant opioid-dependent women in Norway, Sweden and Denmark

Tasks of the supporting team around the pregnant woman

The teams obtain information concerning the woman's situation, such as mental and somatic health, financial and housing situation, employment status, relationship with partner and family and other relevant aspects of life. All these factors may be important for the future child-rearing environment. The woman and her partner's resources and expectations with regard to becoming parents are mapped; with a particular focus on health problems associated with a history of injection drug use, and information about the use of illegal drugs, alcohol, tobacco, and prescription drugs during the months before, and during, pregnancy.

OMT drugs

During pregnancy, the distribution volume and elimination of the OMT drugs increase, and as a result, the serum concentrations of the drugs fall, and some women may experience abstinence. Before increasing the dose, the guidelines recommend the intake of OMT drug dose at two time-points. If the woman still

experiences abstinence after splitting the dose, it is recommended to increase the total daily dose.

Other prescription drugs

Women using benzodiazepines and other prescription drugs with abuse potential should be advised to gradually taper use of these in a safe manner.

Preparing for the possibility that the child is born with neonatal abstinence syndrome (NAS)

More than half of children born to mothers in OMT are born with neonatal abstinence syndrome (NAS) (Welle-Strand et al., 2013). In all countries, the parents should be informed about the incidence, symptoms, typical duration, and treatment of NAS, and be given guidance on how to care for their child. Watching a child with NAS is heartbreaking, and parents should be offered additional follow-up (Bakstad & Welle-Strand, 2011; Danish National Board of Health, 2010). In Norway, the new-born should stay in the hospital for at least seven days after birth to ensure that NAS needing treatment is discovered; and in Sweden, babies with risk of NAS will be observed for a longer period at the maternity ward. If parents in Denmark object to observation and treatment, the social authorities should be informed.

Summary of OMT in pregnancy in the Scandinavian countries

Norway and Denmark have national guidelines for OMT to pregnant women with opioid use disorders, while no such guidelines exist in Sweden. The guidelines have many similarities but also some differences. An important aspect is that they ensure a reduction in geographical differences in treatment in each county, and because of the similarities in the guidelines, also between the two countries. In Sweden, the social services have overall responsibility and

support the family, and regional guidance occurs as part of the OMT programmes.

Another important aspect of OMT is the establishment of a multidisciplinary team around the pregnant woman in Norway and Denmark. When it is considered to be required, such teams are also established in Sweden. The teams are intended to facilitate in a broad range of areas for the parents and the expected child. These teams are part of the free-of-charge national healthcare system, which reduces the risk that pregnant women with opioid use disorders live under conditions harmful for the foetus.

In Norway, a standard plan for obstetric care is established for this patient group, while this is not described in Sweden or Denmark. In Denmark, easy and speedy contact with specialist healthcare is assured when needed. In Sweden, when needed contact is established with support from different specialists and other healthcare teams, with particular focus on foetal growth and possible adverse pregnancy outcomes.

In contrast to the WHO guidelines, which recommend methadone as the OMT drug for pregnant women, all the Scandinavian guidelines today recommend buprenorphine as the first drug of choice. One reason for this may be the possibility for a closer follow-up of pregnant women, which reduces the risk of relapse to illicit opioids; the risk of relapse was the main reason for the WHO's recommendation of methadone over buprenorphine.

A strong focus on other prescription drugs with abuse potential is present in all three countries. Urine screening tests are performed as control measures in all three countries, but in Denmark and Sweden, informed consent is required to take these tests. A primary difference between the countries is that in Norway, involuntary admission to treatment centres is possible if a pregnant woman uses illicit or prescription drugs that might harm the foetus, and that healthcare professionals who becomes aware of such use are obliged by law to report this.

In all three countries, contact with necessary welfare and health services is assured before the mother and new-born leave the hospital after birth, with the intention to follow the child routinely until school age.

A Scandinavian cohort of pregnant women in opioid maintenance treatment: Long-term consequences for the child – the ScopeOMT project

The focus on early intervention and a holistic focus around the pregnant woman including multidisciplinary teams may be the most important reason that the Scandinavian countries are a suitable setting to study the effects OMT treatment might have for the developing foetus. Recently, a consensus panel in Norway has recommended larger focus on tapering of OMT drugs during pregnancy because it cannot be ruled out that the treatment might harm the developing foetus, for instance by causing protracted NAS (Konsensuspanelet, 2017). This is a controversial recommendation, which contradicts the WHO's recommendations. However, the decisions also underscore the importance of more and stronger methodological research in this field. We believe that the Scandinavian Registry cohort study of pregnant women in OMT during pregnancy (ScopeOMT) will contribute to this.

The vast majority of studies of the consequences of prenatal exposure to OMT have been conducted in the US (Brogly, Saia, Wallely, Du, & Sebastiani, 2014). Furthermore, much of the research is plagued by methodological limitations such as small samples, selected groups of women being included in studies, and lack of sufficient control confounders. Studies on child outcomes beyond the neonatal period are rare. The primary objective of ScopeOMT is therefore to study long-term outcomes in children exposed to OMT during foetal life in a large pregnancy cohort in a Scandinavian setting.

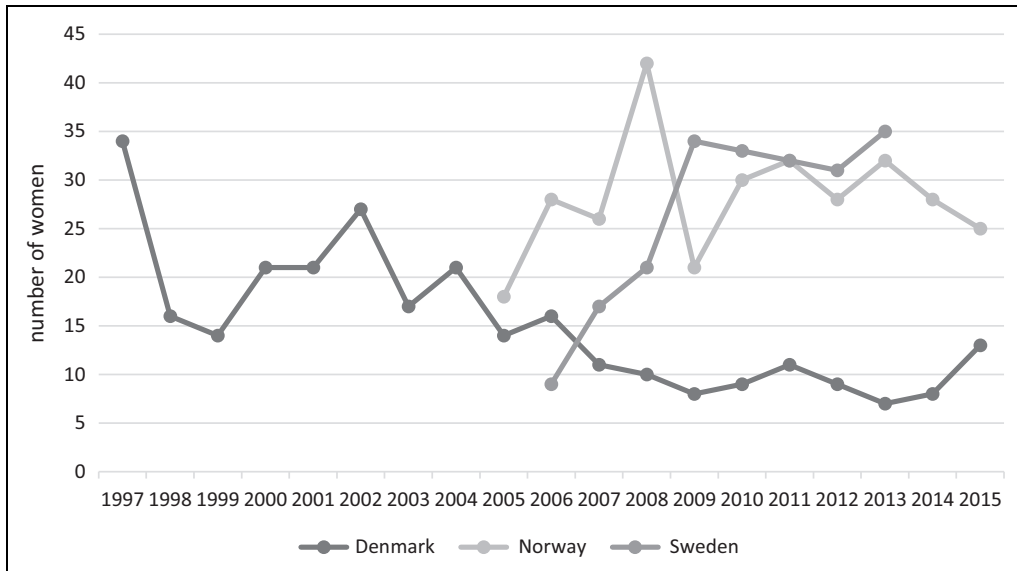


Figure 1. Numbers of pregnant women in opioid maintenance treatment (OMT) per year in Norway, Sweden, and Denmark.

This project is a registry-linkage study with data from Norway, Sweden, and Denmark. The health registers in Scandinavia represent an invaluable source of data (Bliddal, Broe, Pottegard, Olsen, & Langhoff-Roos, 2018; Gabrhelik et al., 2016; Maret-Ouda, Tao, Wahlin, & Lagergren, 2017); they include high-quality data that, primarily, are organised similarly regarding data structure and complete population coverage. The use of a unique personal identity number (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekblom, 2009; Schmidt, Pedersen, & Sorensen, 2014) makes it possible to link the data from the different registers. The project includes data from the following Scandinavian registries: (1) prescription databases, (2) birth registries, (3) patient registries, (4) data from primary healthcare in Norway, and (5) data on socio-economic status from Statistics Norway and Denmark. To identify pregnant women in OMT during pregnancy we link the birth registries and the prescription registries. Any pregnant woman who is dispensed an OMT drug at least once during pregnancy, according to the prescription registries,

is defined as a pregnant woman in OMT. In recent years, a majority of patients is dispensed OMT drugs in pharmacies, and all dispensed prescription drugs are recorded in the prescription registers. By using registry linkage, about 800 pregnant women in OMT were identified. The numbers of pregnant women in OMT during the study period in the three Scandinavian countries are shown in Figure 1.

The outcomes will mainly be identified as ICD-10 diagnoses from contact with specialist healthcare (the patient registry). Data on dispensed drugs registered in the prescription databases may also act as a proxy for long-term outcomes; for instance, antiepileptic drugs may serve as a proxy for epilepsy.

Most previous studies compare the new-borns of women in OMT with new-borns of women from the general population (Konijnberg & Melinder, 2011). Women in these groups have a very different confounder distribution, and comparison between them is therefore not suitable. By using registry data, we can identify more appropriate comparison groups, such as women who were in OMT before

pregnancy, but who discontinued treatment before they became pregnant. The use of more appropriate comparison groups makes it possible to come closer to unbiased associations.

To assess risks, multivariable regression analyses will be performed, propensity scores will be calculated, and we will apply inverse probability of treatment weights based on the propensity scores to adjust for confounders.

The research in ScopeOMT has received ethical approval from ethical committees in Norway, Sweden and Denmark, and the Norwegian Research Council has supported the project financially (Grant no 240197/H10).

By using the unique register data in Scandinavia that includes the entire populations, we can establish large study populations and follow all the study participants over time. By creating relevant comparison groups and using relevant information from several registers as possible confounding factors, we believe that the project will be able to produce new high-quality research that might guide future treatment guidelines and choices for this vulnerable patient group.

Ethical approval

The use of data was approved by the Regional Ethical Research Board in Norway (2014/358/REK sør-øst D) and the Regional Ethical Review Board in Stockholm, Sweden (2009/775-31/4, 2016/152-32, and 2017/1159-32), and the Norwegian (16/01326-2/SBO) and the Danish Data Protection Agency (J.nr. 2013-41-1789). The national parliaments have, on behalf of their populations, given informed consent to be included in the registers. According to Danish legislation, no ethical permission is needed for registry-based research in Denmark.

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