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Validation of assisted reproductive technology in the Medical Birth Registry of Norway versus the Norwegian Prescription Database

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Data and computing code: The dataset analyzed during the current study is not freely available due to national regulations, but the data are gathered from official registries, and both national and international researchers may obtain the same data.

Abstract

Background Increasing attention has been given the long-term effects of assisted reproductive technology (ART). This study assessed the validity and completeness of ART as registered in the Medical Birth Registry of Norway (MBRN) using drug prescription data from the Norwegian Prescription Database (NorPD) as reference.

Methods In this nationwide registry validation study, we included all pregnancies recorded in the MBRN between 2005 and 2017. We estimated sensitivity, specificity, and positive and negative predictive value (PPV and NPV) of the MBRN, using data from the NorPD as reference. We obtained the total percentage of ART-pregnancies that could be identified (completeness) from both registries using the capture–recapture method. We analyzed subgroups by maternal age, gestational length, mode of ART treatment, health region, and mode of registration of ART (ART institution or birth notification form).

Results 23,718 of a total 765,789 pregnancies were registered as ART-pregnancies through the MBRN, and 20,807 as ART-pregnancies through the NorPD. The sensitivity of the MBRN was 85.1% (95% confidence interval (CI) 84.7–85.6) and the PPV was 74.7% (74.1–75.2). Sensitivity declined with increasing maternal age: 71.5% (69.4–73.7) in the age group 40–44 years, and 40.7% (22.2–59.3) in the ages above 45 years. Completeness when combining data was 96.2% (96.0–96.5).

Conclusion Our analysis shows that, when identifying women pregnant through ART, NorPD data complemented MBRN data to obtain a more complete count of all women giving birth following ART in Norway.

Keywords

Assisted reproduction; registry study; validation study; medical birth registry; pharmacoepidemiology; health administrative data

Background

The increasing use of assisted reproductive technology (ART) worldwide[1] and in Norway[2] has led to interest in long-term maternal and infant outcomes. A recent meta-analysis suggested elevated risks of preterm birth, preeclampsia, and other obstetric complications,[3] and several original reports have indicated increased risk of postpartum hemorrhage[4] and cancer [5-7] among women pregnant after ART. Norway does not have a nationwide cycle-based ART-registry. Information on ART-exposure can be obtained from the Medical Birth Registry, self-reported information, medical records or information on prescribed drugs from the Norwegian Prescription Database (NorPD). A large Norwegian study on cancer risk among women and children exposed to ART found slightly different results in risk depending on whether the source of exposure was the Medical Birth Registry of Norway (MBRN) or the Norwegian Prescription Database (NorPD).[6 8 9] The study populations were not exactly the same and the differences could either be due to incomplete data in one of the two registries or the registries capturing slightly different populations. However, the results highlighted the need for a validity study to assess the ART variable in the MBRN.

Electronic health registry data are increasingly used in health research, and validation studies of registry data have been called for.[10 11] Validation studies give information on data precision and allow for estimates of measurement error. Biased data from registries can lead to improper healthcare policy recommendations and may distort patient outcome measures.

The objective of this study is to validate the registration of ART pregnancies in MBRN, using data on specific ART drugs from NorPD as a reference. Due to different data collecting methods, some ART pregnancies may only be represented in one of the two databases. This study will also estimate the number of ART-pregnancies that can be obtained by combining information from MBRN and NorPD.

Methods

Study population

This nationwide registry study includes data on all births registered in the MBRN between 1 January 2005 and 31 December 2017. Data were merged with the NorPD on ART drug prescriptions in the period 1 January 2004 through 31 December 2017 by using the 11-digit personal identification number unique to every citizen of Norway. The study cohort comprised all pregnancies of known gestational length that ended during the study period. We adhered to the STARD (Standards for Reporting of Diagnostic Accuracy Studies) guidelines for reporting of diagnostic accuracy.[12] The MBRN was denoted the index test, and the NorPD was denoted the reference standard, in accordance with the guidelines.

The Medical Birth Registry of Norway - The index test

The index test was the mode of conception as recorded in the MBRN (either *ART* or *not ART*). The MBRN records data on all deliveries after week 12 in Norway based on a birth notification form filled out by midwives. All institutions licensed for ART in Norway are required by law to report information on ART treatments that result in a pregnancy to the MBRN. As soon as a pregnancy is established by ultrasound (usually within gestational week 12) reporting is done directly to the MBRN from the ART institution. To ensure completeness, reporting of ART pregnancies may also be done on the birth notification form. In addition to ART (yes/no), we obtained data on type of treatment (conventional IVF, IVF with intracytoplasmic sperm injection (ICSI), other or unspecified ART procedures), ART institution, and demographic data from the MBRN.[2]

For each birth, we calculated the last menstrual period (LMP) of the mother before the pregnancy by subtracting the gestational length (as registered in the MBRN) from the delivery date.

The Norwegian Prescription Database - The reference standard

The NorPD records all prescribed drugs dispensed at Norwegian pharmacies to non-institutionalized individuals , since 1 January 2004.[13] Reporting is mandatory by Norwegian law. Drugs are classified according to the international Anatomical Therapeutic Chemical (ATC) classification system. For this study, NorPD provided data on ATC code (eTable 1 ; http://links.lww.com/EDE/B682) and date of dispensing for drugs used in ART between 1 January 2004 and 31 December 2017.

Controlled ovarian hyperstimulation (COH) is the process of using drugs to obtain several mature oocytes in a single menstrual cycle for use in ART. Hormone protocols used to obtain COH vary and, among Norwegian clinics, there are no consensus documents on choice of drugs and dose. However, most standard protocols consist of the following three drugs: Gonadotropin releasing hormone (GnRH) analogues (agonists or antagonists), gonadotropins, and human chorionic gonadotropin (hCG). For drug doses, we refer to the Summary of Product Characteristics (SPC) in the NoMA medicine database for information.[14].

Mothers who were prescribed and dispensed all three drugs within a specified time prior to LMP and up to 1 month after LMP, were considered pregnant through ART as registered in the NorPD. We conducted initial analyses with both 2- and 4-month exposure periods prior to LMP. We ultimately employed the 4-month cut-off for all analyses, to capture as many exposed as possible. For further sensitivity analyses, we obtained estimates following exposure to at least two of the three drugs, as well as at least one of the three.

Analyses

We compared the validity of the MBRN in identifying women giving birth after ART to data from the NorPD . We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the index test (MBRN), compared to the reference (NorPD)

for the whole cohort, with 95% confidence intervals (CI) (eAppendix 1 ; http://links.lww.com/EDE/B682).

We stratified the analyses by maternal age at delivery (<20, 20–24, …, 40–44 and ≥45 years), gestational length in weeks (12–18, 19–23, 24–29, 30–34, 35–36, 37–42 and ≥43 weeks), mode of ART treatment (In vitro fertilization, (IVF), intracytoplasmic sperm injection (ICSI) , IVF and ICSI, artificial insemination by husband (AIH), other), health region at delivery (Health Region South-East , West, Mid- Norway, North), and mode of registration of ART (ART institution or birth notification form).

We estimated the number of ART pregnancies that can be obtained by combining information from NorPD and MBRN, referred to as completeness, by the capture–recapture method[15] shown in eAppendix 2 ; http://links.lww.com/EDE/B682. This method was developed to estimate the number of animals in a closed population, but has also been used to estimate completeness of cancer and other disease registries.[15 16] The method requires that the linkages of records can be carried out successfully. In this study we ensured a correct classification of the women who have conceived a child after ART treatment (cases) by the use of the personal identification number. Moreover, the method is based upon two assumptions: First, there should be no dependency between the sources. This means that a case can be registered in either MBRN or the NorPD independent the other source. Second, the cases must have the same probability of being captured. In this study we treated the MBRN and the NorPD as two independent sources, and we summed up the number of women that were captured by one, both or none of the sources using the formula in eAppendix 2 ; http://links.lww.com/EDE/B682.

Ethics statement

This research was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research of South/East Norway.

Results

During the study period there were 789,087 births (singletons and multiples) registered in MBRN. Of these 5,436 had unknown gestational length and 4,723 did not have an ID for the mother. These data were excluded, leaving a remaining 778,928 births from 765,789 pregnancies (Figure). The remaining 765,789 pregnancies constitute the study cohort, out of which 23,718 were ART pregnancies according to the MBRN (Table 1). In 27,225 of the pregnancies the mother had at least one prescription fill of an ART drug. A total of 3,204 women had been prescribed one of the three drugs for ART, whilst 3,214 had been prescribed two of the three, and 20,807 women had been prescribed all three drugs (eTable 2 ; http://links.lww.com/EDE/B682). Demographic data of the two groups are shown in Table 2. Among the cases with only one registered drug, the drug prescribed was hCG in 2,318 cases (72%) (eTable 3 ; http://links.lww.com/EDE/B682).

When using exposure time of ART drugs two months prior to LMP instead of four months, 2,717 fewer pregnancies were classified as ART pregnancies in NorPD (eTable 2 ; http://links.lww.com/EDE/B682).

Sensitivity of the MBRN in detecting ART pregnancies was 85.1% (95% CI 84.7–85.6) (Table 3). The positive predictive value was 74.7% (74.1–74.7). When using one of the three possible drugs as a measure of ART, PPV was 84.0% (83.6−84.5), and for two of three it was 81.2% (80.7–81.2).

The specificity when using all three drugs was 99.2% (99.2–99.2), and the negative predictive value was 99.6% (99.6–99.6) (Table 3).

When we stratified on maternal age, there was an inverse association between high maternal age and both sensitivity and PPV. In the group of maternal age 30–34 years, the sensitivity was 87.5% (86.7–88.2), and the PPV was 75.0% (74.2–75.9). With maternal age 40–44 years the sensitivity was 72.0% (0.72−0.72) and PPV was 70.0% (0.70−0.70). Numbers were very low for women age 45 years and above; the sensitivity was 40.7% (22.2–59.3) and the PPV was 10.4% (CI 4.6–16.2) (data not shown).There were few differences in sensitivity and PPV across categories of parity, gestational length and health region (eTable3 ; http://links.lww.com/EDE/B682).

We estimate completeness to be 96.2% (96.0–96.5) when combining data from the two registries (Table 3).

Discussion

In this study we have validated the registration of ART pregnancies in MBRN, using drug prescription data from NorPD as a reference. Our results show that MBRN has a sensitivity of 85% and a PPV of 75% for detecting ART pregnancies. Thus, one quarter of pregnancies registered in MBRN as ART were not registered with a dispensed combination of ART-drugs within the defined time period prior to the pregnancy. When looking at pregnancies where the mother had one prescription fill for ART drugs, the PPV increased to 84%. The 16% that were not recorded in the NorPD may represent women who received treatments and also all medications abroad, or women who received ART without hormones in a natural cycle.[17] i

In subgroup analyses we found the sensitivity and PPV to be fairly constant, although the sensitivity was lower among older women (72% among women between 40 and 44 years old at delivery, and 41% among those above 45 years old).

Our study suggests that to identify ART patients in future studies, data from NorPD represent a valuable complementary data source for ascertaining all pregnancies that are a result of ART. As NorPD was established in 2004, data on ART prior to this must rely solely on MBRN. Only 75% of women registered as ART through MBRN were registered with ART drugs in NorPD. Women treated with ART abroad or women pregnant by natural cycle IVF will not be captured by data from NorPD, and this might explain at least part of this inconsistency.

There are some limitations to our study. Selected data from MBRN have been validated in previous studies, such as uterine rupture,[18] hyperemesis,[19] and preeclampsia.[20] In these previous studies, hospital records were used as the gold standard, while we used data from NorPD as a reference. Norwegian women travel abroad for ART treatment mainly because the legislation in Norway is stricter than in other countries: egg donation, for instance, is illegal. It is not known whether women travelling abroad for ART treatment are dispensed ART drugs from pharmacies in Norway, or to what extent clinics in other countries offer all medications at hand. In the latter cases ART treatment will not be captured by the NorPD, which may partly explain the low (75%) PPV of the NorPD data. Certainly for older women, where the need for oocyte- and embryo donation may necessitate treatment abroad, this may explain the even lower rates of registration in the MBRN. Furthermore, frozen embryo transfers in a natural cycle (without dispensed drugs) could also explain part of this discrepancy.

Alternatively, another possible scenario is that women are prescribed hCG in combination with clomiphene citrate or gonadotropins as a treatment of anovulation aiming at natural conception. In this case, the women would be classified as ART women, although no assisted reproduction has taken place. We could not obtain the types of stimulation protocols used for COH from the NorPD, and there is no national consensus method for how COH is carried out in

Norwegian clinics. This underlines the importance of establishing a cycle-based registry with a more precise registration of the specific drugs used, their dose and combinations.

In our study we have no estimate of ART use in women who did not achieve a pregnancy; although this question is of interest, it is beyond the scope of this article. While Sweden has a cycle-based registry of ART, [21] unfortunately no such registry has yet been established in Norway. Only ART trials that result in a pregnancy past 12 weeks are recorded, as this is mandatory. Recent reports estimate that 2,500 children are born after ART annually in Norway[2]. Given a success rate of ART at an estimated 30-50%,[1] as many as 2,000-3,000 women may annually be going through ART cycles, without a subsequent pregnancy and birth. These are not recorded in the MBRN, and represent a problem when epidemiologic studies aim to identify exposure to ART.

We observed that there were inconsistencies in our two populations, implying incompleteness in data for both registries. When aiming to identify ART women, neither the NorPD nor the MBRN alone are sufficient for capturing all women undergoing ART in Norway. By using data from both registries, we estimated that it is possible to capture 96 % of all ART-pregnancies (>12 weeks). The capture–recapture method is, however, based upon the assumptions that the cases have the same probability of being captured by both registries, and that there are no dependencies between the sources. This is not possible to test directly in this study, and the method may lead to under- or over-estimated case numbers if either of the assumptions are incorrect.

To conclude, our analysis shows that, when identifying women pregnant through ART, NorPD data complemented MBRN data to obtain a more complete count of all women giving birth following ART in Norway

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Figure Legend

Figure

STARD (Standards for Reporting of Diagnostic Accuracy Studies) diagram to describe the study cohort

Footnote:

ART: assisted reproductive technology; MBRN: Medical Birth Registry of Norway; NorPD: Norwegian Prescription Database.

[a] Pregnancies were considered to be a result of ART treatment when prescribed a combination of all three medications (gonadotropin releasing hormone (GnRH) analogues (agonists or antagonists), gonadotropins and human chorionic gonadotropin (hCG)) within four months prior to or one month after the last menstrual period.

TABLE 1

		ART by NorPD		
		Yes	No	Total
ART by MBRN	Yes	17714	6004	23718
	No	3093	738978	742071
	Total	20807	744982	765789

TABLE 2

	ART by MBRN	%	ART by NorPD	%	Total	%
Total number	23718		18090		765789	
Mean gestational age (days, standard deviation)	272.4 (23.6)		272.0 (23.6)		277.2 (18.1)	
Mean birth weight (grams, standard deviation)	3316.6 (734.1)		3282.8 (721.3)		3500.5 (604.4)	
Maternal age at delivery (years)						
<20	2	0.0	1	0.0	13726	1.8
20-24	437	1.8	375	1.8	103911	13.6
25-29	4278	18.0	3661	17.6	242525	31.7
30-34	9323	39.3	7998	38.4	256442	33.5
35-39	7849	33.1	7051	33.9	124207	16.2
40-44	1723	7.3	1694	8.1	23745	3.1
≥45	106	0.4	27	0.1	1233	0.2
Total	23718	100	20807	100	765789	100
Registered place of birth (region in Norway)						
South-East	13247	90.7	11694	56.2	422578	55.2
West	5661	23.9	4981	23.9	173026	22.6
Mid-Norway	3409	14.4	2842	13.7	102391	13.4
North	1338	5.6	1241	6.0	66302	8.7
MISSING	63	0.3	49	0.2	1492	0.2
Total	23718	100.0	20807	100.0	765789	100.0
Parity						
Nulliparous	14599	61.6	13358	64.2	323306	42.2
Parous	9119	38.4	7449	35.8	442483	57.8
Total	23718	100	20807	100.0	765789	100
Pregnancy length (weeks)						
12-18	108	0.5	101	0.5	1725	0.2
19-23	169	0.7	147	0.7	3294	0.4
24-29	270	1.1	236	1.1	3553	0.5
30-34	785	3.3	687	3.3	10071	1.3
35-36	1010	4.3	898	4.3	15539	2.0
37-42	20715	87.3	18192	87.4	705573	92.1

≥43	661	2.8	546	2.6	26034	3.4
Total	23718	100	20807	100.0	765789	100
IVF method						
IVF	11578	48.8				
ICSI	9540	40.2				
IVF AND ICSI	113	0.5				
AIH	454	1.9				
other	150	0.6				
missing	1883	7.9				
total	23718	100.0				

Table 3

	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI	Completeness	95% CI
At least one of three drugs	73.2%	72.7–73.7	99.5%	99.5–99.5	84.0%	83.6–84.5	99.0%	99.0–99.0	95.7%	95.5–95.9
Two or more of three drugs	80.2%	79.7–80.7	99.4%	99.4–99.4	81.2%	80.7–81.2	99.4%	99.3–99.4	96.1%	0.95–0.97
All of the three drugs	85.1%	84.7–85.6	99.2%	99.2–99.2	74.7%	74.1–74.7	99.6%	99.6–99.6	96.2%	96.0–96.5

Figure 1