

Data Resource Profile: The Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS) cohort

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Data Resource Basics

Over the last decades, the use of assisted reproductive technology (ART) has steadily increased, due to a combination of higher availability and success rates of treatment (1), but also societal changes with postponement of parenthood to age ranges with a low natural fertility (2). ART comprises all methods of fertilization outside the female body with subsequent embryo transfer to the uterus, including standard in vitro fertilization (IVF) and the more invasive method intracytoplasmic sperm injection (ICSI). Worldwide more than seven million children have been born after ART and in Europe more than 170 000 children are conceived by ART every year (1, 3). Today, one in six couples experience some form of infertility problem (4). The Nordic countries have a high availability of assisted reproduction, resulting in more than 12 000 children conceived after ART annually, corresponding to 3-5% of the birth cohorts in 2014 (1, 5).

The Committee of Nordic ART and Safety (CoNARTaS) was established in 2008 by initiative from members of the European IVF Monitoring group in the European Society of Human Reproduction and Embryology (ESHRE) and researchers from the University of Copenhagen (Denmark), University of Helsinki and THL National Institute for Health and Welfare (Finland), Norwegian University of Science and Technology (Norway), and University of Gothenburg (Sweden). Initially, the main aim was to study perinatal health after ART conception, using a matched cohort design with data from the national health registries. This matched cohort included data on all ART children and a sample of

naturally conceived children born between the year when the national ART registration was established in each country and the end of 2007 (6).

More recently, the collaboration expanded to investigate both short and long term health for children born after ART and for their mothers, compared to the background population of naturally conceived children and their mothers, respectively. Main outcomes include perinatal health, pregnancy complications, endocrine diseases (including diabetes mellitus), imprinting diseases, pubertal disturbances, cardiovascular diseases, cancer and mental health.

The inclusion period for the present data linkage depends on the availability of data on ART conception in each country: 1994-2014 in Denmark, 1990-2014 in Finland, 1984-2015 in Norway and 1985-2015 in Sweden. The Swedish registration of ART deliveries began in 1982, but the number of ART deliveries in 1982-1984 was very limited and these birth cohorts were therefore excluded. From each country, children and mothers from all deliveries registered in the Medical Birth Registries (MBR) during the study period are included. In total, the CoNARTaS cohort contains information on 172 161 ART children and 7 681 797 naturally conceived children, as well as 127 317 mothers with at least one delivery after ART and 4 003 455 mothers with deliveries only after natural conception. An overview of the study population is provided in Table 1.

[Table 1 here]

Data collected

Dataset production

All data in the CoNARTaS cohort were obtained from national health registries, disease-specific quality registries and other nationwide databases in each country. These nationwide registries are of high quality and are comparable, although not identical, in structure and content across the four countries. Data from the different registries are linked at an individual level using the national

identity number assigned to all residents in each Nordic country at birth or immigration. This number follows the resident throughout life to ensure correct identification in all contact with the public sector and selected parts of the private sector, including health care services, thus enabling individual follow-up in registry data (7). For most national health registries in the Nordic countries, reporting is mandatory by law (8-11).

The CoNARTaS study population consists of all live and stillborn children, as well as their mothers, registered in the MBRs during the study period. Information from the MBRs has been linked to data from national ART registries or ART databases to determine which deliveries resulted from ART. To enable long term follow-up, data on all children and mothers were linked to data from other health registries providing information on diagnoses, causes of death, and drug prescriptions. Socio-economic data including educational level and emigration status were also retrieved. This overview focuses on the baseline registrations of ART conception, pregnancy and delivery. Other health registries and data sources used in this cohort are summarized in Table 2 and many of these have previously been described in detail from a Nordic collaboration perspective (12-14).

[Table 2 here]

Medical Birth Registries

The national Medical Birth Registries have recorded data on deliveries since 1973 in Denmark, 1987 in Finland, 1967 in Norway, and 1973 in Sweden. Live births at any gestational age are recorded, as well as stillbirths of varying gestational ages according to national criteria (15). For each delivery, a notification is sent from the delivery unit to the registry administrative authorities with information on maternal and child identity, date of birth, plurality, gestational age, vital status, birthweight, obstetric management and interventions. Furthermore, information on maternal smoking status, height and weight is recorded. The mother's national identity number is reported in each delivery

and thus linked to the child. In Denmark and Norway, the father's national identity number is also reported, whereas in Finland and Sweden, information on the father can be obtained from population registries. In each country, medical conditions are coded according to the International Classification of Diseases (ICD) with national adaptations. In Finland, Norway and Sweden, perinatal health and maternal health before or during pregnancy is reported directly to the MBRs. The Danish MBR was included as a separate module in the Danish National Patient Registry (NPR) in 1997, and information on perinatal and maternal health during pregnancy and delivery can be extracted from the general NPR records and linked to the birth module based on national identity numbers and dates of birth. This system often results in a higher proportion of pregnancies or deliveries being registered with a specific diagnostic code as compared to direct reports to the MBRs from the delivery unit (15). Maternal diagnoses during pregnancy and delivery have been reported to the Finnish MBR since 2004, and therefore data from the Finnish NPR were used as a supplement throughout the study period.

National Patient Registries

In the national patient registries, hospital admissions have been registered at an individual level since 1977 in Denmark, 1967 in Finland, 2008 in Norway and 1987 in Sweden. Outpatient visits in public hospitals and specialised health care in private clinics have been included since since 1998 in Finland, 2008 in Norway and 2001 in Sweden. In Denmark, outpatient visits in public hospitals have been registered since 1995 and specialised health care in private clinics has been reported since 2003. Following each contact, at least one ICD-diagnosis is registered. The registries have a high degree of completeness and validity studies indicate positive predictive values in the range 81-94% in Denmark (three-digit code level for primary and secondary diagnosis combined) (16), 75-99% for common diagnoses in Finland (17), 80-95% in Norway (18-21), and 85-95% in Sweden (three-digit code level) (22).

ART registration

In Denmark, the national ART registry was established in 1994 with mandatory registration of all ART cycles for both public and private ART clinics with almost 100% completeness (23). Since 2007, data on intrauterine insemination and ovulation induction are also included. All data can be linked to data on deliveries in the MBR using the mother's national identity number. In Finland, no national ART registry exists, but ART conception has been registered at an individual level at delivery as a dichotomous variable in the MBR from 1990 to 2003. From 2004 to 2016, dichotomous information on intrauterine inseminations and ovulation inductions were collected separately, and since 2017, distinction between different types of ART treatment can be made. Norwegian public and private ART clinics notify the MBR of detailed information on all ART cycles that result in pregnancies verified by ultrasound in gestational week 6-7. Furthermore, ART conception is included in the MBR notification form based on information provided by the mother during delivery, allowing for registration of children conceived after ART treatment abroad. In Sweden, deliveries after ART were reported to the National Board of Health and Welfare between 1982 and 2006. Since 2007, all ART cycles in Sweden have been reported to the National Quality Registry of Assisted Reproduction (24) and can be linked to the MBR using maternal identity. Details on ART registration in each country are provided in Table 3.

[Table 3 here]

Data harmonisation

A major part of collaborative registry-based research consists of data harmonisation to enable pooling of data. Detailed knowledge about the clinical practice and registration procedures in each country throughout the study period is needed to ensure a reliable set of data for analyses. Specific

differences between the Nordic countries comprise registration of stillbirths at early gestational ages, malformations, pregnancy complications and causes of infertility. Subtle differences between the national adaptations of the ICD system requires particular attention. Often, the common denominator is a categorisation less detailed than the original national registration for each country.

Ethical and legal approvals

Approvals for data retrieval and linkage were obtained in each country. In Denmark and Finland, ethical approval is not required for scientific projects solely based on registry data. In Norway, ethical approval was given by the Regional Committee for Medical and Health Research Ethics (REK-Nord, 2010/1909). In Sweden approval was obtained from the Ethical committee in Gothenburg, Dnr 214-12, T422-12, T516-15, T233-16, T300-17, T1144-17, and T121-18. In addition, data retrieval was approved by the registry-keeping authorities in each country (Denmark: Region H 22-06-2016 (DT-journal number 2012-58-0004, local journal number AHH-2016-033, I-suite number: 04790); Finland: THL National Institute for Health and Welfare (Dnro THL/1070/5.05.00/2015) and Statistics Finland (Dnro TK-53-1132-15); Norway: Norwegian Institute of Public Health, Statistics Norway, Norwegian Directorate of Health and the Cancer Registry of Norway; Sweden: National Board of Health and Welfare, Statistics Sweden and several National Quality Registries for additional data on morbidity. Due to Norwegian legislation, data managed by Statistics Norway may not be exported outside Norway (25). In all four countries, the approvals apply to specific research questions on health and safety in relation to ART treatment.

After data extraction from the relevant national health registries, the registry keeping authorities replace the national identity numbers with a study-specific participant numbers before making data available to the researchers. This linkage key is stored by the registry keeping authorities in each country and is unavailable to the researchers, but can be used for updates or corrections of data

within a limited time period. A comprehensive discussion of legal and ethical aspects of registry-based epidemiology in the Nordic countries is provided elsewhere (26).

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Data Resource Use

In a matched cohort design with data on deliveries throughout 2007 (6), we used the first CoNARTaS data linkage to study time trends in perinatal outcomes (27) and risk of malformations after ART deliveries (28), risk of stillbirth and infant death (29), risk of cancer in children conceived after ART (30), perinatal outcome in children conceived after embryo cryopreservation (31), risk of hypertensive disorders in ART pregnancies (32), as well as the differential influence of maternal age on perinatal outcomes (33).

Research topics for the second data linkage, described here, include long-term follow-up with focus on risk of diabetes mellitus and cardiovascular diseases, mental health and cancer for children and mothers, as well as analyses of potential adverse outcomes of techniques implemented in assisted reproduction over the last decades, such as embryo cryopreservation with vitrification and culture of

embryos to blastocyst stage. Inclusion of the entire background population with complete birth cohorts of naturally conceived children in combination with data on maternal identity, enables sibling comparisons and intergenerational studies.

With data on up to three decades of assisted reproduction, the CoNARTaS cohort is well suited for studies of time trends in ART treatment. Over time, children born after ART comprise an increasing proportion of the national birth cohorts in all the Nordic countries (Figure 1a), reaching 3-5% in the latest years. Treatment policies are comparable between the four countries, with a relatively conservative use of ICSI which is primarily used for couples with a male component cause of infertility and not exceeding 40-50% of all children born after ART (Figure 1b). This is in contrast to many other European countries where ICSI may comprise up to 90% of all ART cycles (1). A prominent feature of assisted reproduction in the Nordic countries is the elective single embryo transfer (eSET) policy (34, 35), resulting in a commendable reduction of multiple pregnancies (Figure 1c). A major factor enabling high birth rates following ART, in particular after implementation of the eSET policy, is the increasing rate of embryo survival and implantation after cryopreservation and thawing of surplus embryos from a cycle of controlled ovarian stimulation in ART. The percentages of ART children born after cryopreservation has increased strongly since year 2000 (Figure 1d), recently approaching 30-40%.

Strengths and Weaknesses

A major strength of the CoNARTaS data is the large sample size, with inclusion of all individuals born during the entire registration period of ART treatment in the Nordic countries, as well as their mothers. This enables follow-up of ART children up to age 30 years, which is longer than most previous studies on individuals conceived after ART. The prospective data collection and population-based design reduce the risk of recall bias and selection. The linkages include a wide range of data

on pre-pregnancy health such as causes of infertility, maternal smoking and body mass index, ART treatment details, and long-term follow-up for chronic diseases of major public health interest.

The Nordic countries are sufficiently comparable in terms of demography, culture, health care systems and social security to justify pooling of health data for most outcomes. ART treatment is highly subsidized in the public health care systems in the Nordic countries and the decision of ART treatment is therefore based on medical indications rather than the couple's financial situation.

Prenatal care is free of charge and provided by the public healthcare systems. During most of the study period, women with ART pregnancies and deliveries have followed the same prenatal care schemes as the general population. However, it is possible that couples who conceive after ART have a lower threshold for seeking medical attention, which could result in earlier or increased detection of medical conditions.

Weaknesses stem mainly from limitations in data availability and differences in registration practice between the countries. Information on fathers in the current linkage is limited to paternal identity and age from Denmark, Norway and Sweden, and paternal educational level and selected co-morbidities from Denmark and Sweden. Information on fertility treatments other than ART, such as ovulation induction and intrauterine insemination, is available only in Denmark since 2007 and in Finland since 2004. Hence, these children will be registered as natural conceptions, but the resulting misclassification will be very limited, due to low numbers compared with the true natural conceptions. Some aspects of the legal regulations of ART are more conservative in the Nordic countries than other parts of the world, and reproductive tourism is an increasing phenomenon. ART conceptions abroad that lead to deliveries in the mother's country of residence are not registered as ART, except in Finland and Norway where this may be registered if the mother informs the midwife at delivery. Details on ART treatment ranges from no details in Finland to reporting of all cycles in Denmark from 1994 and Sweden from 2007. Baseline information on maternal health and the couple's causes of infertility, as well as pregnancy complications, were obtained from different

sources in the different countries (MBRs, ART registries and databases, and patient registries), which may have led to differences in registration accuracy for these factors. Changes in registration practice during the study period has occurred in all countries in one or more of the included registries, but always in the direction of more detailed registration.

Data Resource Access

After initial examination in each country, data were uploaded at a secure data platform maintained by Statistics Denmark, where data management, pooling of data and statistical analyses are carried out by the researchers (6). Data are accessed through personal log-in using a safe remote connection, and requires approval by the project group, the ethical committees and other relevant agencies in each country, as well as Statistics Denmark and the Danish collaborating institutions in the Capital Region. Individual level data cannot be exported from the server, neither by the researchers, nor by Statistics Denmark. However, pooling CoNARTaS data with data from other cohorts is feasible within Statistics Denmark, although this requires amendments to the current ethical and legal permissions obtained for the CoNARTaS project. A practical limitation is that data on maternal education from Norway cannot be exported. Analyses including this information must currently be conducted on a national level with subsequent meta-analysis for all four countries if necessary.

Each of the four participating countries is represented by two members in CoNARTaS. Researchers interested in topics related to ART, where the CoNARTaS cohort can be valuable, are welcome to contact the CoNARTaS members. Please see www.conartas.com for contact information.

CoNARTaS cohort in a nutshell

- The Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS) cohort is a Nordic cohort set up from national health registry data to investigate health and safety for children born after assisted reproductive technology (ART) and for their mothers.
- The basis for the CoNARTaS cohort is that in the Nordic countries, individual level data on all residents are routinely collected by the national health registries and may be linked using the unique national identity number of each resident.
- The CoNARTaS cohort consists of 7 853 958 children, including 172 161 children conceived by ART, as well as 4 130 772 mothers, including 127 317 mothers after ART, identified from the Medical Birth Registries in Denmark (1994 to 2014), Finland (1990 to 2014), Norway (1984 to 2015) and Sweden (1985 to 2015)
- Data on type of ART treatment, pregnancy and perinatal health, selected diagnosis from specialised health care including detailed information on cancer, and causes of death are available for all individuals in the cohort.
- Interested research collaborators can contact the CoNARTaS researchers at www.conartas.com

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TABLES

Table 1. Number of children and mothers in the registry-based Committee of Nordic Assisted Reproductive Technology (ART) and Safety (CoNARTaS) cohort¹

	Denmark 1994-2014		Finland 1990-2014		Norway 1984-2015		Sweden 1985-2015		CoNARTaS total	
Children born after ART, total (n)	45 761		29 800		34 124		62 476		172 161	
Singletons, n (%)	3 944	(67.6)	22 097	(74.2)	24 128	(70.7)	50 207	(80.4)	127 376	(74.0)
Twins, n (%)	14 395	(31.5)	7242	(24.3)	9426	(27.6)	11 658	(18.7)	42 721	(24.8)
Higher order multiples, n (%)	422	(0.9)	461	(1.5)	570	(1.7)	611	(1.0)	2064	(1.2)
Mean follow-up ¹ from birth ² , years (SD)	8.6	(5.5)	10.2 ⁴	(6.4)	9.4	(6.8)	9.3	(6.7)	9.3	(6.4)
Children born after natural conception (NC), total (n)	1 285 675		1 466 387		1 756 989		3 172 746		7 681 797	
Singletons, n (%)	1 246 012	(96.9)	1 430 110	(97.5)	1 710 090	(97.3)	3 096 625	(97.6)	7 482 837	(97.4)
Twins, n (%)	38 597	(3.0)	35 559	(2.4)	45 785	(2.6)	74 428	(2.3)	194 369	(2.5)
Higher order multiples, n (%)	1066	(0.08)	718	(0.05)	1114	(0.06)	1693	(0.05)	4591	(0.06)
Mean follow-up ² from birth ³ , years (SD)	10.5	(6.1)	12.7 ⁴	(7.4)	15.2	(9.2)	15.1	(9.2)	13.9	(8.6)
Mothers, total (n)	752 542		765 752		934 784		1 686 784		4 130 772	
ART children only, n (%)	22 110	(2.9)	13 089	(1.7)	15 142	(1.6)	30 616	(1.8)	80 957	(2.0)
ART and naturally conceived children, n (%)	10 248	(1.4)	9427	(1.2)	9274	(1.0)	17 411	(1.0)	46 360	(1.1)
Naturally conceived children only, n (%)	711 094	(95.7)	743 236	(96.1)	910 368	(97.4)	1 638 757	(97.2)	4 003 455	(96.9)
Mean follow-up ² from 1 st ART delivery, years (SD)	8.7	(5.6)	10.1 ⁴	(6.4)	9.4	(6.8)	9.2	(6.7)	9.3	(6.4)
Mean follow-up ² from 1 st delivery after NC, years (SD)	11.8	(6.4)	14.3 ⁴	(7.7)	16.7	(9.9)	16.4	(9.7)	15.2	(9.1)

¹ All deliveries between 22+0 and 44+6 weeks gestation and known maternal identity recorded by the Medical Birth Registry in each country during the study period. ² Follow-up to date of death, date of emigration, December 31st 2014 (Denmark, Finland) or December 31st 2015 (Norway, Sweden). ³ Stillbirths excluded. ⁴ Data on emigration not available for Finland.

Table 2. Data sources other than registrations of assisted reproductive technology (ART) used in the Committee of Nordic ART and Safety (CoNARTaS) cohort, with period of availability in current data linkage

	Denmark	Finland	Norway	Sweden
National health registries				
Medical Birth Registry	1994-2014	1990-2014	1984-2015	1985-2015
Patient Registry	1977-2014	1987-2014	2008-2015 ¹	1985-2015 ¹
Cancer Registry	1943-2014	1953-2014	1953-2015	1958-2015
Registry on Birth Defects	NI	1990-2014	Included in MBR	1964-2015
Cause of Death Registry	1994-2014	1990-2014	1984-2015	1985-2015
Pathology Registry	1997-2014	NR	NR	NR
Psychiatry Registry	1969-2014	Included in Patient Registry	Included in Patient Registry	Included in Patient Registry
Prescribed Drug Registry	1997-2014	NI	NI	2005-2015
National quality registries				
Childhood Diabetes Registry	1996-2014	NR	NI	2000-2015
Diabetes Registry	NI	NR	NI	1996-2015
Childhood Obesity Registry	NI	NR	NR	2005-2015
Registry for Neonatal Care	NR	NI	NI	2001-2015
Childhood Cancer Registry	NI	NR	NI	1982-2015
Eating Disorder Registry	NR	NR	NI	1999-2015
Other data sources				
Population Registry	NI	1990-2014	NI	1985-2015
National Education Database	1994-2014	1990-2015	1984-2015	1990-2015 ²

NR – no registry, NI – not included. ¹Selected ICD-codes. ²Highest level of education every five years

Table 3. Information on assisted reproductive technology (ART) included in the Committee of Nordic ART and Safety (CoNARTaS) cohort, with period of availability

	Denmark	Finland	Norway	Sweden
Establishment of ART registration	1994	1990	1984	1982
Type of ART registration with possibilities for individual level linkage	Cycle based ART Registry linked with Medical Birth Registry	Medical Birth Registry, no cycle-based information at national level	Pregnancy based registration of ART linked with Medical Birth Registry	Deliveries from ART registries linked with Medical Birth Registry
Data available in the CoNARTaS cohort				
ART conception	1994-2014	1990-2014	1984-2015	1985-2015
Cause of infertility	1994-2014	-	2000-2015	1994-2015
Duration of infertility	2010-2014	-	2000-2015	1985-2015
Type of ART medication used	2007-2014	-	-	2005-2015
In-vitro fertilization	1994-2014	-	1984-2015	1985-2015
Intracytoplasmic sperm injection	1994-2014	-	1996-2015	1992-2015
Non-ejaculated sperm	2006-2014	-	2005-2015	1996-2015
Cryopreservation of embryo	1994-2014	-	1988-2015	1990-2015
Cryopreservation method	2009-2014	-	-	2006-2015
Number of oocytes retrieved	1994-2014	-	-	2002-2015
Number of embryos transferred	1994-2014	-	1984-2015	2002-2015
Number of embryos cryopreserved	1994-2014	-	-	2002-2015
Culture duration	1994-2014	-	2011-2015	1985-2015
Donor semen	1994-2014	-	-	2007-2015
Donor egg	1994-2014	-	NL	2005-2015
Preimplantation genetic diagnostics	2006-2014	-	-	2010-2015
Number of gestational sacs (week 7-8)	2010-2014	-	-	2002-2015
Number of live fetuses (week 7-8)	2010-2014	-	1984-2015	NI

NL – not legal, NI – not included

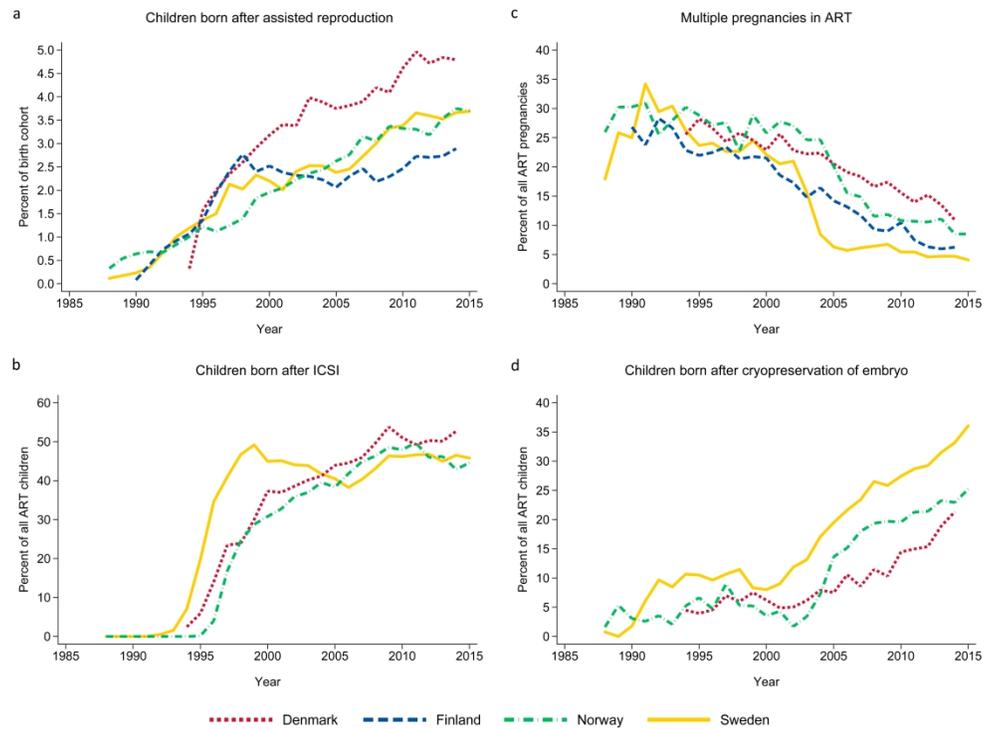


Figure 1. Time trends in assisted reproduction technology (ART) in the Nordic countries Denmark, Finland, Norway and Sweden: a) Percentage of children born after ART in each birth cohort, b) Percentage of ART children conceived after intracytoplasmic sperm injection (ICSI) as opposed to conventional in-vitro fertilization, c) Multiple pregnancies (twins, triplets and quadruplet) after ART as a percentage of all ART pregnancies and d) Percentage of ART children born after embryo cryopreservation and thawing/warming before transfer.

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Pocket Profile

Title:

Data Resource Profile: The Committee of Nordic Assisted Reproduction and Safety (CoNARTaS) cohort

Authors

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Keywords

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Data Resource Basics

The use of assisted reproductive technology (ART) is increasing and worldwide more than seven million children have been born after ART conception. The Committee of Nordic ART and Safety (CoNARTaS) cohort is a Nordic cohort set up from national health registry data to investigate short and long term health and safety for children born after ART and for their mothers. The cohort consists of 7 853 958 children, including 172 161 children conceived by ART, as well as 4 130 772

mothers, including 127 317 mothers with at least one delivery after ART conception, identified from the Medical Birth Registries (MBRs) in Denmark (1994 to 2014), Finland (1990 to 2014), Norway (1984 to 2015) and Sweden (1985 to 2015). Mean follow-up for children born after ART conception is 9.3 years (standard deviation 6.3 years) for the total cohort.

Data Collected

All live births and stillbirths reported to the nationwide MBR in each country during the study period were included. Using the unique national identity numbers assigned to all residents in the Nordic countries, information from the MBRs was linked to information from ART registries or databases to identify deliveries after ART. Background information and long-term follow-up was obtained by linkage with registries on specialised health care, education, cancer, prescriptions and causes of death.

Data Resource Use

Data from the CoNARTaS cohort have so far been used to study health in pregnancy and the perinatal period for mothers and children following ART conception, as well as cancer in children, compared to a matched sample of the background population. The current linkage enables long-term follow-up for diabetes mellitus, cardiovascular disease, cancer, mental health and mortality in both children and mothers after ART. Inclusion of individual level data on the entire background population permits comparison with natural conception, including the naturally conceived siblings of ART children. The study period spans three decades of ART treatment and is therefore well suited for studies of time trends. During this period, children born after ART comprised an increasing proportion of birth cohorts and a marked reduction of multiple pregnancies after ART treatment took place (Figure 1).

Reasons to be cautious

Treatment policies for assisted reproduction in the Nordic countries differ from those in many other countries. Some data are not available from all four countries. Information on fathers is limited.

Collaboration and data access

Data are stored at a research server hosted by Statistics Denmark. Access requires approval by the project group, the ethical committees and other relevant agencies in each country, as well as Statistics Denmark and the Danish collaborating institutions in the Capital Region.

Funding and competing interests

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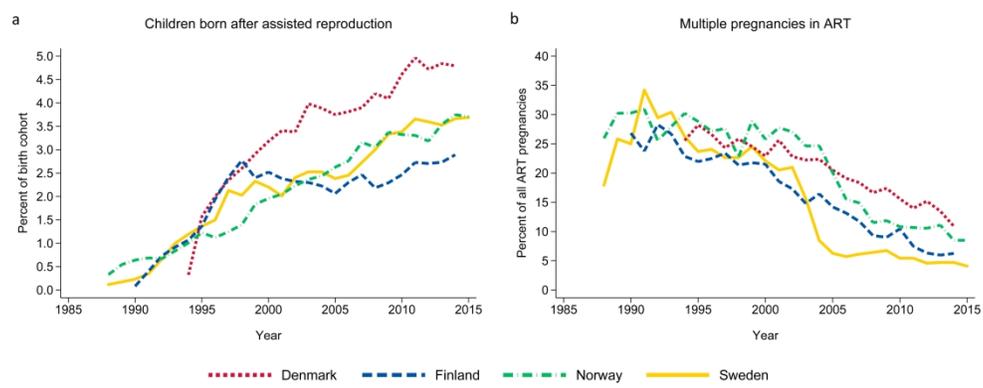


Figure 1. Time trends in assisted reproduction technology (ART) in the Nordic countries Denmark, Finland, Norway and Sweden: a) Percentage of children born after ART in each birth cohort and b) Multiple pregnancies (twins, triplets and quadruplet) after ART as a percentage of all ART pregnancies.

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