

ORIGINAL RESEARCH ARTICLE

Reproductive changes among women in their 40s: A cross-sectional study

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Abstract

Introduction: The aim was to describe and compare changes in the reproductive pattern of women in their 40s observed over a decade in Scandinavia.

Material and Methods: Cross-sectional study using the total population of women aged 40–49 years between 2008–2018 in Denmark, Norway and Sweden (on average $n = 1.5$ million). Aggregated data concerning birth and induced abortion rate were collected and analyzed from national health registers. National data on redeemed prescriptions of hormonal contraceptives in the three countries were collected from prescription registers. Births after spontaneous and assisted conceptions were identified by using cross-linked data on deliveries from the Medical Birth Registers and National Registers of Assisted Reproduction in the three countries.

Results: Use of hormonal contraception increased among women aged 40–44 years in Denmark from 24% to 31%, in Sweden from 27% to 30%, and in Norway from 22% to 24%. The levonorgestrel-releasing intrauterine device was the most frequently used method in all countries. Birth rates among women 40–44 years increased continuously from 9.5 to 12/1000 women in Denmark and from 11.7 to 14.3/1000 in Sweden, but remained stable in Norway at ~11/1000 women. There was a doubling of assisted conceptions in Denmark from 0.71 to 1.71/1000 women, Sweden from 0.43 to 0.81/1000 and Norway from 0.25 to 0.53/1000 women 40–49 years of age. Sweden had the highest induced abortion rate (7.7 to 8.1/1000 women) in women aged 40–49 years during the study period.

Conclusions: From 2008 to 2018, birth rates continuously increased among women aged 40–49 years in Denmark and Sweden and births resulting from assisted reproductive technology doubled in all three countries.

KEYWORDS

abortion, assisted reproductive technologies, birth, fertility, hormonal contraception

Abbreviations: ART, assisted reproductive technologies; LNG-IUD, levonorgestrel-releasing intrauterine device.

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1 | INTRODUCTION

Women are changing their reproductive behavior in Europe as well as in the USA. The age at first birth is increasing as many women postpone their parenthood due to education at university level and career opportunities, higher income level, and the fact that more women live alone and choose to become single parents.¹ In the USA the birth rate for women aged 40–44 years rose 4% from 7.4 to 11.4/1000 women during 2015–2016. In England/Wales, the birth rate for women above 40 years reached its highest rate in 2016 (15.9/1000 women).^{2,3} Access to birth control pills and other forms of contraception such as long-acting reversible contraceptives have profoundly changed society. In particular, long-acting reversible contraceptives use has decreased the risk of unplanned pregnancies.^{4,5} There are also women in their late 30s and 40s underestimating their fertility, resulting in unplanned pregnancies among those who are not using any contraception or who are using less effective contraceptive methods.¹

The increasing proportion of women and couples planning to have children at an advanced age are probably not aware of the age-related decrease in fecundity, which may increase the need for assisted reproductive technology (ART). More than 9 million children have been conceived following ART globally, and in Europe more than 195 000 children were conceived by ART in 2016.⁶ The 20th European Society of Human Reproduction and Embryology (ESHRE) report on ART shows a continuing expansion of both treatment numbers and variability in treatment modalities, resulting in a rising contribution of ART to birth rates in most participating countries.⁶

Higher female age is linked not only to involuntary childlessness but also to an increased risk for adverse reproductive outcomes such as preterm birth and stillbirth. The increasing risk of preterm birth and stillbirth starts at around 35 years, with a more pronounced effect >40 years.^{7,8} There is an increased risk of spontaneous abortions with age that is well documented after natural as well as assisted conception.⁷ Women of advanced maternal age are also at increased risk of pregnancy complications such as hypertensive disorders of pregnancy and gestational diabetes.⁹

Perinatal outcome of ART has been described in several large registry studies, systematic reviews and meta-analyses,¹⁰ many of them from the Nordic countries.^{11,12}

Most of these studies, however, focused on younger women and there is a lack of data on comparisons of ART, birth rates, induced abortion rates and hormonal contraceptive use for women in their 40s. The aim of this study was to describe and compare changes in hormonal contraceptive use, birth, induced abortion and use of ART for women in their 40s observed over a decade in Denmark, Norway and Sweden.

2 | MATERIAL AND METHODS

Data on hormonal contraception, births after spontaneous conception and ART, and induced abortion rates among women 40–49 years of age were collected from the three Nordic countries, Denmark, Norway and Sweden, from 2008 to 2018.

Key message

This study confirms the trend of postponing childbirth observed for most of Europe and demonstrates the important role of assisted reproductive technology on birth rates in this age group. The study provides valuable information to improve women's knowledge on their fertility.

2.1 | Data on birth and induced abortion

Aggregated data concerning birth and induced abortion rates were collected from the National Health Registries and the Tigrab database (nationwide quality register covering early pregnancies and abortions)¹³ in Denmark, the National Institute of Public Health in Norway, and the National Board of Health and Welfare in Sweden. We defined birth rate after spontaneous and ART conception. Both rates were defined according to international praxis per 1000 women and year.¹⁴ Age was further categorized into two groups, 40–44 and 45–49 years of age. In Sweden the collection of abortion data was temporarily stopped in 2013 but was resumed from January 2014.

2.2 | Data on ART

Data on ART were collected from Norway using cross-linkage data of deliveries from the Medical Birth Registry of Norway and the ART-pregnancy notification system that is a part of the Medical Birth Registry of Norway. Similarly, ART data from Denmark were derived from a merging of Danish Medical Birth Registry and National Register of Assisted Reproduction, Tigrab report¹³ and in Sweden by merging the Swedish Medical Birth Registry and the National Register of Assisted Reproduction (Q-IVF). This was possible using the unique personal identification number allocated to every citizen. ART rates were defined according to international praxis as births after ART, fresh and frozen cycles, per 1000 women and year.

Information about policies and restrictions concerning ART was collected from each of the three countries by members of the research group (Table S1). There was no information regarding children born after ART performed abroad unless the mothers provided this information to health professionals during pregnancy.

2.3 | Collected data on different hormonal contraception

National data on redeemed prescriptions of hormonal contraceptives 2008–2018 were collected from the Danish National Registry of

Medicinal Product Statistics, the Norwegian Prescription Database, NIPH, Oslo and the Swedish Prescribed Drug Registry.

The collected data provides information on sold packages or items of different types of contraceptives, expressed as defined daily doses/100 women and day (%).

To be able to compare defined daily doses/100 women and day for the levonorgestrel-releasing intrauterine device (LNG-IUD) with the other contraceptive methods, the mean duration of use for two of the LNG-IUD (approved for 5 and 3 years, respectively, during the study period) were set to 4 years¹⁵ and 2 years, respectively.¹⁶ In a similar way we calculated the equivalent mean duration of use for an etonogestrel-releasing implant (approved for 3 years) to be 2 years according to the average duration of use reported in previous studies.¹⁵ The mean duration for use of levonorgestrel-releasing implants was set to 4 years.

There were no data available with a personal identification number for hormonal emergency contraceptives and therefore these methods are not included. Since the use of copper intrauterine devices, condoms, diaphragms, and fertility awareness methods are not registered in any national registries, the use of these methods remains unknown.

2.4 | Statistical analyses

These are purely descriptive assessments; no confidence limits were calculated for the country-specific rates. That was due to both the large sample sizes making even small differences highly significant, and the use of complete national data from each country, making such calculations redundant.

2.5 | Ethical approval

The legal aspects of utilization of registry data for study purposes were performed in accordance with national legislation. Specific permissions were received from the following relevant bodies: Norway—REK North (ID no.: 2019/598/REK nord), DPIA assessment from Norwegian Center for Research Data (project no 808142 v4), and assessment from the Board of NorPD (project no. NPD 2778). First date approved: 25 April 2019. In Denmark, permission was granted by Datatilsynet (journal no. 2010-41-4778). In Sweden, ethical permission was granted by the local ethical committee (EPN Gothenburg, dnr 2018-882-18). First date approved 3 December 2018.

3 | RESULTS

The total number of women in Denmark, Norway and Sweden, ie all women 40–49 years of age, varied between 1.4 and 1.5 million from 2008 to 2018.

3.1 | Hormonal contraceptive use, birth and induced abortion rates

Figure 1A (40–44 years) and Figure 1B (45–49 years) display hormonal contraceptive use, birth and induced abortion rates for Denmark, Norway and Sweden during the period 2008–2018.

3.1.1 | Women 40–44 years old

Use of hormonal contraception gradually increased from 24% to 31% in Denmark, from 22% to 24% in Norway, and from 27% to 30% in Sweden during the study period (2008–2018) (Figure 1A).

LNG-IUD use dominated in all three countries, and the proportion of LNG-IUD use increased over the period in Denmark from 9% to 20% and in Sweden from 14% to 19%. The use of progestogen-only pills remained higher in Sweden than in the other two countries for the entire study period.

Birth rates increased continuously in Denmark from 9.5/1000 to 12.3/1000 women, and in Sweden from 11.7/1000 to 14.3/1000 women but remained stable in Norway at ~11/1000 women. Induced abortion rates were generally low in Denmark and Norway during this period, whereas Sweden had a 30%–50% higher induced abortion rate between 2008 and 2013 (Figure 1A).

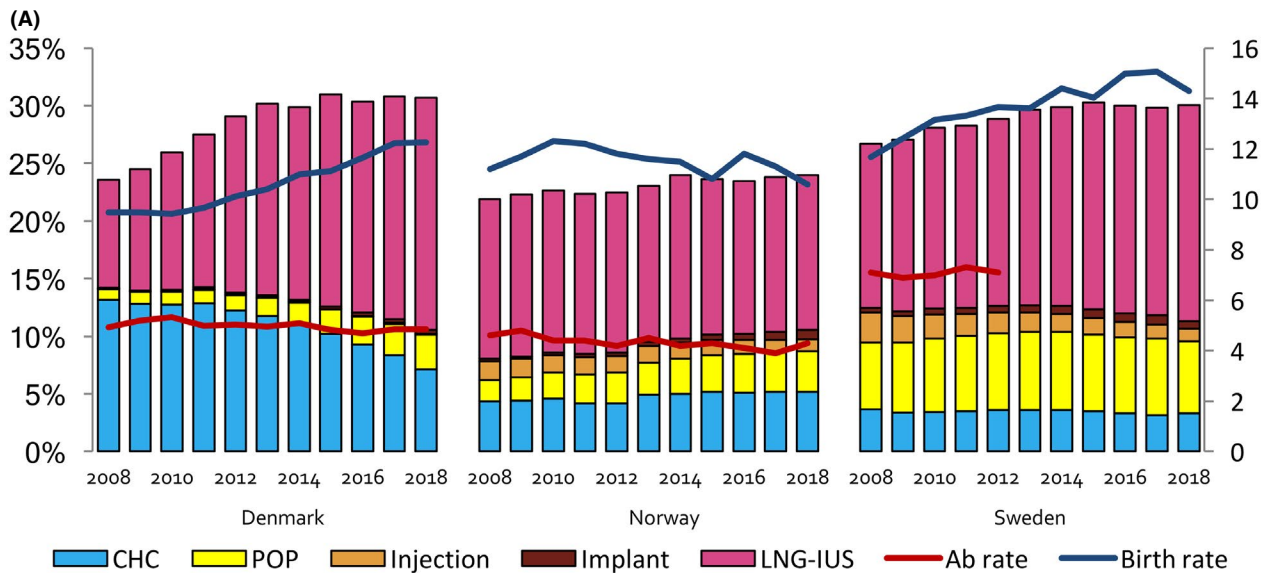
3.1.2 | Women 45–49 years old

The use of hormonal contraception increased throughout the study period in all three countries: Denmark 15%–22%, Norway 11%–17% and Sweden 17%–24%. LNG-IUD was the most commonly used method with a clear increase for all three countries, especially in Denmark and Sweden (Figure 1B). Birth rates showed a small increase, still at a low level in all three countries but induced abortion rates remained at the same level in Denmark and Norway (0.43 and 0.30/1000) 2008–2018, and at a higher level (0.7/1000) in Sweden 2008–2012. (Figure 1B).

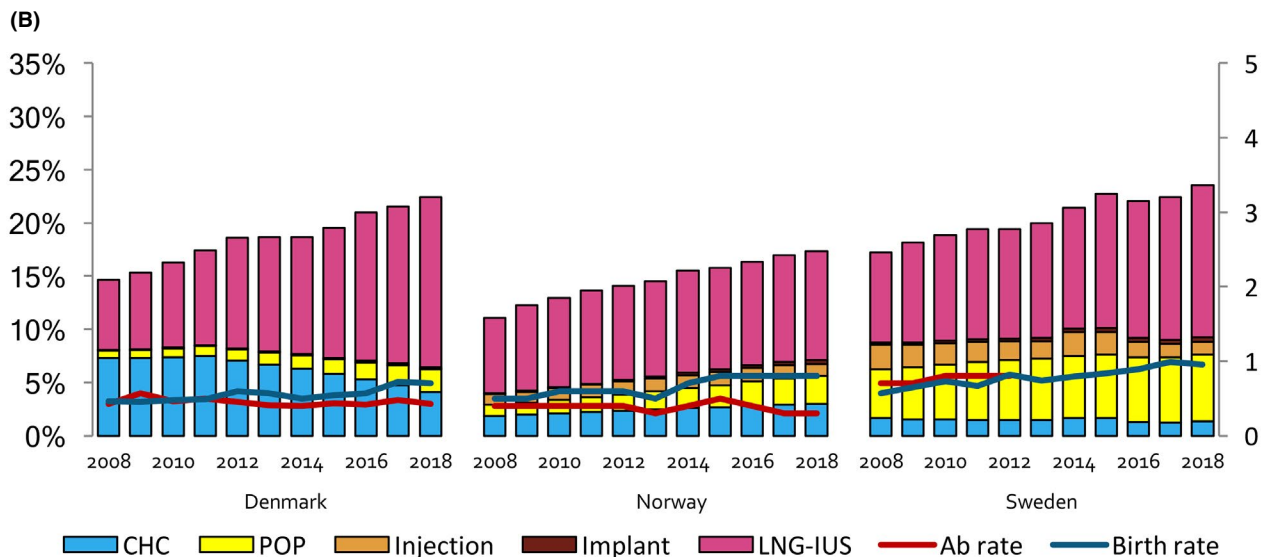
It was not possible to retrieve stratified data on age-specific induced abortion rates for Sweden for the period 2014–2018. Therefore we provided data for the entire age group 40–49 years to enable a comparison between the countries. A small decrease in induced abortion rates was seen during the study period in Denmark from 2.9 to 2.6/1000 women and in Norway from 2.6 to 2.2/1000 women. Sweden had higher rates, increasing from 7.7/1000 to 8.1/1000 women.

3.2 | Assisted conceptions

In all countries there was a gradual increase in births after ART in women aged 40–49 years from 2008 to 2018. Denmark experienced the greatest increase, from 0.71 to 1.71/1000 women, followed by



Y1 (left): Use of hormonal contraception (%). Y2 (right): Birth and induced abortion rates (number of women/1000 women and year). Please note the different scales. Age-stratified abortion rates were not available for 2013-18 for Sweden. CHC = combined hormonal contraception (subgroups oral, vaginal and transdermal); POP = middle or low dose progestogen-only pill; Injection = depot medroxyprogesterone acetate (DMPA); LNG-IUD = levonorgestrel-releasing intrauterine device.



Y1 (left): Use of hormonal contraception (%). Y2 (right): Birth and induced abortion rates (number of women/1000 women and year). Please note the different scales. Age-stratified abortion rates were not available for 2013-18 for Sweden. CHC = combined hormonal contraception (subgroups oral, vaginal and transdermal); POP = middle or low dose progestogen-only pill; Injection = depot medroxyprogesterone acetate (DMPA); LNG-IUD = levonorgestrel-releasing intrauterine device.

FIGURE 1 (A) Hormonal contraceptive use, birth and induced abortion rates among women 40–44 years of age in Denmark, Norway and Sweden 2008–2018. (B) Hormonal contraceptive use, birth and induced abortion rates among women 45–49 years of age in Denmark, Norway and Sweden 2008–2018

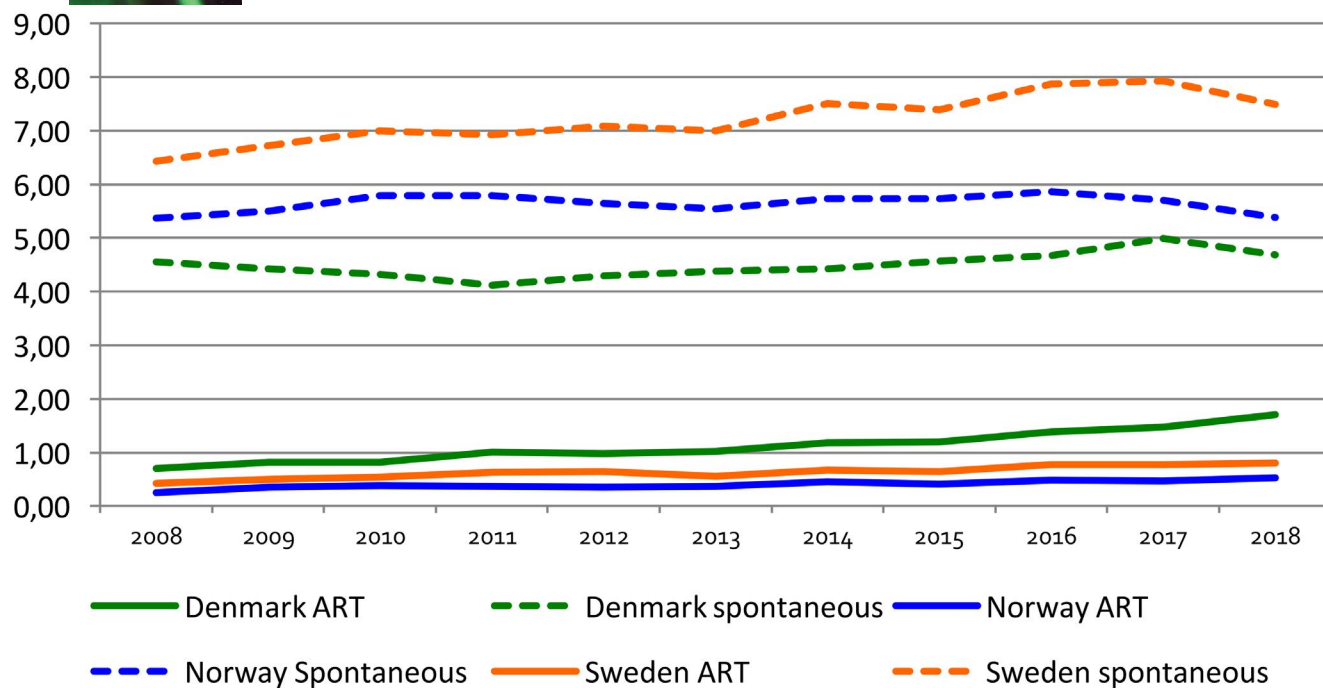


FIGURE 2 Births after ART and spontaneous pregnancy/1000 women 40–49 years of age in Denmark, Norway and Sweden 2008–2018

Sweden (0.43 to 0.81/1000 women) and Norway (0.25 to 0.53/1000 women). Births after spontaneous pregnancies were most frequent in Sweden (Figure 2).

The distribution of births after ART conceptions increased during these 10 years, although the highest numbers of births followed spontaneous pregnancies (Figure S1).

When comparing the distribution of births after ART in nulliparous and parous women, the figures were quite similar, although Denmark and Sweden had higher numbers of nulliparous women (40–49 years) (Figure 3A). A majority of parous women gave birth after a spontaneous pregnancy (Figure 3B).

Distribution of births after assisted conceptions and spontaneous pregnancies reported by age groups 40–44 and 45–49 years for Denmark, Norway and Sweden are presented as Figure S2A,B.

4 | DISCUSSION

During the decade 2008–2018, birth rates among women 40–49 years of age increased continuously in Denmark and Sweden. This is in line with the trends in the rest of Europe, where the relatively low fertility rates are due to a large extent to a growing proportion of women giving birth later in life.¹⁷ Births conceived from ART doubled from 2008 to 2018. Induced abortion rates remained largely unchanged during these 10 years in Denmark and Norway, and at a low level. However, Sweden showed a higher and increasing induced abortion rate. Hormonal contraceptive use increased more in Denmark and Sweden than in Norway. The LNG-IUD dominated hormonal contraceptive use during this period for all three countries.

The main strengths of this study were the use of national register data, which included all women 40–49 years of age in Denmark, Norway, and Sweden. These registries are considered highly reliable and almost complete. A limitation is that the registers do not include data on non-hormonal contraceptive methods including sterilization, where comparisons between the countries were not possible due to missing data. In Norway and Denmark, LNG-IUD are also inserted in the gynecological speciality practices where women buy the IUDs from the gynecologists without individual prescriptions. Furthermore, the Swedish collection of abortion data was temporarily stopped in 2013 and, when resumed in 2014, no age-specific data for women age 40 or above was available. As we have limited information on mothers who had undergone ART made abroad, ART may play a larger role in the birth rates than the estimates conveyed in this study imply.

An increase in children conceived after ART among nulliparous women was seen in Denmark and Sweden. Delaying the first pregnancy may result in an increased demand for ART treatment due to an increased rate of subfertility with advanced age. The annual report in 2018 from the European Union (EU) explained the relatively low levels of fertility in the EU with the growing proportion of live births to mothers aged ≥ 40 years. This may be linked to women choosing to establish a career before starting a family, lower levels of job security and the increasing cost of raising children, etc.¹⁷ The same report ranked six capital regions with the highest crude birth rate (14.4 births/1000 persons, 2018) in Belgium followed by France, Slovakia, Ireland, Sweden and Denmark. This is in agreement with our results, where Danish and Swedish women maintained both high spontaneous and ART birth rates. With lower birth rate, Norway also reported a steeper decline in fertility rates during the study period from 1.96 to

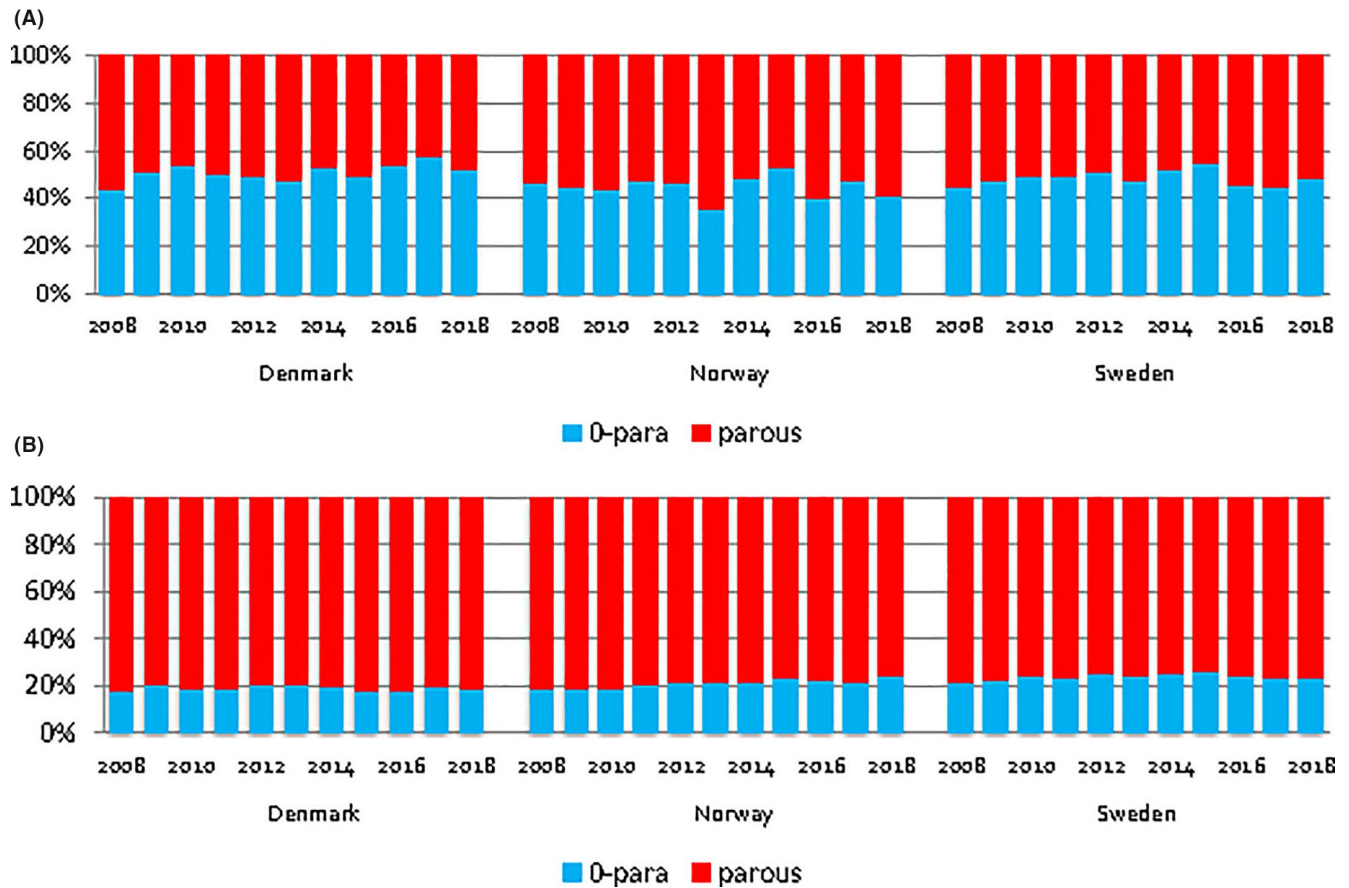


FIGURE 3 (A) Birth after ART distributed according to parity among women 40–49 years of age in Denmark, Norway and Sweden 2008–2018. (B) Spontaneous pregnancies distributed according to parity among women 40–49 years of age in Denmark, Norway and Sweden 2008–2018

1.56, compared with Denmark (1.89–1.73) and Sweden (1.91–1.76).¹⁸ A Norwegian survey¹⁹ suggested that the low fertility rate in Norway was the result of increased childlessness, higher age at first birth, and a smaller proportion of two-child mothers having a third child. The same report proposed that longer parental leave and shorter normal working time with full wage compensation for parents might contribute to increased fertility. This may reflect the differences in birth rates between the countries as well as Sweden's longer parental leave.²⁰

The use of ART is highly variable in many countries, sometimes due to differences in regulations. All three countries in this study had regulations that in many ways were similar. The regulation to start any treatment of ART in publicly financed clinics during this time period was only permitted until the day the woman turned 40 years of age in all three countries. It may be presumed that a proportion of women in our study turned to private clinics where the age limit has been extended to 45 years or more. However, an exception in publicly financed clinics is the use of frozen embryos from previous treatments in which case age limits have been extended to 45 years of age in Denmark and Sweden. The number of ART treatments allowed, differed between the countries, as Denmark and Norway provided three treatments from the year 2000 compared with Sweden, where a change from two to three treatments was implemented in 2015. Also, the prerequisites for

single women differ, since ART has been allowed for single women in Denmark and Sweden from 2007 and 2016, respectively, but is not available in Norway. The explanation of Denmark's higher utilization of ART could be the high availability of services, positive attitudes towards ART, anonymity for sperm donors and treatment in public clinics. It has been discussed that different forms of regulation, access to reimbursement of treatment costs as well as cultural determinants may have an impact on development and utilization of in vitro fertilization (IVF).²¹ It has been concluded that countries with more liberal social eligibility regulations have a higher level of IVF utilization, and that this diminished as the countries' policies became more restrictive. The same study added that they underscored a generous number of cycles and share of costs publicly financed.²¹ Another study suggests that cultural acceptance of ART is the most important factor in the varying ART treatment across European countries.²²

The induced abortion rate was low during this study period compared with other European countries, although Sweden was at a higher level (8.1/1000 women). There are some small differences in abortion legislation between the countries. Abortion on request is available until gestational week 12 in Denmark and Norway, and until week 18 in Sweden. We cannot address what impact differences in legislation have on induced abortion rates in a study where

a study population is restricted to women 40 years or older. In a previous study, we reported that induced abortion rates are higher in Sweden than in Norway and Denmark at ages 15–44 years.²³ Whether this finding is a result of legislative or cultural differences requires much more detailed data. However, one of many reasons may be differences in fecundity as well as lifestyle between Sweden and the other countries. For example, England and Wales reported an abortion rate for women ≥ 35 years of 6.7/1000 women in 2008, increasing to 9.2/1000 women in 2018.²⁴ The impact of parental age on children's health outcomes was summarized in a recent review²⁵ and the most pronounced effect of older maternal age is observed for chromosomal aberrations, particularly trisomy 21. Some birth defects also showed a higher incidence in older mothers.²⁵

A reason for unplanned pregnancies among women in their 40s may be underestimation of their fertility and the need for contraception. Although increasing age is accompanied by a general decline in fecundity, each individual needs to be aware of her risk of becoming pregnant. A survey from the USA²⁶ stated that there are limited data on contraceptive practices in the USA as well as other high-income countries for women above 40 years of age. Most studies from Europe are 15–20 years old and contain data only up to the age of 44 years.²⁶

The use of hormonal contraception increased in Denmark and Sweden during 2008–2018 in both age groups. Since the last study from the Nordic countries, combined oral contraceptives have been replaced by increasing use of progestogen-only pills and, to a larger extent, by LNG-IUD use.²³ This pattern of increasing LNG-IUD use was also seen in other European countries such as England²⁷ and may reflect increasing medical management of abnormal uterine bleeding, commonly seen among women 40 years or above.²⁸

5 | CONCLUSION

The results from this study are in line with the trend of postponing childbirth. The use of LNG-IUD gives an opportunity to plan and postpone reproduction and ART has an important role for realizing fertility goals for women at the end of their reproductive career. The complexity of continuing fertility in women in their 40s deserves further in-depth investigation.

CONFLICT OF INTEREST

IL has received compensation from Gedeon Richter and Exeltis for lectures and participation in an Advisory Board during the previous 3 years. FES has no conflicts of interest disclose over the past 3 years. KGD has served ad hoc on advisory boards or as invited speaker for Bayer AG, Merck/MSD, Actavis, HRA-Pharma, Exelgyn, Mithra, Exeltis, Cirqle, Medincell and Gedeon Richter. OH has served ad hoc on advisory boards or as invited speaker for Bayer AG, MSD, Actavis, Exelgyn and Gedeon Richter; HH has had no relationships with any company in the previous 3 years. ØL has within the last 3 years received honoraria for presentation/lectures from Campus Pharma AB. CB has received honoraria for lectures from Ferring and Merck during the previous 3 years.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. All authors, external and internal, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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