

# The long-term prognosis for live birth in couples initiating fertility treatments

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Submitted on January 11, 2017; resubmitted on March 14, 2017; accepted on April 20, 2017

**STUDY QUESTION:** What are the long-term chances of having a child for couples starting fertility treatments and how many conceive with ART, IUI and without treatment?

**SUMMARY ANSWER:** Total 5-year live birthrates were strongly influenced by female age and ranged from 80% in women under 35–26% in women  $\geq 40$  years, overall, 14% of couples conceived naturally and one-third of couples starting treatments with intrauterine insemination delivered from that treatment.

**WHAT IS KNOWN ALREADY:** Few studies report success rates in fertility treatments across a couple's complete fertility treatment history, across clinics, evaluating live births after insemination, ART and natural conceptions.

**STUDY DESIGN, SIZE, DURATION:** This register-based national cohort study from Denmark includes all women initiating fertility treatments in public and private clinics with homologous gametes in 2007–2010.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Women were identified in the Danish ART Registry and were cross-linked with the Medical Birth Registry to identify live births. Subfertile couples were followed 2 years ( $N = 19\,884$ ), 3 years ( $N = 14\,445$ ) and 5 years ( $N = 5165$ ), or until their first live birth. Cumulative live birthrates were estimated 2, 3 and 5 years from the first treatment cycle, in all women, including drop-outs. Birthrates were stratified by type of first treatment (ART/IUI), mode of conception (ART/IUI/natural conception) and female age.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Within 5 years, in women aged  $< 35$  years ( $N = 3553$ ), 35–39 years ( $N = 1156$ ) and  $\geq 40$  years ( $N = 451$ ), a total of 64%, 49% and 16% had a live birth due to treatment, respectively. Additionally, in women aged  $< 35$  years, 35–39 years and  $\geq 40$  years, 16%, 11% and 10% delivered after natural conception, yielding total 5-year birthrates of 80%, 60% and 26%. In women starting treatments with IUI ( $N = 3028$ ), 35% delivered after IUI within 5 years, 24% delivered after shift to ART treatments and 17% delivered after natural conception. Within 5 years from starting treatments with ART ( $N = 2137$ ), 53% delivered after ART, 11% delivered after natural conception and 0.6% delivered after IUI.

**LIMITATIONS, REASONS FOR CAUTION:** Birthrates are most likely higher compared to countries without national coverage of treatments and results are influenced by laws and regulations. Information on duration of infertility prior to treatment was not available. Future prospective intervention studies should focus on the role of expectant management.

**WIDER IMPLICATIONS OF THE FINDINGS:** Our results can provide couples with a comprehensible age-stratified prognosis at start of treatment.

**STUDY FUNDING/COMPETING INTEREST(S):** This study was unconditionally funded by Ferring Pharmaceuticals and the Augustinus foundation. All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: S.S.M. received an unconditional grant from Ferring Pharmaceuticals; A.A.H. has received personal fees from Ferring Pharmaceuticals not related to this work; A.N.A. reports grants and personal fees from Ferring Pharmaceuticals, personal fees from Merck Serono, grants and personal fees from MSD, outside the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

**TRIAL REGISTRATION NUMBER:** The study was approved by the Danish Data Protection Agency (J.nr. 2012-41-1330).

**Key words:** assisted reproductive technology / intrauterine insemination / cumulative live birthrates / natural conception / long-term prognosis / fertility treatments

## Introduction

When assessing success rates after fertility treatments, longitudinal studies are increasingly replacing the traditional per treatment-based estimates (Bland and Altman, 1998; Daya, 2005; Maheshwari et al., 2015). However, very few studies have evaluated a complete course of treatments, across all treatment types, with follow-up irrespective of shift between clinics and on both treatment related and treatment-independent births (Pinborg et al., 2009; Donckers et al., 2011; Aanesen and Westerbotn, 2014).

In Denmark, fertility treatments are highly accessible and additionally reimbursed by the National Health System, in childless couples where the woman is below 40 years of age. Three fresh ART treatments are reimbursed, including adjacent frozen embryo transfers. Treatments with IUI are also reimbursed, a maximum of three to six cycles is recommended. Unlike most countries in the world, insemination treatments exceed the use of ART (<http://www.fertilitetssekskab.dk>). IUI is first-line treatment to couples with unexplained infertility, mild to moderate male factor infertility, and is also used in anovulatory infertility (combined with ovulation induction), according to guidelines from the Danish fertility society (<http://www.fertilitetssekskab.dk>). Fewer side-effects and lower costs in IUI treatments may justify this treatment strategy, but little is known of long-term results, since few studies assess long-term live birthrates including shifts between IUI- and ART treatments (Sundström et al., 1997; Pinborg et al., 2009; Donckers et al., 2011; Aanesen and Westerbotn, 2014).

In Denmark, all public and private fertility clinics have mandatory reporting of treatment activity to the national ART Registry, and all births are registered in the Medical Birth registry. With the registries, the individual couple can be followed over time; between IUI- and ART cycles, between fertility clinics, to conception and birth, both natural conceptions and as a result of fertility treatment.

The purpose of this study was to obtain a comprehensive long-term prognosis, suitable for counseling couples entering treatment. Further, to assess the Danish treatment strategy, using IUI as first-line treatment to a selected group of infertile couples. The objective was to estimate cumulative live birthrates at 2, 3 and 5 years after the first treatment with ART or IUI, basing estimates on observed live births after treatment and natural conception, including only couples treated with homologous gametes and with no previous births due to fertility treatments but including couples with previous live birth after natural conception.

## Methods

### Study design and patients

This is a national cohort study based on the Danish ART registry and the Medical Birth registry. The Danish ART registry includes all ART treatment-cycles performed in public and private fertility clinics in Denmark since 1994; IUI-cycles were added in 2006. IUI is performed in

unstimulated as well as stimulated cycles with either clomiphene or gonadotropins; however a clear majority are stimulated with clomiphene (Malchau et al., 2014). Reporting to the ART registry is mandatory for both public and private clinics. A personal identification number enables identification of all treatment cycles received by the same woman, and thereby construction of a complete fertility treatment history.

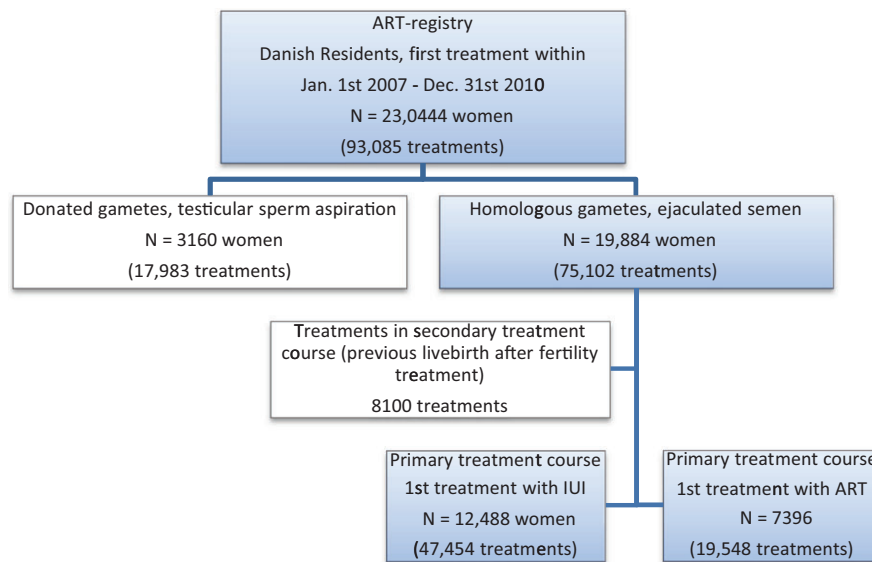
The study included 19 884 couples initiating fertility treatment in the period January 1st 2007 to December 31st 2010. Follow-up on births were available until December 31st 2012, hence a minimum of 2-year follow-up from first treatment, was available. Inclusion criteria were Danish residents, first treatment within the study period, treatment with ART (fresh or frozen-thawed cycles) or IUI with homologous (own) gametes. Couples receiving treatments with donated gametes or testicular sperm aspiration were excluded. Due to strict regulations regarding egg donation during the study period, treatment with egg donation was very limited and included several years on waiting list before treatment. All included and excluded treatment cycles are shown in Fig. 1.

Subjects identified in the Danish ART Registry were cross-linked with the Medical Birth Registry to identify all live births of the same woman. The gestational age at birth, recorded in the medical birth registry, was used to link births to treatment cycles, or to identify births due to natural conception. Women were followed for two, three and 5 years from the first treatment, until the first live birth or until they shifted to treatment with donated gametes. Only the first live birth since start of treatment is reported; later siblings are not included in the birthrates. One treatment cycle is defined as any started fresh or frozen-thawed ART-cycle (including treatments that are canceled before transfer), or insemination treatment.

### Statistical analyses

For non-normal distributed data, the Mann-Whitney *U* test was used to compare distributions between groups. Cumulative live birthrates were estimated as the proportion of women having achieved at least one live birth within follow-up, among all women with complete 2-, 3- and 5-year follow-up. Complete 2-, 3- and 5-year follow-up was available if start date of the first treatment cycle was at least 2, 3 and 5 years prior to Dec 31st 2012. Information on emigration outside Denmark was not available. All birthrates were calculated separately for subgroups according to type of first treatment (IUI/ART). Stratification was made according to mode of conception (IUI/ART/natural conception), female age at time of first treatment, cause of infertility, female body mass index (BMI), smoking status and secondary infertility (defined as previous natural conception-birth). Female BMI > 55 was considered an extreme value most likely due to errors in registration of height or weight, and were excluded in analyses regarding BMI. Missing data was not imputed. Cause of infertility was reported as female factor infertility, male factor, combined female/male factor and idiopathic infertility. Female factor infertility was further stratified in subgroups, such as anovulatory infertility, tubal factor and endometriosis. The subgroups included only women with one type of female factor infertility and did not include couples with combined male/female factor infertility.

Predictors of live birth were analyzed in multivariable logistic regression analysis with spline assessment including categorical and continuous variables; female age (linear spline with break point at 35 and 40 years), smoking (yes, no), BMI (linear spline with break point at BMI 20 and 30),



**Figure 1** Overview of included and excluded treatment-cycles. ART, assisted reproductive technology; IUI, intrauterine insemination.

secondary infertility (yes, no), cause of infertility (categorical, including idiopathic, male factor, combined male/female factor, anovulation, tubal factor, endometriosis, other female factors, two female factors and ovarian factor) and course of treatments (categorical).

Statistical software SAS version 9.4 and IBM SPSS statistics version 19 were used for data management and analyses.

### Role of funding source

The funders had no role in the study design, data collection and interpretation, or decision to submit the work for publication.

### Ethical approval

The study was approved by the Danish Data Protection Agency (J.nr. 2012-41-1330). In Denmark, register-based studies do not require approval from ethics committees.

## Results

Baseline characteristics at time of first treatment are shown in Table I. Women starting treatments with IUI were slightly younger than women starting with ART: 32.4 years versus 33.1 years. Cause of infertility was significantly different in the two groups. In couples starting with IUI, anovulatory infertility and idiopathic infertility were more prevalent. In couples starting with ART, male factor infertility, tubal factor infertility and endometriosis were more prevalent. Prevalence of obesity (BMI  $\geq 30$ ) and smoking were similar in the two groups, but secondary infertility was slightly more prevalent in women starting treatments with IUI.

Complete 2-year follow-up was available for 19 884 women: 12 488 women starting treatments with IUI and 7396 women starting treatments with ART (Table II). Complete 3-year follow-up was available for 8816 women starting treatments with IUI and 5629 women starting treatments with ART. Complete 5-year follow-up was available for

3028 women starting treatments with IUI and 2137 women starting treatments with ART.

### Treatment activity at 2-year follow-up

Among women with complete 5-year follow-up, 92% of all IUI and ART treatments occurred within 2 years from first treatment. The total number of IUI and ART treatments per woman at 2-year follow-up is shown in Fig. 2. The median number of total treatments was 3 (interquartile range, IQR 1–4). For couples starting with IUI, the median number of total IUI and ART treatments was 3 (IQR 2–5). For couples starting with ART, the median number of total treatments was 2 (IQR 1–3), significantly lower compared to women starting treatments with IUI,  $P < 0.0001$ .

All outcomes after 2, 3 and 5 years are shown in Table II. In all women (starting treatments with either IUI or ART) the cumulative live birthrates 2, 3 and 5 years after first treatment were: 57.0%, 65.0% and 71.0%.

### Course of treatments and live birthrates when starting treatments with IUI

The course of treatments is shown in Table III. The majority (49.2%) had 1–3 IUI treatments within the first 2 years. A total of 10.1% had 4–6 IUI treatments. A total of 38.1% of couples starting with insemination subsequently shifted over to ART (26.8% shifted after 1–3 IUI attempts and 11.3% after 4–6 IUI attempts). Details on distribution of IUI treatments are shown in Supplementary Table SI.

Birthrates, stratified on type of first treatment and type of conception, are shown in Table II and illustrated in Fig. 3. In couples starting treatments with IUI, the total live birthrates (after treatment and natural conception) within 2, 3 and 5 years were 59.0%, 68.6% and 75.2%. When stratifying on mode on conception, 34.2% delivered after IUI-conception within 2 years, and birthrates increased to 34.4%

**Table I** Background characteristics at time of first treatment cycle with IUI or ART with homologous gametes in Denmark 1997–2010.

	First treatment with IUI		First treatment with ART	
	Women, N	% [95% CI]	Women, N	% [95% CI]
All	12 488	100	7396	100
Overall cause of infertility				
Female	2418	19.4 [18.7–20.1]	1860	25.1 [24.2–26.2]
Male	2401	19.2 [18.5–19.9]	3158	42.7 [41.6–43.8]
Combined	481	3.9 [3.5–4.2]	527	7.1 [6.5–7.7]
Idiopathic	7188	57.6 [56.7–58.4]	1851	25.0 [24.0–26.0]
Female infertility, specified				
Anovulation <sup>a</sup>	1716	13.7 [13.1–14.4]	307	4.2 [3.7–4.6]
Tubal factor <sup>a</sup>	214	1.7 [1.5–2.0]	1025	13.9 [13.1–14.7]
Endometriosis <sup>a</sup>	87	0.7 [0.6–0.9]	241	3.3 [2.9–3.7]
BMI ≥ 30	1055	11.2 [10.7–11.8]	645	10.7 [10.0–11.4]
Smoking, yes	1563 <sup>b</sup>	16.0 [15.3–16.7]	915 <sup>c</sup>	14.8 [13.9–15.7]
Secondary infertility	3539	28.3 [27.5–29.1]	1575	21.3 [20.4–22.2]
	Mean ± SD	95% CI	Mean ± SD	95% CI
Female age (years)	32.4 ± 4.8	32.3–32.5	33.1 ± 5.1	32.9–33.2

<sup>a</sup>Subgroup of female factor infertility, not all subgroups are reported.

<sup>b</sup>Missing information smoking N = 2710 (21.7%).

<sup>c</sup>Missing information smoking N = 1229 (16.6%).

and 34.9% within 3 and 5 years, respectively. Shift to ART treatment resulted in birthrates after ART-conception of 15.1%, 21.1% and 23.7%, 2, 3 and 5 years from first treatment, respectively (Table II). After 5 years, 16.6% of women starting treatments with IUI had delivered after natural conception.

### Live birthrates when starting treatments with ART

The course of treatments within the first 2 years of treatment, are shown in Table III. The vast majority (76.4%) had 1–3 ART treatments. Only 2.8% of couples starting with ART also had IUI within the first 2 years.

In women where ART was the initial treatment, the cumulative total live birthrates after 2, 3 and 5 years were 52.5%, 60.1% and 64.5% (Table II and Fig. 3). The majority of live births were after ART treatment, with birthrates of 46.1%, 51.1% and 52.9% within 2, 3 and 5 years. Within 5 years 11.2% had given birth after natural conception, but only 0.6% gave birth after IUI.

### Age-stratified analyses

Age-stratified total birthrates (both treatment-related and treatment-independent) are shown in Fig. IV. Live birthrates stratified on age, type of first treatment and mode of conception, are shown in Table IV. For all women, starting treatments with either IUI or ART, the total birthrates at 5-year follow-up were: <35 years 80.0%, 35–39 years 60.5% and >40 years 26.2%. Birthrates for natural conceptions within 5 years in women aged <35, 35–39, >40 were: 15.8%, 11.4% and 10.0%. At 5-year follow-up, there was no difference in total number of treatments between the age-groups.

### Predictors of live birth

Adjusted odds ratios for chances of live birth are shown in Supplementary Table SII. For all women, non-smoking and anovulatory infertility were predictors of high live birthrates. For women starting treatments with IUI, tubal factor infertility was a predictor of lower live birthrates. For women starting treatments with ART, male factor infertility was a predictor of high success rates.

#### Female age

In women starting treatments with IUI and aged less than 35, the adjusted odds-ratio (AOR) for live birth decreased with 1% for each year the women got older, not statistically significant. In women aged 35–39, AOR for live birth decreased significantly with 16% ( $P < 0.0001$ ) for each year the woman was older. In women aged 40 and over, AOR for live birth decreased with 37% ( $P < 0.0001$ ) for each year the woman was older.

In women starting treatments with ART and aged less than 35, AOR for live birth decreased with 4% ( $P < 0.0001$ ) for each year the women was older. Adjusted odds for live birth in women aged 35–39 years decreased with 15% ( $P < 0.0001$ ) each year. In women over 40 years old, chances decreased with 33% ( $P < 0.0001$ ) each year.

#### BMI

In women starting treatments with IUI, who had a BMI under 20, adjusted odds for live birth increased with 11% ( $P = 0.04$ ) for each increasing BMI unit. For women with BMI 20–29, AOR for live birth decreased with 4% ( $P < 0.0001$ ) for each increasing BMI unit. For women with BMI ≥ 30, AOR for live birth decreased with 7% ( $P < 0.0001$ ) for

**Table II** All outcomes 2-, 3- and 5 years after first treatment with IUI or ART with homologous gametes, in women with no previous births due to fertility treatment, Denmark 2007–2010.

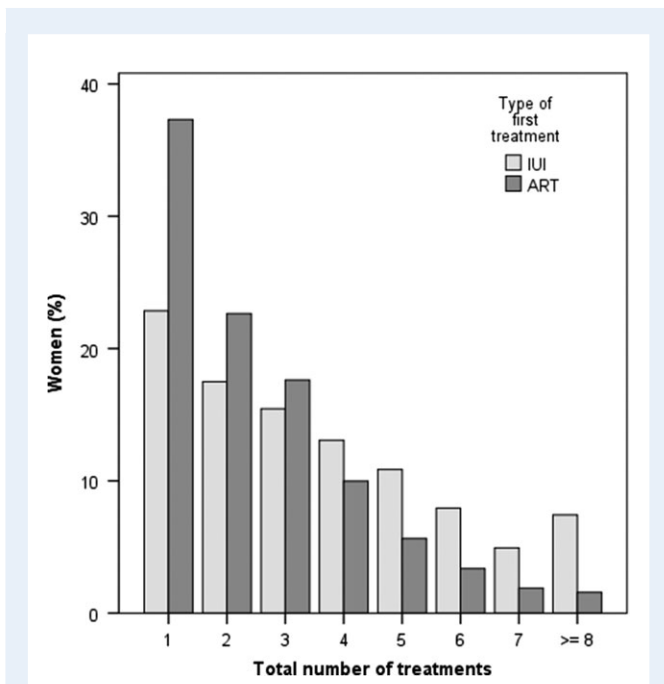
	N Total couples	Live birth % [95% CI]			Total live births	No live birth % [95% CI]			Total % All outcomes <sup>c</sup>	
		IUI-conception	ART-conception	Natural conception		Continue treatment <sup>a</sup>	Shift to donor semen	Shift to donor egg		No live birth <sup>b</sup>
2-year follow-up										
All	19 884	21.7 [21.3–22.3]	26.6 [26.0–27.2]	8.4 [8.0–8.8]	57.0 [56.3–57.7]	12.5 [12.0–13.0]	3.1 [2.9–3.3]	0.9 [0.8–1.0]	26.8 [26.2–27.5]	100
First treatment IUI	12 488	34.2 [33.4–35.0]	15.1 [14.5–15.7]	9.9 [9.4–10.4]	59.0 [58.1–59.9]	13.5 [12.9–14.1]	2.6 [2.3–2.8]	0.6 [0.4–0.7]	24.2 [23.5–25.0]	100
First treatment ART	7396	0.5 [0.3–0.7]	46.1 [45.0–47.2]	5.9 [5.4–6.4]	52.5 [51.5–53.6]	10.8 [10.1–11.6]	4.1 [3.7–4.6]	1.4 [1.2–1.7]	31.3 [30.2–32.3]	100
3-year follow-up										
All	14 445	21.2 [20.5–21.9]	32.8 [32.0–33.6]	11.2 [10.7–11.8]	65.0 [64.2–5.8]	4.9 [4.6–5.3]	3.6 [3.3–3.9]	1.1 [0.9–1.3]	25.3 [24.6–26.0]	100
First treatment IUI	8816	34.4 [33.4–35.4]	21.1 [20.3–22.0]	13.1 [12.4–13.8]	68.6 [67.6–69.6]	5.6 [5.2–6.2]	3.0 [2.6–3.4]	0.7 [0.6–0.9]	22.1 [21.3–23.0]	100
First treatment ART	5629	0.5 [0.3–0.7]	51.1 [49.8–52.4]	8.5 [7.8–9.2]	60.1 [58.8–61.4]	3.8 [3.4–4.4]	4.4 [3.9–4.9]	1.6 [1.3–2.0]	30.3 [29.1–31.5]	100
5-year follow-up										
All	5165	20.7 [19.6–21.8]	35.8 [34.5–37.1]	14.2 [13.3–15.2]	70.7 [69.5–71.9]	0.5 [0.3–0.7]	4.2 [3.7–4.8]	1.1 [0.9–1.4]	23.5 [22.4–24.7]	100
First treatment IUI	3028	34.9 [33.2–36.6]	23.7 [22.2–25.2]	16.6 [15.3–17.9]	75.2 [73.7–76.7]	0.7 [0.4–1.0]	4.2 [3.5–4.9]	0.8 [0.6–1.2]	19.2 [17.8–20.6]	100
First treatment ART	2137	0.6 [0.3–0.9]	52.9 [50.8–55.0]	11.0 [9.8–12.4]	64.5 [62.4–66.5]	0.2 [0.0–0.4]	4.1 [3.3–4.9]	1.5 [1.1–2.1]	29.7 [27.8–31.7]	100

The table reports the first live birth since start of treatment; later siblings are not reported.

<sup>a</sup>No live birth within follow-up, but record of further treatment beyond follow-up.

<sup>b</sup>No live birth or record of further treatment until 31st Dec 2012.

<sup>c</sup>Live birth + no live birth.



**Figure 2** Total number of treatments with ART or IUI within 2 years from first treatment in women receiving fertility treatments with homologous gametes in Denmark 2007–2010, stratified on type of first treatment. Based on women with complete 2-year follow-up: 12 488 women starting treatments with IUI and 7396 women starting treatments with ART.

each increasing BMI unit. Similar results were found in women starting treatments with ART.

Live birthrates stratified on type of first treatment, female age, type of conception, cause of infertility and female characteristics are shown in Supplementary Tables SIII and SIV.

## Multiples

Multiples rates stratified on type of conception are displayed in Supplementary Table SV. In couples who conceived with IUI, twin rates were 11.3% [10.4–12.3], which was lower compared to couples conceiving with ART. Among ART-conceived deliveries, twin rates were 14.0% [13.1–15.0]. Triplet and quadruplet rates were 0.2 and 0.0 in both groups.

## Discussion

In couples receiving fertility treatments with their own gametes, 57% gave birth as a result of treatment within 5 years, and 14% conceived naturally. Female age was the most important factor to predict outcome, and the total live birthrates within 5 years declined from 80% in women under 35–26% in women aged 40 and over. Most treatments (92%) occurred within the first 2 years, and the median number of total treatments was then 3 (IQR 1–4). Couples starting treatments with IUI had higher birthrates after treatments and natural conceptions, probably related to less severe infertility than in couples allocated directly to ART treatment.

In couples starting treatments with IUI, 34% conceived with IUI within 2 years, with a minimal increase between years 2 and 5, which reflect the Danish treatment guidelines: to offer a maximum of 3–6 cycles of IUI before shifting to ART (<http://www.fertilitetssekskab.dk>). IUI is a well-tolerated and inexpensive alternative to ART, but it is also known to be less efficient per treatment cycle (Goverde et al., 2000; Steures et al., 2007; Jeon et al., 2013; Schorsch et al., 2013). Only a few smaller studies have investigated the long-term prognosis for live birth after ART and IUI (Sundström et al., 1997; Pinborg et al., 2009; Donckers et al., 2011; Aanesen and Westerbotn, 2014). A Danish questionnaire study, based on reports from 1338 couples, showed that 70% gave birth within 5 years (Pinborg et al., 2009). Of these couples, 55% gave birth after ART, 18% after natural conception and only 10% after IUI. However, the majority of couples had received fertility treatments with IUI prior to inclusion in the study, which may explain the low birthrate after IUI-conceptions. A Swedish prospective cohort study of 380 couples, reported total live birthrates of 57% within 2.5 years (Aanesen and Westerbotn, 2014). Of all couples, 19% delivered after IUI or ovulation induction, 30% delivered after ART and 12% delivered after natural conception. The birthrate after IUI is lower than in our study, but numbers cannot be directly compared, since 22% of couples in the Swedish study never had IUI treatments. A Dutch study, with a cohort of 946 couples, found that 51% had a live birth and that 28% had a naturally conceived pregnancy (Donckers et al., 2011). Cumulated pregnancy rates of 25–30% after four IUI-cycles, in women under 35, are previously reported in two smaller, single center studies from Korea and Germany (Jeon et al., 2013; Schorsch et al., 2013). A randomized trial from the Netherlands compared birthrates after a maximum of six fresh cycles of IVF or six cycles of IUI in couples with idiopathic or male subfertility (Goverde et al., 2000). Even though per-cycle birthrates were higher in the ART group, so were the drop-out rates, leading to similar cumulated outcome in the groups. A Dutch trial from 2015 compared live birthrates in 602 couples with idiopathic or mild male subfertility, randomized to start treatment with either three fresh IVF treatments (plus subsequent frozen-thawed cycles), six natural-cycle IVF treatments, or six insemination treatments with ovarian stimulation. Live birthrates were similar in the three groups, indicating that both types of IVF treatments are non-inferior to IUI with ovarian stimulation (Bensdorp et al., 2015). A Scottish randomized controlled trial reports live birthrates of 17% after 6 months of expectant management, birthrates of 23% after 6 months of natural-cycle IUI and birthrates of 14% when treatment was clomiphene citrate alone. The differences were non-significant, indicating that expectant management may be as effective as natural-cycle IUI or clomiphene alone (Bhattacharya et al., 2008). A Dutch study randomized 253 couples to 6 months of expectant management or treatment with IUI and ovarian stimulation. There was no significant difference in the ongoing pregnancy rates between the groups (23% in the intervention group versus 27% in the expectant group) (Steures et al., 2006). In this study the ongoing pregnancy rate per started IUI cycle was only 4.1%. Further, 20% of couples in the expectant group started IUI treatments within 3–5 months from randomization.

Our results show, that in couples who start with insemination treatments 34% delivered after IUI-conception, and 38% changed to ART treatments within 2 years. The national guidelines recommend that couples with idiopathic, mild male factor as well as anovulatory infertility should initiate treatments with insemination. Our numbers indicate

**Table III** Course of treatments by patient within 2 years from first treatment in couples receiving fertility treatments with homologous gametes in Denmark 2007–2010, overall and stratified by cause of infertility.

First treatment with IUI	Total couples, N	1–3 IUI % [95% CI]	4–6 IUI % [95% CI]	1–3 IUI → ART % [95% CI]	4–6 IUI → ART % [95% CI]	Other % [95% CI]
Overall	12 488	49.2 [48.3–50.0]	10.1 [9.5–10.6]	26.8 [26.0–27.6]	11.3 [10.7–11.8]	2.7 [2.4–3.0]
Female factor infertility	2418	54.3 [52.3–56.3]	9.9 [8.7–11.1]	25.5 [23.8–27.2]	8.6 [7.6–9.8]	1.7 [1.2–2.3]
Anovulation <sup>a</sup>	1716	54.8 [52.5–57.2]	11.0 [9.6–12.6]	23.1 [21.2–25.2]	9.2 [7.9–10.6]	1.8 [1.3–2.5]
Tubal factor <sup>a</sup>	214	43.5 [36.9–50.2]	7.0 [4.2–11.0]	42.1 [35.6–48.7]	7.0 [4.2–11.0]	0.5 [0.1–2.2]
Endometriosis <sup>a</sup>	87	49.4 [39.1–59.8]	3.4 [1.0–8.9]	37.9 [28.3–48.4]	6.9 [2.9–13.7]	2.3 [0.5–7.2]
Male factor infertility	2401	46.6 [44.6–48.6]	8.6 [7.5–9.7]	32.0 [30.2–33.9]	11.0 [9.8–12.3]	1.8 [1.3–2.4]
Combined male female factor	481	49.5 [45.0–53.9]	11.9 [9.2–15.0]	26.4 [22.6–30.5]	10.0 [7.5–12.9]	2.3 [1.2–3.9]
Idiopathic infertility	7188	48.3 [47.1–49.4]	10.5 [9.8–11.2]	25.6 [24.6–26.6]	12.3 [11.6–13.1]	3.3 [2.9–3.8]

First treatment with ART	Total N	1–3 ART % [95% CI]	4–6 ART % [95% CI]	7 + ART % [95% CI]	ART → IUI % [95% CI]
Overall	7396	76.4 [75.5–77.4]	17.9 [17.0–18.8]	2.9 [2.6–3.3]	2.8 [2.4–3.2]
Female factor infertility	1860	76.3 [74.3–78.2]	18.0 [16.3–19.8]	2.9 [2.2–3.7]	2.8 [2.2–3.7]
Anovulation <sup>a</sup>	307	73.3 [68.1–78.0]	13.7 [10.2–17.9]	3.6 [1.9–6.1]	9.4 [6.6–13.1]
Tubal factor <sup>a</sup>	1025	76.4 [73.7–78.9]	19.6 [17.3–22.1]	2.7 [1.9–3.9]	1.3 [0.7–2.1]
Endometriosis <sup>a</sup>	241	76.8 [71.1–81.8]	19.1 [14.5–24.4]	2.5 [1.0–5.1]	1.7 [0.6–3.9]
Male factor infertility	3158	76.5 [75.0–77.9]	18.5 [17.2–19.9]	3.0 [2.4–3.6]	2.0 [1.6–2.6]
Combined male female factor	527	82.7 [79.3–85.8]	13.9 [11.1–17.0]	1.9 [1.0–3.3]	1.5 [0.7–2.8]
Idiopathic infertility	1851	74.7 [72.7–76.7]	17.8 [16.1–19.6]	3.1 [2.4–4.0]	4.3 [3.5–5.3]

One ART-cycle is defined as any started fresh or frozen-thawed cycle. <sup>a</sup>Subgroup of female factor infertility, not all subgroups are reported.

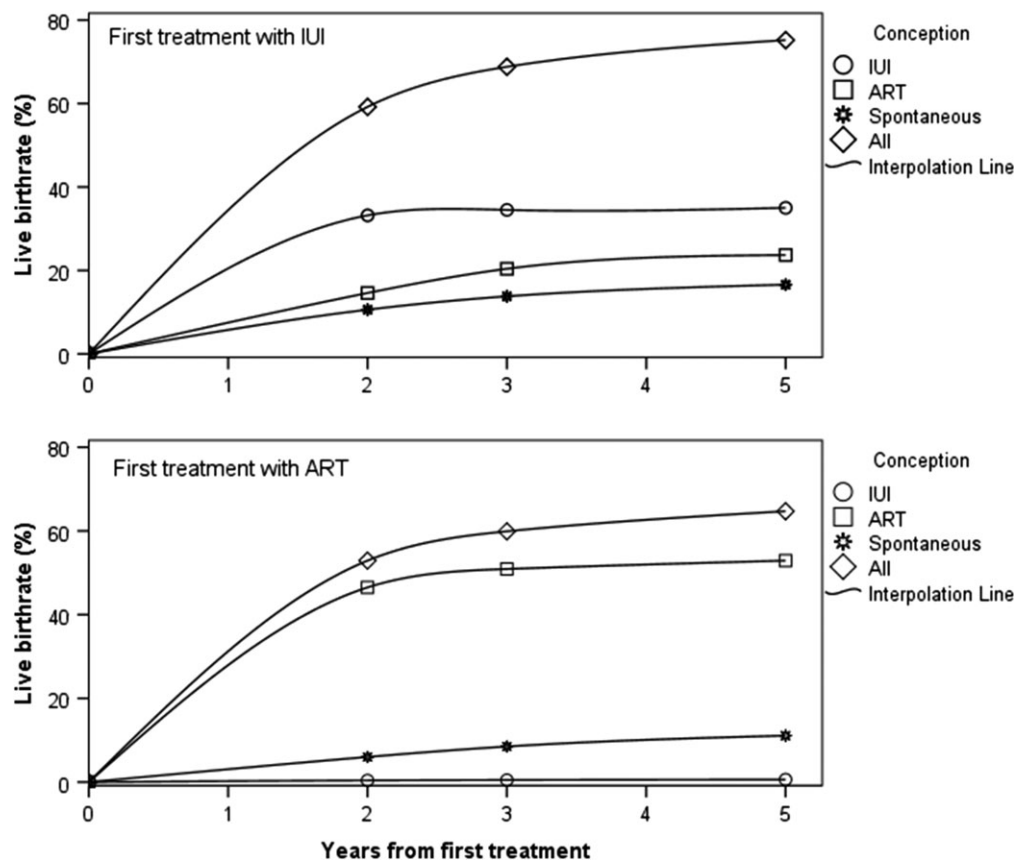
that this may be a feasible treatment program, especially in women under 35, were 45% in the anovulation group had a live birth due to IUI within 2 years, as did 38% in the idiopathic group, and 32% in the male factor group. Considering the benefits of the non-invasive IUI treatments, we believe that it qualifies as a first-line option to couples with these specific causes of infertility.

The role of expectant management is not addressed in this study. According to national guidelines, treatments are offered to couples who have been trying to conceive for at least 1 year. Two Danish studies, a prospective survey and a randomized controlled trial, report a mean duration of infertility of 3 and 4 years prior to inclusion. However in these studies the couples may have had previous insemination treatments (Pinborg *et al.*, 2009; Toftager *et al.*, 2016). The Danish ART registry does not contain individual data on how long the couples had tried to conceive before treatments, but even with that information, the question of expectant management cannot be addressed properly in a retrospective cohort analysis, where all couples had treatments. We do not know how many couples conceived while on the waiting list for treatments, and active treatment prevents natural conception; thus the potential for natural conception with expectant management in a subfertile cohort, is not reflected in our estimates. However, information on natural conceptions is vital to this report, to identify the true treatment-failures, and to give a complete prognosis. In women starting treatments with IUI, 10% delivered after natural conception within 2 years, increasing to 17% within 5 years.

A total of 53% of couples initiating treatments with ART, conceived with this treatment within 5 years. The vast majority had less than

four treatment cycles. Few women starting with ART had both ART and IUI treatments. Comparing with previous studies from Sweden and the US, birthrates are similar to conservative estimates after 3–5 cycles (Olivius *et al.*, 2002; Malizia *et al.*, 2009; Stern *et al.*, 2010). A UK study presented lower conservative estimates of 44% after eight fresh cycles with possible adjacent frozen-thawed cycles. None of the studies included birthrates after natural conception. In our study, natural conceptions occurred in women of all ages and in all causes of infertility. Birthrates after natural conception increased from 6% within the first 2 years to 11% within 5 years. Even though natural conceptions occur, we believe that treatments should not be postponed in women over 35, considering the rapidly declining treatment-success with increasing age.

Even though mandatory by Danish legislation, the Danish ART Registry is not 100% complete. Although underreporting of cycles not resulting in a pregnancy may occur, missing treatments may also be random losses of information due to administration, such as the conversion from paper to electronic reporting in 2006, and later changing the software for the electronic forms. Further, since IUI treatments were included in 2006, couples who had IUI treatment but no ART prior to 2006, and no treatment activity at all in 2006, may be misclassified as starting treatments with ART if returning for ART treatment within the study period. Missing treatments may lead to an overestimation of the success-rate per treatment cycle, but not of the cumulated birthrate 2, 3 and 5 years after first treatment. Missing births in the medical birth registry are unlikely, thus information on live births is complete. Since most women have repeated treatments, it is unlikely that we have underestimated the number of women with no birth, but



**Figure 3** Live birthrates 2, 3 and 5 years after first treatment in women receiving fertility treatments with homologous gametes in Denmark 2007–2010, stratified on type of conception and type of first treatment. Based on women with complete 5-year follow-up: 3028 women starting treatments with IUI and 2137 women starting treatments with ART.

we may have allocated treatment-related births to natural conception births. Even though information on cause of infertility appear to be complete in the cohort, the fraction of couples with combined male/female factor infertility is lower than expected and this may be due to missing information in one partner.

Our results are influenced by national treatment guidelines, reimbursement rules and legislation.

The national treatment guidelines recommend IUI treatments with homologous semen as first-line treatment to couples with idiopathic, mild male factor infertility and anovulatory infertility. Couples with severe male factor infertility, tubal factor infertility or severe endometriosis are recommended to start treatments with ART (<http://www.fertilitssekskab.dk>).

Inseminations and ART treatments are reimbursed in childless couples if the woman is below 40 years old. If the woman turns 40 during treatments, and still has frozen embryos, they may be transferred with reimbursement. Three fresh ART treatments are reimbursed, plus subsequent frozen embryo transfers. Further fresh cycles are at the couples own expense. It is recommended that all frozen embryos are used before proceeding to the next fresh cycle, but this is not regulated by legislation. The number of reimbursed ART treatments is unaffected by possible previous IUI treatments. The number of

reimbursed insemination treatments is not strictly regulated, but a maximum of six inseminations is recommended. Our numbers indicate that this recommendation is followed in 97% of couples starting treatments with insemination, while 1.4% of couples have seven IUI-cycles, and 1.5% of couples have eight or more IUI-cycles in total. Legislation prohibits treatments to women above 45 years.

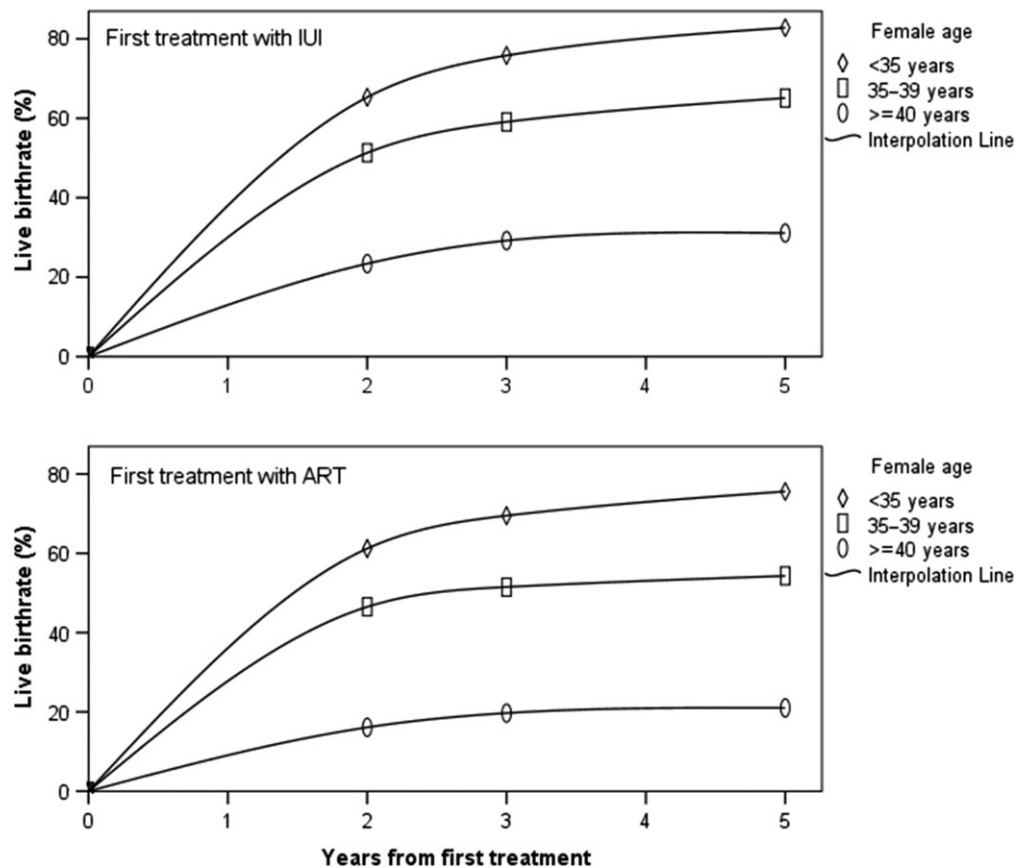
The national coverage of fertility treatments lead to inclusion of all socio-economic levels in our cohort, and exclude financial reasons for dropping out within the first three fresh ART cycles. Birthrates are most likely higher than in countries without reimbursement. The regulations concerning female age lead to a younger cohort, compared to other countries. The total number of treatments was similar across the age-groups, probably because the youngest women need fewer treatments to conceive, and that treatment activity in the highest age-group is limited by reimbursement rules. Because women over 40 finance their treatments personally, this may lead to selection-bias with regard to socio-economic level, which may be related to fertility potential. This may also be true for couples who receive more than three fresh ART cycles.

When assessing longitudinal outcome after fertility treatments, decisions regarding the time axis and censoring of drop-outs, have major influence on the estimates. This is demonstrated in a UK study



**Table IV** Age-stratified live birthrates by patient 2, 3 and 5 years after first treatment with homologous gametes in Denmark, 2007–2010.

Female age	first treatment with IUI					first treatment with ART				
	N, total	IUI-conception, live birthrate [95% CI]	ART-conception, live birthrate [95% CI]	Natural conception, live birthrate [95% CI]	Total live birthrate [95% CI]	N, total	ART-conception, live birthrate [95% CI]	IUI-conception, live birthrate [95% CI]	Natural conception, live birthrate [95% CI]	Total live birthrate [95% CI]
2-year follow-up										
<35 years	8753	37.8 [36.8–38.8]	16.8 [16.0–17.6]	10.6 [10.0–11.2]	65.2 [64.2–66.2]	4857	53.3 [51.9–54.7]	0.7 [0.5–0.9]	6.3 [5.6–7.0]	60.3 [58.9–61.7]
35–39 years	2897	29.7 [28.0–31.4]	12.7 [11.5–13.9]	8.4 [7.4–9.4]	50.7 [48.9–52.5]	1769	39.3 [37.0–41.6]	0.3 [0.1–0.6]	5.1 [4.1–6.1]	44.8 [42.5–47.1]
≥40 years	833	12.4 [10.2–14.6]	5.6 [4.0–7.2]	7.6 [5.8–9.4]	25.6 [22.6–28.6]	753	15.5 [12.9–18.1]	0 [0–0.005]	5.6 [4.0–7.2]	21.1 [18.2–24.0]
3-year follow-up										
<35 years	6229	37.8 [36.6–39.0]	23.6 [22.6–24.7]	13.9 [13.0–14.8]	75.4 [74.3–76.5]	3707	59.0 [57.4–60.6]	0.7 [0.4–1.0]	9.3 [8.4–10.2]	69.1 [67.6–70.6]
35–39 years	1981	30.2 [28.2–32.2]	17.3 [15.6–19.0]	11.3 [9.9–12.7]	58.9 [56.7–61.1]	1328	44.7 [42.0–47.4]	0.2 [0.0–0.4]	6.6 [5.3–7.9]	51.5 [48.8–54.2]
≥40 years	601	13.1 [10.4–15.8]	7.5 [5.4–9.6]	9.7 [7.3–12.1]	30.3 [26.6–33.4]	580	15.5 [12.6–18.5]	0 [0–0.006]	7.4 [5.3–9.5]	22.9 [19.5–26.3]
5-year follow-up										
<35 years	2152	37.9 [35.9–40.0]	26.9 [25.0–28.8]	18.0 [16.4–19.6]	82.8 [81.2–84.4]	1401	62.2 [59.7–64.7]	0.9 [0.4–1.4]	12.5 [10.8–14.2]	75.6 [73.4–77.9]
35–39 years	651	32.4 [28.8–36.0]	18.9 [15.9–21.9]	13.8 [11.2–16.5]	65.1 [61.4–68.8]	505	45.7 [41.4–50.0]	0.2 [0.2–0.6]	8.3 [5.9–10.7]	54.3 [50.0–58.6]
≥40 years	222	13.5 [9.0–18.0]	6.8 [3.5–10.1]	10.8 [6.7–14.9]	31.1 [25.0–37.2]	229	11.8 [7.6–16.0]	0 [0–0.02]	9.2 [5.5–12.9]	21.0 [15.7–26.3]



**Figure 4** Total live birthrates after treatment and natural conception 2, 3 and 5 years after first treatment, in women receiving fertility treatments with homologous gametes in Denmark 2007–2010, stratified on female age and type of first treatment. Based on women with complete 5 years follow-up: 3028 women starting treatments with IUI and 2137 women starting treatments with ART.

from 2016 were birthrates after eight complete cycles were analyzed both in a conservative and optimistic way, yielding estimates of 44% and 82%, respectively (McLernon et al., 2016). The conservative estimate is the proportion of women who deliver out of all couples entering treatment, including drop-outs (Malizia et al., 2009; McLernon et al., 2016). Optimistic estimates are assessed with survival analyses, such as Kaplan–Meier, where the time axis corresponds to the number of cycles and women are censored when they drop out of treatments (Olivius et al., 2002; Malizia et al., 2009; McLernon et al., 2016). Such estimates are made on the assumption that censored couples would have reached the same birthrates as the couples who continue treatments, had they continued (Bland and Altman, 1998; Daya, 2005; Maheshwari et al., 2015). Previous studies have raised concern that the assumption, independent censoring, may not be met in an infertile population, where drop-outs/censored women have been shown to be older, have higher FSH levels on day three of menstrual cycle, lower peak estradiol levels, have fewer retrieved oocytes and fewer frozen embryos, and higher anxiety levels, thus are more likely to have a poor prognosis (Daya, 2005; Malizia et al., 2009; Smeenk et al., 2004). Further, natural conceptions in treatment pauses may be a reason for drop out. Therefore drop-outs may represent the couples with the best and

the worst prognosis. Considering this, information on natural conceptions is crucial when assessing birthrates in longitudinal studies, and an important strength in this study.

## Conclusion

Overall, 71% of the women had a live birth within 5 years from the first treatment, of which 57% conceived after treatment and 14% conceived naturally. Insemination treatments may be a feasible first-line option to couples with idiopathic and mild male factor as well as anovulatory infertility. Based on these results, we are able to provide couples with a comprehensible and individual, age-stratified long-term prognosis at start of treatment.

## Supplementary data

Supplementary data are available at *Human Reproduction* online.

## Acknowledgements

We gratefully acknowledge the efforts of Danish fertility clinics, reporting their treatment activity.

## Authors' roles

S.S.M., A.A.H., A.L., J.F., A.N.A. and A.P. contributed substantially to the study design, analysis and interpretation of the data. S.R. cross-linked treatment cycles in the ART registry with the MBR-registry. S.R. and S.S.M. were responsible for data management. The first draft of the manuscript was written by S.S.M. All co-authors revised the manuscript. All co-authors approved the final manuscript.

## Funding

This study was partly and unconditionally funded by Ferring Pharmaceuticals and the Augustinus foundation. The funders had no role in the study design, data collection and interpretation, or decision to submit the work for publication.

## Conflict of interests

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: S.S.M. received an unconditional grant from Ferring Pharmaceuticals; A.A.H. has received personal fees from Ferring Pharmaceuticals not related to this work; A.N.A. reports grants and personal fees from Ferring Pharmaceuticals, personal fees from Merck Serono, grants and personal fees from MSD, outside the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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