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ORIGINAL ARTICLE *Reproductive epidemiology*

Prospective longitudinal cohort study on cumulative 5-year delivery and adoption rates among 1338 couples initiating infertility treatment

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BACKGROUND: The objective was to assess crude 5-year delivery rates after assisted reproductive technology (ART) treatment, intrauterine inseminations (IUI), spontaneous conceptions (SC) and adoptions in a large infertile cohort.

METHODS: A prospective longitudinal survey comprised 1338 infertile couples starting public infertility programmes offering IUIs and three free ART cycles during 2000–2001. The cohort was cross-linked with the National Medical Birth Register to obtain delivery rates for all 1338 couples. More detailed data were available from 817 women responding to a 5-year follow-up questionnaire (response rate 74.7%). Fifty-seven percent (466/817) of the couples had received treatment prior to inclusion in the study with an average of 4.1 ± 2.8 infertility treatments before referral.

RESULTS: Of the 1338 couples, 69.4% had at least one delivery within 5-years of follow-up. For women <35 years 74.9% had delivered compared with 52.2% of those aged ≥35 years. The mean number of children was 1.6, and 52.1% had more than one child. Of the 817 women who provided questionnaire data, 18.2% (149/817) delivered after SC, two-thirds of these after a previous ART delivery. Adoption of a child occurred for 5.9% (48/817) of the women. Positive prognostic factors for delivery were male infertility, female age <35 years, <3 years of infertility and less than three previous treatment cycles.

CONCLUSIONS: A crude delivery rate of 69.4% in the total population 5 years after referral to tertiary hospital centres with 6.6% deliveries after SC in the subpopulation responding to the questionnaire indicates a high efficacy of modern infertility treatments.

Key words: adoption / IVF/ICSI/IUI / crude delivery rate / prognostic factors / spontaneous conception

Introduction

The literature on efficacy of assisted reproductive technology (ART) is comprehensive and generally based on pregnancy or delivery rates per cycle, as reported from Europe and elsewhere (Nyboe Andersen *et al.*, 2008). As the vast majority of data are cycle-based, our knowledge of per-patient crude long-term delivery rates in large infertile populations is scarce. Further, the literature on spontaneous conceptions (SC) and adoption rates is even more limited.

During the development of ART, a limited number of studies have assessed the cumulative delivery rate after treatment restricted to ART done at a single or two clinics, and the main outcome measure has most often been the theoretically calculated ongoing pregnancy or delivery rates using life table statistics (Osmanagaoglu *et al.*, 1999; Stolwijk *et al.*, 2000; Olivius *et al.*, 2002; Sharma *et al.*, 2002; Elizur *et al.*, 2006), and estimated cumulative delivery rates up to 90% have been presented (Elizur *et al.*, 2006). As realized in these studies and discussed in other studies (Witsenburg *et al.*, 2005; Soullier *et al.*, 2008), cumulative birth rates depend on the methods of calculation. Using life table analysis and assuming that dropouts have the same prognosis as those who continue treatment means that the theoretically calculated birth rates will be largely overestimated, if dropouts in reality have a poorer prognosis than those who continue treatment. Current practise takes into consideration those couples who do not wish to or are unable to go through several treatment cycles, and in tertiary care populations observed

cumulative delivery rates after 4–14 IVF/ICSI cycles are now in the range of 36–37% (Elizur *et al*., 2006; Soullier *et al*., 2008) and after 5–6 years of follow-up to 59–60% (Osmanagaoglu *et al*., 1999; Witsenburg *et al*., 2005). These figures indicate that cumulative delivery rates are highly dependent on the patient population and the terms of time frame (number of consecutive ART cycles or years of treatment/follow-up). Based on 20 reports published from 1950 to 2002, Collins and van Steirteghem (2004) developed a model utilizing published evidence about diagnosis, treatment, duration of treatment and the proportion of couples receiving treatment. They considered couples newly identified as infertile and established a model of delivery rates after 3 years assuming the couples would first utilize non-ART treatments and then, of those still not pregnant, up to 50% would have traditional ART. The authors concluded that, even with extensive utilization of ART, typical management of infertility would achieve <50% live births, due to underlying unknown untreatable factors that constituted barriers to higher success rates (Collins and van Steirteghem, 2004).

The aim of the present prospective longitudinal cohort study was to analyse a large infertile population of consecutive newly referred couples treated at four independent large hospital-based tertiary care reproductive centres in Denmark which offered the same frame of public fertility treatment including both intrauterine inseminations (IUI) and *in vitro* fertilization (IVF). Couples were tracked over a prolonged follow-up period of 5 years including also treatment-independent deliveries and adoptions. We consider that this prospective longitudinal cohort design provides realistic information reflecting the chance of a live birth after modern fertility treatment without overestimating cumulative delivery rates. Moreover, our data allows an estimation of the contribution of treatment-independent deliveries.

Materials and Methods

Setting

This study is part of The Copenhagen Multi-Centre Psychosocial Research Program (COMPI), which is a prospective longitudinal cohort study on a large population of infertile couples initiated in year 2000 (Schmidt, 2006). The research programme comprised consecutively all infertile couples newly referred to tertiary clinics starting infertility treatment with IUI, IVF or intracytoplasmic sperm injection (ICSI) in four large public hospital-based tertiary fertility clinics in Denmark from 1 January 2000 to 1 August 2001 ($n = 1338$ couples). According to data from the Danish Fertility Society these four clinics conducted two-thirds of all public ART cycles in Denmark during the inclusion period (http://www.fertilitetsselskab.dk). In Denmark, only couples without a child in common and where the female age is below 40 years are offered reimbursed treatment within the National Health Program. Infertile couples are offered three fully reimbursed IVF or ICSI transfer cycles with fresh embryos, and an unrestricted number of cycles with frozen embryo replacement (FER) or IUI with either husband or donor semen. If the first or second fresh IVF or ICSI cycle results in a live birth, no further fresh IVF/ICSI cycles are offered in the public sector.

Procedure: self-administered questionnaires

Couples were invited to participate in a prospective longitudinal cohort study based on three self-administered questionnaires (at start of treatment (baseline) and after 1-year and 5-years of follow-up). All newly referred couples entering one of the four clinics received a sealed envelope immediately before their first treatment. It contained information about the study and a questionnaire, a form for declaration of non-participation in the study and a stamped pre-addressed return envelope to each partner. The questionnaire was returned to the last author (L.S.) who was not employed at any of the clinics. The non-responders received up to two reminders and a new copy of the questionnaire was included in the second reminder. In total, 83.3% responded to the baseline questionnaire. At baseline, the non-responders were significantly older, more likely to start ICSI treatment or had tubal occlusions in the case of females (for further details about non-responders, see Schmidt, 2006). The 5-year follow-up questionnaire was sent to the participants at their home address together with a stamped, pre-addressed enveloped. Again up to two written reminders were sent, with the second reminder including another copy of the questionnaire. In total, 1093 women received the 5-year follow-up questionnaire and 817 women (74.7%) responded. Fifty women were lost to follow-up (e.g. new address impossible to trace, had died or partner had died). Several studies on patient satisfaction, stress related to infertility, coping and infertility-related communication based on the COMPI cohort from the baseline and 1-year follow-up questionnaire have already been published (Schmidt *et al*., 2003, 2005; Boivin and Schmidt, 2005; Peterson *et al*., 2008), while data from the 5-year follow-up questionnaire only recently have been computed and analysed. In the current study, we used the initial cohort of 1338 infertile couples eligible for treatment in 2000–2001 (study population I) and the sub-cohort of the 817 female respondents of the 5-year follow-up questionnaire (study population II).

Socio-economic position was measured as occupational social class in a descending scale from occupational social class I (high) to occupational social class V (low) (Hansen, 1984) and social class VI which included individuals who received social welfare benefits. Participants impossible to classify according to this scale were categorized as outside classification.

Data sources

All information presented in this paper is based on two data sources, The National Medical Birth Register and the COMPI 5-year follow-up questionnaire. To acquire 5-year cumulative data on all miscarriages, ectopic pregnancies and childbirths of the complete invited cohort of consecutively new couples, irrespective of whether they had responded to the baseline questionnaire or not, the unique personal identification code of each woman in the cohort was cross-linked with The National Medical Birth Register at 1 April 2006. This enabled us to obtain crude long-term pregnancy outcome rates on all 1338 women eligible for the initial cohort (study population I). Ectopic pregnancies and miscarriages were obtained from the National Discharge Register according to the relevant ICD-10 diagnosis codes. Hence, only cases referred to hospital and hospital outpatient clinics were included in the study. Thus, some early losses may not have been included.

As records of IUI treatments and adoptions are not available in the National IVF or Medical Birth Register, we used the sub-cohort of all 817 respondents to the 5-year follow-up questionnaire (study population II) to obtain detailed information on crude childbirth rates after different treatment methods; IUI, IVF, ICSI, FER and SC. Adoption rates, number of previous treatment cycles, causes of infertility and length of involuntary childlessness were not available from the IVF register and hence were only available as self-reported data for study population II. Demographic data for study population II are presented in Table I.

Prognostic variables

Covariates found in previous studies to be of prognostic value of delivery were examined: female age (<35 and ≥35 years), duration of infertility (<3 and ≥3 years), number of treatment cycles prior to the first delivery

in the study period (0–3, 4–6, ≥7), occupational social class, pregnancy history (defined as primary or secondary infertility at inclusion in COMPI) and diagnostic categories of ART: tubal pathology, ovulatory disorder, mixed female factor (both tubal pathology and ovulatory disorder), male factor, mixed female and male factor and unexplained infertility.

Statistical analysis

Statistical analysis was performed using SAS for Windows (Statistical Analysis Software) version 8.02. A *P*-value of < 0.05 was considered statistically significant. Differences of means of continuous parametric data were analysed with the use of Student's *t*-test. Risk estimates were calculated as odds ratios (OR) with 95% confidence intervals (95% CI) and distributions between groups were compared with Pearson's chi-square test.

For each woman the cumulative delivery rate of the first birth was calculated for 1, 2, 3, 4 and 5 years after treatment start. Further, the cumulative delivery rate of first birth after the different treatment modalities (IUI; IVF; ICSI; FER) and SC was calculated 1, 2, 3, 4 and 5 years after baseline, respectively.

Multivariate logistic regression analysis was performed as backward stepwise selection to estimate the predictive effect on live birth of the prognostic variables listed above.

Results

National Medical Birth Register data (study population I)

Based on the National Medical Birth Register, the crude delivery rate in the total cohort (study population I) was 69.4% (929/1338) after 5-years of follow-up, i.e. almost 70% of the infertile women had at least one delivery within 5 years of treatment start (Fig. 1). The proportion of women <35 years of age, who had given birth was significantly higher 74.9% (762/1018) than in the group aged ≥35 years (52.2%) (167/320) ($P < 0.001$). Almost two-thirds of the couples in the initial cohort delivered their first child within the first 3 years after inclusion in COMPI (61.7%, 826/1338 (Fig. 1). Of the 929 women, who had given birth during the 5-year follow-up period, 826 (88.9%) delivered within the first 3 years, hence 11.1% delivered their first child during the fourth and fifth year after start of treatment.

From the complete National Medical Birth register data it was found that among women with at least one delivery the mean number of children was 1.6 per female and the mean number of deliveries was 1.4. In women less than and beyond 35 years of age the mean number of children after 5-year follow-up was 1.7 and 1.4, respectively ($P < 0.001$). The percentage of women with 1, 2, 3, ≥4 children was 47.9, 43.7, 7.7 and 0.6%, respectively. Thus, 52.1% of those who delivered had two or more children. Of women with two children, 158/415 (38%) had twins and of couples with three children, 56/73 (76.7%) had twins and 5/73 (6.8%) had triplets, of the five couples with ≥4 children all children were from multiple pregnancies. According to the National Medical Birth Register, overall 1298 childbirths were observed in study population I (82.2% singleton, 17.1% twin and 0.7% triplet births). Of the initial cohort 4.7% of women had at least one ectopic pregnancy (63/1338) and 13.8% had a miscarriage (185/1338) after inclusion in COMPI.

Table I Characteristics of study population II

	Study population II (respondents to questionnaire), *n* = 817 women
Sociodemographic	
Age at inclusion (years), Mean (SD)	31.8 (3.5)
Occupational social class, *n* (%)	
High, I+II	143 (17.5)
Medium, III+IV	480 (58.6)
Low, V+VI	125 (15.3)
Outside classification	69 (8.5)
Medical	
Ever pregnant prior to inclusion, *n* (%)	255 (31.2)
Missing, *n* (%)	6 (0.7)
Length of infertility at inclusion (years)	
Mean (SD)	4.1 (2.3)
Median (variance)	4.0 (5.2)
Range	1–17
Distribution, %	
≤1 year	5.1
2–3 years	43.1
4–5 years	32.8
6–9 years	15.2
≥10 years	3.9
Diagnostic category, *n* (%)	
Tubal pathology	147 (18.0)
Ovulatory disorder	49 (6.0)
Mixed female factor[a]	20 (2.5)
Male factor	244 (29.9)
Mixed female+ male	70 (8.6)
Unexplained	252 (30.8)
Missing	35 (4.3)
Treatment cycles	
No. couples with no previous treatment, *n* (%)	351 (43.0)
No. Couples with previous treatment, *n* (%)	466 (57)
No. of treatment cycles prior to inclusion	
Mean (SD)	4.1 (2.8)
Median (variance)	3.0 (8.1)
Range	1–21
Distribution, %	
1–3 cycles	51.7
4-5 cycles	23.4
6–9 cycles	20.8
>10 cycles	4.1
No. of treatment cycles during 5-year follow-up, Mean (SD)	3.5 (2.4)

Continued

Table I *Continued*

	Study population II (respondents to questionnaire), *n* = 817 women
Median (variance)	3.0 (5.9)
Range	0–15
Distribution, %	
0 cycles	0.9
1–3 cycles	56.9
4-5 cycles	25.3
6–9 cycles	13.8
>10 cycles	3.2
Total no. of treatment cycles	2846
Type of treatment cycles, *n* (%)	
IUI	569 (20.0)
IVF	1294 (45.5)
ICSI	632 (22.2)
FER	272 (9.6)
Others	24 (0.8)
Missing	35 (1.2)
Deliveries and adoptions	
Number of deliveries after fertility treatment in total *n* = 672, *n* (%)	
IUI	97 (14.4)
IVF	355 (52.8)
ICSI	163 (24.3)
FER	43 (6.4)
Others	8 (1.2)
Missing	6 (0.9)
Total	672 (100%)
Total no. of deliveries after SC	176
Women with at least one SC delivery, *n* (%)	149 (149/817=18.2%)
Total number of adoptions	58
Women with at least one adoption, *n* (%)	48 (48/817=5.9%)

n = 817 women, who responded to the COMPI 5-year follow-up questionnaire. [a]Mixed female factor is tubal disorder and ovulatory disorder in combination. SC, spontaneous conception.

COMPI 5-year follow-up questionnaire data (study population II)

The following results were generated from the 5-year follow-up survey returned by 817 women (study population II) and questionnaire data including fertility history of this subpopulation are listed in Table I. Except maternal age these data are not available for study population I. The mean age at inclusion in COMPI in the initial cohort (study population I) and the respondents to the 5-year follow-up questionnaire (study population II) was 31.5 ± 3.5 years and 31.8 ± 3.5 years, respectively, and without statistical significance. The mean length of infertility at inclusion in COMPI was 4.1 ± 2.3 years and 57% (466/817) of the couples had received fertility treatment prior to inclusion in the study. The mean number of treatment cycles prior to inclusion among these couples was 4.1 ± 2.8. The mean number of treatment cycles (IUI, IVF, ICSI and FER) during the follow-up period was 3.5 ± 2.4 per woman (range 0–15). Figure 2 shows the proportion of all deliveries occurring after each type of treatment per year in the 817 women, who returned the 5-year follow-up questionnaire. In total, 848 births were observed (*n* = 672 after IUI and ART and *n* = 176 after SC). When classified according to conception method, 41.8% of births were after IVF, 19.1% after ICSI, 11.5% after IUI, 6.9% after FER and 20.7% after SC. Figure 3 illustrates the distribution of different ART methods and SC resulting in the first delivery per year after treatment start in study population II. After 5-years of follow-up, 610/817 (74.7%) had given birth to at least one child, 556/817 (68.1%) had their first child after IUI or ART and 54/817 (6.6%) after SC. The distribution of conception methods resulting in the first delivery after 5-years of follow-up was as follows: IUI 9.9% (81/817), IVF 37.8% (309/817), ICSI 16.8% (137/817), FER and other 3.5% (29/817), SC 6.6% (54/817) (Fig. 3).

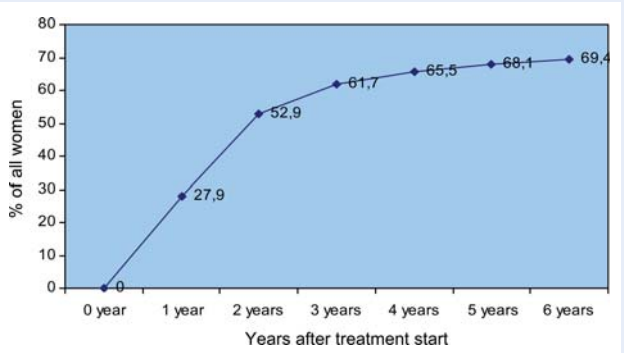

Figure 1 Cumulative percentage of the initial cohort in the 1338 women (study population I) with at least one delivery after 5 years of follow-up based on complete follow-up data from the National Medical Birth Register.

Regarding those women who had their first delivery after IUI-H or IUI-D, 64 (64/610, 10.5%) women had not been treated with IVF or ICSI previous to the IUI-birth. Of the women who had their first birth after IVF/ICSI treatment only 31 had received IUI treatment prior to the ART birth and these women had a mean of 2.55 IUI cycles per woman (79/31).

Of all women responding to the 5-year follow-up questionnaire, 18.2% (149/817) had a delivery after SC, out of which 10.7% (16/149) had changed their partner during the follow-up period. As reported above, a total of 176 births after SC were observed, hence some of the 149 women with SC had more than one birth after SC. Of the 149 women delivering after SC, 54 (36.2%) had their first delivery after a SC, 94 (63.1%) after a previous ART delivery and 1 (0.7%) after adoption of a child. Overall, 3.1% delivered after SC without any ART treatments prior to the conception. Forty-eight women (5.9%) had adopted a child during the 5-year follow-up period of which only 10 adopted more than one child.

Of all couples giving birth to a child after fertility treatment during the 5-year follow-up period 92.9% remained together, compared with those who did not give birth after treatment of whom only 79.3% stayed together ($P < 0.001$).

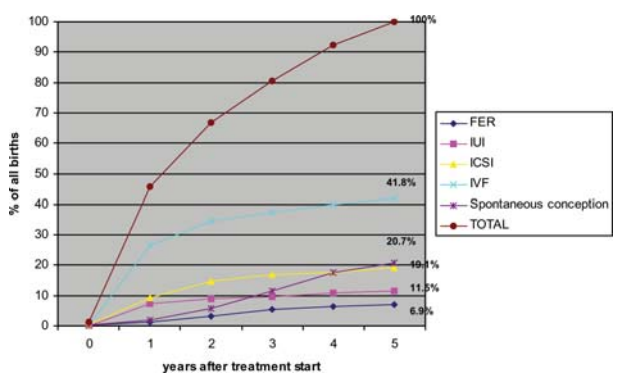

Figure 2 The proportion of all deliveries occurring after each type of treatment in the 817 women (study population II) responding to the 5-year follow-up questionnaire classified according to conception method.

In total, 848 births were reported ($n = 672$ after ART and $n = 176$ after spontaneous conception).

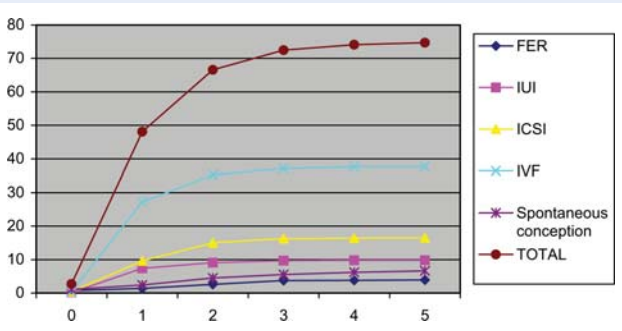

Figure 3 Cumulative rates of first delivery ($n = 610$; $n = 556$ after ART and $n = 54$ after spontaneous conception) in the women ($n = 817$) responding to the 5-year follow-up questionnaire according to conception method.

After 5 years of follow-up, 610/817 (74.7%) of the women had a delivery with 37.8% after IVF, ICSI 16.8%, IUI 9.9%, FER 3.5% and spontaneous conception 6.6%, respectively. X-axis, years after treatment start. Y-axis, percentage of respondents to the 5-year follow-up questionnaire.

Table II shows the distribution of infertility diagnoses in relation to the first delivery. Tubal pathology was the diagnosis category with the lowest cumulative delivery rate (61.9%), whereas male factor infertility had the highest (82.0%) ($P < 0.001$). The highest delivery rates after SC were seen in women with anovulatory infertility (12.2%) and unexplained infertility (8.3%), which was statistically significantly ($P < 0.001$) different from those diagnostic categories with the lowest delivery rate after SC (tubal pathology, mixed female infertility and mixed female and male factor).

Predictors of first delivery

In Table III, the results of the multivariate logistic regression models are shown for first delivery. The most significant predictors of first delivery were female age <35 years (OR 2.1, 95% CI 1.3–3.2), less than three treatment cycles (OR 4.4, 95% CI 2.9–6.6) and duration of infertility <3 years (OR 2.3, 95% CI 1.4–3.9). The most favourable diagnosis of predicting birth was male factor infertility, which was chosen as the reference category and the poorest was tubal pathology, OR 0.36 (95% CI 0.21–0.61). As pregnancy history and occupational social class were not statistical significant in the univariate analyses, these covariates were omitted in the final model.

Discussion

This is the first study to show that cumulative delivery rates after public tertiary care infertility treatment in Denmark are high, as 69.4% of all women in an infertile population had given birth to a child within 5 years of the start of treatment. According to the subpopulation of respondents to the 5-year follow-up questionnaire only 6.6% delivered their first child after SC. A mean of 1.6 children were born per woman who delivered. Fifty-seven percent (466/817) of the couples had received fertility treatment before referral to one of the four large tertiary clinics participating in COMPI and on average these couples had received 4.1 treatments prior to inclusion. The overall population eligible for the COMPI study had thus been subject to a selection, as none of the couples had conceived. It should also be noted that the high cumulative delivery figure was obtained in a population with an average of 4.1 years of infertility prior to inclusion, and that 57% of that population had been through fertility treatment previously. Of those who delivered 52.1% had more than one child. One of the main findings of the study was that, of the women who responded to the 5-year follow-up questionnaire, 18.2% had a delivery after SC. However, just above one-third of these 18.2% delivered after SC without a previous ART delivery (6.6%) and thus birth of a spontaneously conceived second child after the first ART child was observed in about two-thirds of the 18.2%.

Strengths and limitations

One strength of the study is the prospective longitudinal design with complete per-patient delivery rates from infertile couples consecutively newly referred to tertiary infertility clinics from the Medical Birth Register during a prolonged follow-up period of 5 years. Additionally, the study involved four independent tertiary care clinics and hence data are likely to be representative regarding cumulative birth rates in Denmark. All clinics offered IUI with no formal restrictions, but according to National Guidelines no more than three to six IUI treatments should be performed and up to three ART transfers within the same frame of public infertility treatment. Treatment strategy is recommended by National guidelines by the Danish Fertility Society (http://www.fertilitetsselskab.dk).

Another strength is the combination of data from national registers with complete follow-up on deliveries and the 5-year follow-up questionnaire enabling assessment of deliveries after a wide range of fertility treatments such as IVF, ICSI, IUI, FER and SC plus adoptions, which is unique, as most studies only deal with cumulative delivery rates after IVF or ICSI alone, and follows the couples only until the end of treatment or first delivery (Engmann *et al.*, 1999; Stolwijk *et al.*, 2000; Olivius *et al.*, 2002; Sharma *et al.*, 2002; Witsenburg *et al.*, 2005;

Table II Infertility diagnosis related to the first delivery classified after ART or SC based on study population II (*n* = 817 women)

	ART delivery	Delivery after SC conception	No delivery	Total
No. of women, *n* (%)				
Tubal pathology	89 (60.5)	2 (1.4)	56 (38.1)	147 (100)
Ovulation factor	31 (63.2)	6 (12.2)	12 (24.5)	49 (100)
Tubal pathology plus ovulation disorder	14 (70.0)	0	6 (30.0)	20 (100)
Male factor	184 (75.4)	16 (6.6)	44 (18.0)	244 (100)
Mixed factor	45 (64.3)	2 (2.9)	23 (32.9)	70 (100)
Unexplained	168 (66.7)	21 (8.3)	63 (25.0)	252 (100)
Total	531 (67.9)	47 (6.0)	204 (26.1)	782 (100)

Male factor was chosen as the reference category.
Combined female were women with both tubal pathology and ovulation disorder.
In 35 women the infertility diagnosis was unknown, thus the total number of women was *n* = 782. SC, spontaneous conception.

Table III Multivariate logistic regression analysis of predictors of delivery based on study population II from the 5-year follow-up questionnaire (*n* = 817 women)

	OR	95% CI	*P*-value
Delivery as outcome			
Age			
<35 years	*ref.*		
≥35 years	0.49	0.32–0.75	<0.001
Duration of subfertility			
<3 years	*ref.*		
≥3 years	0.43	0.26–0.72	0.001
No. of treatment cycles			
0–3	*ref.*		
4–6	0.23–0.15–0.34	<0.0001	
≥7	0.13	0.07–0.24	<0.0001
Diagnostic category			
Male infertility[1]	*ref.*		
Ovulation disorder	0.91	0.38–2.18	NS
Tubal pathology	0.36	0.21–0.61	<0.001
Combined female[2]	0.32	0.11–0.95	0.04
Mixed male and female	0.41	0.21–0.81	0.01
Unexplained	0.63	0.38–1.04	NS

Risks are reported as odds ratios (OR) with 95% confidence intervals (95% CI).

Soullier *et al*., 2008). On the other hand, data based on self-reported questionnaires involve a possibility of positive selection bias, which cannot be overlooked. The questionnaire results (study population II) revealed a cumulative delivery rate of 74.7%, whereas the true cumulative delivery rate based on complete data from the National Medical Birth Register in the total population was 5.3% lower, namely 69.4%. This difference in cumulative delivery rate is probably explained by positive selection bias, as the questionnaire response rate was higher in women with delivery than in those without. The cumulative delivery rate after SC of 18.2% in study population II is probably also overestimated due to positive selection bias and hence the true delivery rate after SC in the total population may be lower.

The response rate in our study was 83.3% at baseline and 74.7% at the 5-year follow-up among the participants who received the follow-up questionnaire. Previous questionnaire-based follow-up studies among infertile women including from 52 to 385 women showed an approximately 1-year follow-up response rate ranging from 34 to 53% (Leiblum *et al*., 1987; Sabourin *et al*., 1991; Schover *et al*., 1992). Verhaak *et al*. (2007) have to our knowledge published the only study with a follow-up period of 3–5 years after last IVF treatment cycle. They had a baseline response rate of 84% among women and a final follow-up response rate of 78%, which is comparable to the COMPI cohort response rates. We have used several strategies to increase response rates as, e.g. stamped return envelopes and general questions at the end of the questionnaire, which have recently in a Cochrane review been shown to increase response rates (Edwards *et al*., 2007). A systematic review of follow-up response rates after more than 1 year has shown that follow-up response rates above 60% should be regarded as satisfactory, as it is very hard to obtain higher response rates (Professor M. Osler, University of Copenhagen, personal communication). The response rate at the 5-year follow-up comprised 61% of the initial invited cohort. The response rate differed by 5% between patients who delivered and those who did not. The potential selectiveness related to this difference should be noted, particularly with regard to the cumulative delivery rate and the reported proportion of deliveries after SC (6.6%), as positive selectiveness may have inflated this figure above the true proportion.

Positive selection bias in the survey data can also be the case in the proportion of couples, who remained together after 5-years of follow-up, which was 92.9% in those couples who had a child after fertility treatment versus 79.3% in those who did not.

Comparison with other studies

Our crude delivery rate per woman was better than in previous per-patient based studies from 1950 to 2002, which reported crude pregnancy rates ranging from 19 to 52% (Collins and van Steirteghem, 2004). The conclusion from these studies was that typical infertility

management resulted in <50% live births with no improvement in overall IVF success rates over time. Our study based on an infertile cohort referred to tertiary clinics in 2000/2001 has shown more convincing results with a cumulative crude birth rate of 69.4% in the total population with 6.6% of deliveries occurring after SC according to the subpopulation of respondents to the questionnaire. However, the study of Collins and van Steirteghem (2004) analysed couples first identified as infertile and estimated delivery rates after 3 years, and assumed that couples would first utilize non-ART treatments, and then, of those still not pregnant, up to 50% would have traditional ART. Therefore, that study is not directly comparable to the present study.

Different patient populations, treatment modalities, time frame of follow-up and problems with dropouts and treatment-independent pregnancies makes it very difficult to compare studies of cumulative delivery rates in infertile populations. The present figures exceeded the most recent longitudinal Scandinavian cohort studies from Norway 1980–1989 ($n = 629$ couples) with follow-up of 3–12 years and from Denmark 1990–1992 ($n = 300$ couples) with follow-up of 4–6 years with crude delivery rates of 42 and 47%, respectively (Sundström *et al*., 1997; Rex *et al*., 1998). This could be explained by improvement in the ART techniques, since both studies are more than 10 years older than ours, and ICSI was then an emerging technology. Indeed, the increased birth rates found in the present study could be due to the introduction of ICSI, as well as the use of IUI. The Danish study (Rex *et al*., 1998) included only IVF couples who in general completed three treatment cycles, indicating a poorer patient prognosis than in our study, where 10% of the deliveries occurred after IUI. Treatment-independent deliveries were not dealt with in the Danish study (Rex *et al*., 1998), but in the Norwegian study 47% conceived independent of treatment (Sundström *et al*., 1997). The number of treatment-independent deliveries in our series is much smaller. One reason could be that 57% of the patients had received an average of four treatments, probably mainly IUI, before referral to the tertiary centres, hence those with the best prognosis may have been already pregnant and thus not referred.

A recent Dutch longitudinal study with 1456 couples initiating IVF/ICSI treatment in the period 1996–2000 with follow-up until 2003 showed cumulative first delivery rates of 59.1% (Witsenburg *et al*., 2005). The 10% higher cumulative delivery rate in our study can be explained by the contribution of IUI and treatment-independent deliveries, which were not encountered in the Dutch study. Further, slightly more FER deliveries were observed in our study (6.9%) versus 4% in the Dutch study. The latter showed improved cumulative live birth rates over time from the period 1996–1997 (54.8–54.9%) to 1998–2000 (60.2–67.1%). We consider that the message regarding fertility treatment success rates is positive and suggests that cumulative delivery rates may indeed have improved by ~10% during the latest decade.

Longitudinal cohort studies of observed deliveries provide accurate data, which do not overestimate success rates and thus reflect the actual performance of present practise. However, the full potential of modern infertility treatment will be underestimated, as drop out will occur even from free of charge public programmes (Olivius *et al*., 2002; Smeenk *et al*., 2004). Soullier *et al*. (2008) recently addressed the issue of success estimations in IVF programmes and showed that the observed delivery rate in two French IVF units was 37%, whereas the Kaplan–Meier-based estimated delivery rate was 52%. Their data also allowed the use of multiple imputations taking into account treatment interruptions to provide a more realistic estimate and this method gave an estimate of 46% which lies between the two other figures (Soullier *et al*., 2008). Our data cannot be used to calculate delivery rates this way, but stresses that the 63% delivery rate after treatment (69.4–6.6% = 62.8%) within 5 years is a minimum figure, and that even higher delivery rates are obtainable by minimizing the number of couples who discontinue treatments.

In Denmark, all IUI and three fresh ART transfer cycles are reimbursed by the public health system and Denmark has the highest utilization of ART per inhabitant in Europe (Nyboe Andersen *et al*., 2008). Clearly, the high crude delivery rates observed in the present study indicate that couples understand and accept the need for repetitive cycles. Evidence of a similar acceptance of this concept comes from the Netherlands, where a recent study looked at cumulative pregnancy rates (CPR) after a maximum of nine cycles of modified natural cycle IVF (MNV-IVF) and found a CPR of 40.6%, while the CPR including treatment-independent pregnancies was 44.4% (Pelinck *et al*., 2007). Though only good-prognosis patients were included in this study, these results show that even protocols without ovarian stimulation can lead to relatively high CPR today (Pelinck *et al*., 2007).

Spontaneous conceptions

Treatment-independent pregnancies occur in infertile populations. We found a 5-year cumulative delivery rate of 18.2% after SC with 6.6% of these children born before the birth of an ART child, which is in agreement with previous studies, showing the effectiveness of IVF versus expectant management in patients with severe reproductive disorders and Fallopian tube patency (Evers *et al*., 1998; Hughes *et al*., 2004; Eijkemans *et al*., 2008). Expectant management may be justified in couples with unexplained infertility on a waiting list for IUI. In an RCT including 253 patients with unexplained infertility of a mean duration of 1.9 years, randomly assigned to either expectant management or IUI with controlled ovarian hyperstimulation for 6 months, Steures *et al*. (2006) observed an ongoing pregnancy rate of 23% in the IUI versus 27% in the expectant group. The authors concluded that expectant management is justified in this group of patients. The main reason for the considerably lower first delivery rate after SC (8.3%) in our unexplained infertility group is that Steures *et al*. only included couples with a 30–40% spontaneous pregnancy chance, according to the model by Hunault *et al*. (2004). Our eligible population from tertiary care centres had more severe reproductive disorders, as they were also candidates for IVF/ICSI treatment. Further, the mean duration of infertility was twice as long in our study (4.1 years) as in the Dutch study (1.9 years) and the mean number of treatment cycles prior to inclusion in our study was 4.1. Though Denmark has a very high availability of ART, the mean duration of infertility was 4.1 years, which indicates that 'high availability' does not necessarily lead to 'over-treating' in terms of lack of expectant management, at least in the tertiary ART units.

Evers *et al*. (1998) studied treatment-independent pregnancy rates in patients with severe reproductive disorders. The 12 months CPR for patients on their waiting list was 2.4% for tubal pathology, 5.9% for unexplained infertility and 6.6% for male subfertility. The corresponding figures in our population were quite similar; 1.4% for tubal

pathology, 8.3% for unexplained infertility and 6.6% for male factor infertility.

Hughes et al. (2004) performed the first multi-centre randomized controlled trial of 3 months expectant management versus a first cycle of IVF in women with tubal patency. They found live birth rates in the IVF and the expectant management group of 29 and 1%, respectively. The authors concluded that first cycle IVF increases the likelihood of live birth more than 20-fold and treating four women with tubal patency with one cycle of IVF each is required to achieve a single additional birth (Hughes et al., 2004). Hence, the number needed to treat to achieve an additional live birth after IVF was four. This is in agreement with our findings of only 1.4% couples with delivery after SC in the tubal pathology group.

In a very recent prospective cohort study on pregnancy rates of 5962 couples on an IVF/ICSI waiting list, the cumulative probability of treatment-free ongoing pregnancy was 9% at 12 months (Eijkemans et al., 2008). In multivariate Cox regressions, hazard ratios were 0.95 ($P < 0.001$) per year of the female age, 0.85 ($P < 0.001$) per year of duration of infertility and 0.71 ($P = 0.005$) for primary versus secondary infertility (Eijkemans et al., 2008). However, the authors also stated that for selected patient groups the rate of an ongoing pregnancy without treatment might be as high as 25% within 1 year. The highest rates were found for unexplained infertility. Earlier reports have found 12 months cumulative spontaneous pregnancy rates in subfertile populations of 11.2–27.4% with the highest rates found in primary care populations and the lowest in secondary/tertiary care populations (Collins et al., 1995; Vardon et al., 1995; Gleicher et al., 1996; Snick et al., 1997). Obviously, spontaneous pregnancy rates in subfertile populations are dependent on the length of the expectant management period and the severity of the reproductive disorders in the study populations. In our material of a tertiary care population a treatment-independent delivery rate of 6.6% with the lowest seen in tubal pathology patients, is rather low and the much higher delivery rates after treatment support the conclusion that 'over-treatment' is not of any significant concern. Couples with a poor prognosis of SC, i.e. tubal pathology and mixed female and male factor, should be considered of higher priority on fertility treatment waiting lists, while others, e.g. unexplained infertility could be allowed a longer expectant period. A cumulative treatment-independent delivery rate of 18.2% shows that considerable spontaneous pregnancy potential may be present in a population starting ART and that some of these patients would have become pregnant without ART, if only they had waited long enough.

Predictors of the first delivery following treatment

In our study, female age <35 years, less than three previous treatment cycles and <3 years duration of infertility were significant predictors of the first delivery. Male factor infertility was the most favourable diagnostic category predicting first delivery, while women with tubal disorder had the poorest prognosis. Several papers have reported rising maternal age as a negative prognostic factor for delivery in treated patients (Witsenburg et al., 2005; Lintsen et al., 2007). In the study by Witsenburg et al., the cumulative first delivery rate after IVF/ICSI treatment was 64.6% for women <36 years, but only 48.7% for women ≥36 years of age. Similar figures were obtained in our dataset with cumulative first delivery rates of 74.9 and 52.2% in women <35 and ≥35 years, respectively.

In couples where female age is below 40 years with a mean number of four treatments prior to referral, a crude delivery rate of 69.4% can be achieved 5 years after the start of treatment in tertiary reproductive clinics. According to our questionnaire subpopulation only 6.6% of deliveries are treatment-independent. This prognosis is reassuring and crucial for clinicians to counsel patients entering a modern infertility programme.

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