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ORIGINAL ARTICLE ***Infertility***

Cumulative live birth rates after one ART cycle including all subsequent frozen–thaw cycles in 1050 women: secondary outcome of an RCT comparing GnRH-antagonist and GnRH-agonist protocols

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STUDY QUESTION: Are cumulative live birth rates (CLBRs) similar in GnRH-antagonist and GnRH-agonist protocols for the first ART cycle including all subsequent frozen–thaw cycles from the same oocyte retrieval?

SUMMARY ANSWER: The chances of at least one live birth following utilization of all fresh and frozen embryos after the first ART cycle are similar in GnRH-antagonist and GnRH-agonist protocols.

WHAT IS KNOWN ALREADY: Reproductive outcomes of ART treatment are traditionally reported as pregnancies per cycle or per embryo transfer. However, the primary concern is the overall chance of a live birth. After the first ART cycle with fresh embryo transfer, we found live birth rates (LBRs) of 22.8% and 23.8% ($P = 0.70$) for the GnRH-antagonist and GnRH-agonist protocols, respectively. But with CLBRs including both fresh and frozen embryos from the first oocyte retrieval, chances of at least one live birth increases. There are no previous randomized controlled trials (RCTs) comparing CLBRs in GnRH-antagonist versus GnRH-agonist protocols. Previous studies on CLBR are either retrospective cohort studies including multiple fresh cycles or RCTs comparing single embryo transfer (SET) with double embryo transfer (DET).

STUDY DESIGN, SIZE, DURATION: CLBR was a secondary outcome in a Phase IV, dual-center, open-label, RCT including 1050 women allocated to a short GnRH-antagonist or a long GnRH-agonist protocol in a 1:1 ratio over a 5-year period using a web-based concealed randomization code. The minimum follow-up time from the first IVF cycle was 2 years. The aim was to compare CLBR between the two groups following utilization of all fresh and frozen embryos from the first ART cycle.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All women referred for their first ART cycle at two public fertility clinics, <40 years of age were approached. A total of 1050 subjects were allocated to treatment and 1023 women started standardized ART protocols with recombinant human follitropin-β (rFSH) stimulation. Day-2 SET was planned and additional embryos were frozen and used in subsequent frozen–thawed cycles. All pregnancies generated from oocyte retrieval during the first IVF cycle including fresh and frozen–thaw cycles were registered. Ongoing pregnancy was determined by ultrasonography at gestational week 7–9 and live birth was irrespective of the duration of gestation. CLBR was defined as at least one live birth per allocated woman after fresh and frozen cycles. Subjects were censored out after the first live birth. Cox proportional hazard model was used to evaluate the relative prognostic significance of female age, BMI, the number of retrieved oocytes and the diagnosis of infertility in relation to the CLBR.

MAIN RESULTS AND THE ROLE OF CHANCE: Baseline characteristics were similar and equal proportions of patients continued with frozen–thaw (frozen embryo transfer, FET) cycles after their fresh ART cycle in the GnRH-antagonist and GnRH-agonist arms. When combining all fresh and frozen–thaw embryo transfers from first oocyte retrieval with a minimum of 2-year follow-up, the CLBR was 34.1% (182/534) in the GnRH-antagonist group versus 31.2% (161/516) in the GnRH-agonist group (odds ratio (OR):1.14; 95% CI: 0.88–1.48, $P = 0.32$). Mean time to the first live birth was 11.0 months in the GnRH-antagonist group compared to 11.5 months in the GnRH-agonist group ($P < 0.01$). The total number of deliveries from all FET cycles where embryos were thawed were higher in the antagonist group 64/330 (19.4%) compared to the agonist group 43/355 (12.1%) ((OR): 1.74; 95% CI: 1.14–2.66, $P = 0.01$). The evaluation of prognostic factors showed that more retrieved oocytes were associated with a significantly higher CLBR in both treatment groups. For the subgroup of obese women (BMI >30 kg/m^2), the CLBR was significantly higher in the GnRH-antagonist group ($P = 0.02$).

LIMITATIONS, REASONS FOR CAUTION: The duration of the trial is a possible limitation with introduction of new methods as 'Freeze all' and 'GnRH-agonist triggering', but as these treatments were used in only few women, a systematic bias is not likely. Blastocyst culture of surplus embryos for freezing was introduced to both groups simultaneously, thereby minimizing the risk of bias. Furthermore, with a minimum of 2-year follow-up, a minority (<1%) still had cryopreserved embryos and no live birth at the end of the trial. The *post hoc* prognostic covariate analyses with multiple strata should be interpreted with caution. Finally, the physicians were not blinded to GnRH treatment group after randomization.

WIDER IMPLICATIONS OF THE FINDINGS: With the improvement of embryo culture, freezing and thawing methods as well as a strategy of elective SET, CLBR until first live birth provides an all-inclusive success rate for ART. When comparing GnRH-antagonist and GnRH-agonist protocols, we find similar CLBRs, despite more oocytes being retrieved in the GnRH-agonist protocol.

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Introduction

Traditionally, the success of ART has been reported as the ongoing pregnancy rates per fresh IVF cycle or per fresh embryo transfer. With improvements in ART, both the numbers of frozen–thawed embryo transfers (de Mouzon *et al.*, 2010) and the related pregnancy rates have increased (Roque *et al.*, 2013). An increasing use of single embryo transfer (SET) strategies to reduce multiple pregnancies increases the chances of additional frozen–thawed embryo transfers and this has increased the cumulative pregnancy rate per oocyte retrieval (McLernon *et al.*, 2016). New methods such as GnRH-agonist triggering in a combination with a freeze all strategy to prevent ovarian hyperstimulation syndrome (OHSS) in women at risk, make the reproductive outcomes per fresh embryo transfer less relevant to patients and physicians who are more keen to know the chance of a live birth for the individual couple over an entire IVF program (Maheshwari *et al.*, 2015).

It may, however, be more appropriate to estimate the cumulative success rate per woman after one complete cycle; this defined as all fresh and frozen–thawed embryo transfer cycles from one oocyte retrieval (Moragianni and Penzias, 2010, McLernon *et al.*, 2016). By using the definition of one complete ART cycle, the total reproductive potential of one oocyte retrieval provides an all-inclusive success rate which is relevant and meaningful (Jones *et al.*, 1997, Maheshwari *et al.*, 2015).

In the past, several methods have been used to estimate the cumulative live birth rate (CLBR) and there is no consensus on how to report the success rate of ART. To avoid overestimation of the CLBR, we used a competing risk method, where spontaneous pregnancy and use of all cryopreserved embryos are competing risks to the outcome live birth (Viardot-Foucault *et al.*, 2015).

The aim of the present study was to compare CLBRs after one complete ART cycle in an unselected population of women referred for their first ART cycle and allocated to treatment with either a GnRH-antagonist or GnRH-agonist protocol and followed until all frozen embryos were used. This was a secondary outcome in a large randomized controlled trial (RCT).

Materials and Methods

Study design

CLBRs were a secondary outcome in a large Phase IV, dual-center, open-label, randomized controlled study, with the objective to compare short GnRH-antagonist and long GnRH-agonist protocols in an unselected population referred for their first ART. Subjects were randomized in a ratio 1:1 over a period of 5 years from January 2009 to December 2013, and were followed for 2–7 years until December 2015. The protocol is described in detail in Toftager *et al.*, 2016.

Participants

All women younger than 40 years of age and newly referred for their first ART treatment, at two public fertility clinics in Denmark; Hvidovre Hospital, Copenhagen and Dronninglund Hospital, Aalborg, were screened. Exclusion criteria were prior ART cycles, uterine abnormality, use of testicular sperm extraction (TESE) or testicular sperm aspiration (TESA), allergy to the ingredients used for intervention and diminished kidney or liver function.

Treatment protocols

Of 1050 women allocated to treatment, a total of 1023 women, 528 in the short GnRH-antagonist protocol and 495 in the long GnRH-agonist protocol, started a standardized ART treatment with recombinant human follitropin-β (rFSH) stimulation, with fixed rFSH dose of 150 IU or 225 IU according to female age ≤36 years or >36 years and with the option to adjust dose according to response at stimulation Day 6.

To ensure validation of complete cycles, all enrolled subjects agreed to use all frozen embryos before proceeding with a new fresh IVF/ICSI cycle.

Fresh embryo transfer

Day-2 SET was intended for all. However, a minority of patients ($n = 128$), primarily advanced in age received double embryo transfer (DET), according to national guidelines. All were given luteal phase support starting on the day of embryo transfer (Chrinone®, Merck, Hellerup, Denmark). Additional embryos considered viable according to morphologic criteria were frozen for later transfer in subsequent frozen embryo transfer (FET) cycles. The vast majority of these embryos were frozen on Day2. During the study, blastocyst culture was introduced. Hereafter, a few patients with many additional embryos had some of their embryos cultured to the blastocyst stage before vitrification on Day 5 or 6. Embryos not suitable for cryopreservation on Day 2 were cultured to Day 5 or 6 and vitrified if they reach the blastocysts stage.

Frozen–thawed embryo transfer

Embryo transfers of cryopreserved embryos were performed either in hCG-triggered natural cycle by use of 6500 IU hCG (Ovitrelle®; Merck Serono, Hellerup, Denmark) at the day the leading follicle was ≥17 mm or, in case of anovulatory infertility, in estradiol and progesterone substituted cycles (oral estradiol 2 mg three times daily from cycle Days 2–3 and vaginal progesterone was added as luteal phase support 3 days prior to embryo transfer of cleavage stage frozen–thawed embryos and 6 days before transfer of vitrified-warmed blastocysts). Embryos were thawed the day before transfer. Up to two viable Day-2 embryos or one or two surviving blastocysts were transferred. In the hCG-triggered FET cycles, no luteal phase support was provided. According to the Danish legislation cryopreserved embryos must be used within 5 years.

Reproductive outcomes

The reproductive outcome was measured 2 weeks after embryo transfer as a positive hCG, then at gestational week 7–9 as an ongoing pregnancy and finally at delivery as a live birth. Positive hCG was defined as plasma hCG >10 IU/L. Ongoing pregnancy was defined as a living fetus verified by ultrasonography. Live birth was defined as the birth of at least one living child, irrespective of the duration of gestation. The CLBRs were calculated by including the first live birth generated during the complete first IVF cycle as the numerator and censoring additional live births out. The denominator was defined as all women allocated to treatment. In this study, the live birth rate (LBR) is equivalent to the take-home baby rate and live births conceived spontaneously either prior to rFSH stimulation ($n = 21$), after the first fresh cycle ($n = 8$) or between FET cycles ($n = 3$) were included in the analyses of CLBRs. At the end of the trial, nine women had ongoing pregnancies, five with a gestational age (GA) of <24 weeks and four with a GA >28 weeks, and all nine women gave birth to healthy babies.

Sample size calculation and randomization

The sample size for the RCT was based on the primary outcome severe OHSS as described in detail (Toftager *et al.*, 2016).

Although the trial size was dictated by the primary outcome, a retrospective power calculation based on a clinical relevant difference in CLBR of 10% was performed. In a two-sided Fisher's exact test with level of significance set at $P < 0.05$ and the CLBR in the two arms of 30% versus 40% in a total population of 1050 women, the power for the outcome CLBR was 93%. For the presented CLBR results (34% versus 31%), the power was 17% and would require 4000 patients in each arm with alpha 0.05 and beta 0.80. Women were randomized at inclusion in a 1:1 ratio using a web-based concealed randomization code.

Statistical methods

Intention-to-treat analysis was applied in all analyses and included 1050 subjects who did not withdraw their consent and were eligible (Fig. 1).

The Cochran–Mantel–Haenszel test and Van Elteren's extension of the Wilcoxon rank-sum test were used to analyze categorical and continuous variables, respectively, controlling for age group, fertilization procedure (IVF or ICSI) and IVF clinic. The CLBRs in the GnRH-antagonist and GnRH-agonist groups were compared by Gray's test using a competing risk analysis, where spontaneous pregnancies and use of all frozen embryos was considered a competing risk to the outcome live birth after ART treatment. The *P*-values correspond to tests for difference between the two groups with a significance level of 5%. Data are presented as mean (SD) or number (%) as relevant. A per protocol analyses were also performed for the comparison of CLBR between the groups, where only women who started gonadotrophin stimulation were included and patients were analyzed as treated not as randomized.

For the outcome total live birth of subsequent FET cycles, we performed a regression analysis with embryo transfer day and endometrium preparation as independent variables.

Cox proportional hazard model was used to evaluate the relative prognostic significance of female age, BMI, the number of retrieved oocytes and the primary diagnosis of infertility in relation to CLBR. Regression analyses were made for the individual treatment groups and for the pooled data ($n = 1050$). Interactions between the independent covariates were tested. For age, subjects were categorized into three age groups (<30, 30–36 and >36 years). For BMI, subjects were categorized into three groups BMI <25 kg/m^2 (lean), BMI 25–30 kg/m^2 (overweight) and BMI >30 kg/m^2 (obese). The four groups for the number of retrieved oocytes were 1–3, 4–9, 10–15 and >15. For the primary diagnosis of infertility, subjects were categorized into six groups: anovulatory, tubal, endometriosis, male, unexplained and other causes. Chi-square tests were applied to detect differences between the independent covariate strata and between the GnRH-antagonist and agonist arms. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

The study was approved by The Danish Ethics Committee, Capital region of Denmark, Protocol #: H-B-2008–109 and approved by Danish Health and Medicines Authority, EudraCT #: 2008-005452-24. The registration ID on ClinicalTrial.gov isNCT00756028. The study is reported according to the CONSORT guidelines. All participants provided written informed consent.

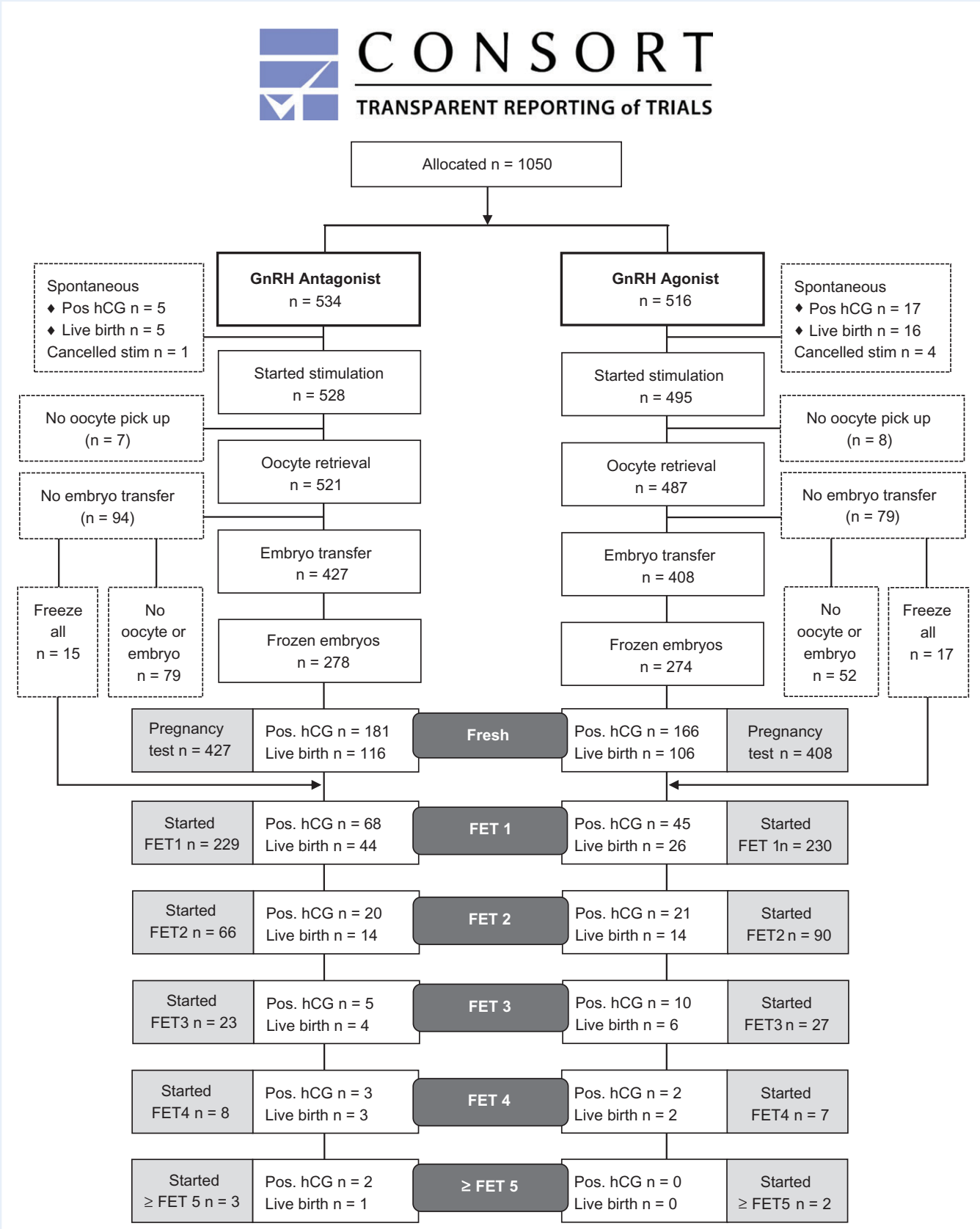

Figure 1 Trial flow chart. An overview of all started cycles (fresh + frozen embryo transfer, FET) and the overall reproductive outcomes in the antagonist and agonist groups. Spontaneously, conceived pregnancies prior to recombinant human follitropin-β (rFSH) stimulation are shown in the top. Spontaneous pregnancies after rFSH and in-between FET treatments were six in both groups, and five and six resulted in live births in the antagonist versus agonist group, respectively (not shown in the figure). Stim: stimulation.

Results

Patient characteristics

Baseline characteristics were comparable with respect to: BMI, age, the distribution of primary diagnosis of infertility, cycle length and the prevalence of women with anovulation or oligomenorrhea (Table I).

Table I Baseline characteristics on menstrual cycle Days 1–3 in women treated with either GnRH-antagonist or GnRH-agonist treatment.

	Antagonist group (*n* = 534)	Agonist group (*n* = 516)
Age at inclusion, mean (SD)	32.0 (4.3)	32.0 (4.1)
BMI (kg/m^2), mean (SD)	24.5 (7.0)	24.7 (7.2)
Cycle length (days), mean (SD)	28.6 (2.8)	29.1 (3.5)
Irregular cycle, *n* (%)*	58 (10.9%)	56 (10.9%)
Duration of infertility (years), mean (SD)	2.5 (1.6)	2.7 (1.7)
Previous pregnancy, *n* (%)**	191 (35.8%)	151 (29.3%)
Previous delivery, *n* (%)	43 (8.1%)	40 (7.8%)
Primary cause of infertility, *n* (%)		
Male	229 (42.9%)	237 (45.9%)
Tubal	66 (12.4%)	68 (13.2%)
Endometriosis	13 (2.4%)	13 (2.5%)
Uterine factor	2 (0.4%)	2 (0.4%)
Anovulatory	42 (7.9%)	39 (7.6%)
Unexplained	144 (27.0%)	126 (24.4%)
Other causes	38 (7.1%)	31 (6.0%)

Including all randomized women treated with either GnRH-antagonist or GnRH-agonist treatment.
*Cycle >35 days. **Including spontaneous and fertility treatments other than ART. SD, standard deviation.

Cumulative pregnancy and LBRs

Cumulative pregnancy and LBRs are listed in Table II. The CLBR after one complete ART cycle including fresh and subsequent frozen–thaw cycles from first oocyte retrieval per allocated woman were similar in the antagonist and agonist group 182/534 (34.1%) and 161/516 (31.2%), respectively (odds ratio (OR): 1.14; 95% CI: 0.88 to 1.48; $P = 0.32$). Only three and six blastocyst transfers contributed to first live births in the antagonist and agonist group, respectively. The average time from randomization to first pregnancy and live birth was significantly shorter in the antagonist group compared to the agonist group ($P < 0.01$) (Table II). In a competing risk analysis, no difference was found in the cumulative incidence of first live birth between the GnRH-antagonist and GnRH-agonist groups ($P = 0.18$) (Fig. 2).

The number of spontaneously conceived pregnancies resulting in a live birth were lower in the antagonist group compared to the agonist group: 10/534 (1.9%) versus 21/516 (4.1%). Spontaneously, conceived pregnancies contributed significantly more to the CLBR in the agonist arm 21/161 (13.0%) compared to the antagonist arm 10/182 (5.5%) (OR: 0.37; 95% CI: 0.17 to 0.81; $P = 0.01$) (Table II). In a per protocol analysis of CLBR, where only live birth resulting from treatment were included, the CLBR for the antagonist group was 174/519 (33.5%) for the antagonist group and 148/504 (29.4%) for the agonist group, $P = 0.33$.

The number of women with unused cryopreserved embryos within the 5 year time limit was 25 in the antagonist group and 17 in the agonist group, out of which only 4 and 6 women, respectively, did not achieve a live birth within the study period.

Frozen–thawed cycles

Of all 1050 allocated patients, the total number of initiated FET cycles with thawed embryos was 330 in the antagonist group and 355 in the agonist group. In the antagonist group 275/330 (83.3%) had a transfer with a frozen–thawed embryo compared to 288/355 (81.1%) in the agonist group. In the majority of FET cycles thawed Day-2 embryos

Table II Cumulative reproductive outcome from one complete cycle including fresh and frozen–thawed embryo transfer till first live birth in women treated either withe GnRH-antagonist or GnRH-agonist treatment.

	Antagonist group (*n* = 534)	Agonist group (*n* = 516)	*P*-value	OR (95% CI)
Cumulative reproductive outcome				
Positive p-hCG (≥10 IU/L)*, *n* (%)	238 (44.6%)	213 (41.3%)	0.27	1.15 (0.90–1.47)
Ongoing pregnancy*, *n* (%)	186 (34.8%)	166 (32.2%)	0.35	1.13 (0.87–1.46)
Live birth*, *n* (%)	182 (34.1%)	161 (31.2%)	0.32	1.14 (0.88–1.48)
After fresh embryo transfer, n (%)	*116/182 (63.7%)*	*106/161 (65.8%)*	*1.00*	*1.00 (0.63–1.58)*
After FET embryo transfer, n (%)	*56/182 (30.8%)*	*34/161 (21.1%)*	*0.09*	*1.55 (0.94–2.55)*
After spontaneous conception, n (%)	*10/182 (5.5%)*	*21/161 (13.0%)*	*0.01*	*0.37 (0.17–0.81)*
Time to pregnancy from inclusion				
Time to first positive p-hCG (in months), mean (SD)	2.5 (2.1)	3.6 (2.8)	<0.01	
Time to first ongoing pregnancy (in months), mean (SD)	3.7 (3.8)	4.3 (2.6)	<0.01	
Time to first live birth (in months), mean (SD)	11.0 (4.0)	11.5 (2.9)	<0.01	

P-value, odds ratio (OR) and 95% CI correspond to tests for difference between the two treatment groups using Cochran–Mantel–Haenszel tests. The tests are performed controlling for the stratification variables (IVF clinic, age group and fertilization procedure (IVF/ICSI)). For continuous variables, the test is equivalent to van Elteren's extension of the Wilcoxon rank-sum test. *Until first pregnancy/ongoing pregnancy/live birth and includes spontaneous pregnancies after randomization. Twins are counted as one live birth.

were transferred. More women had DET in the frozen–thaw cycles than in the fresh cycle and the mean number of Day-2 embryos transferred in all FET cycles was 1.5 (SD 0.5) in both groups (Table III). The median number of FET cycles derived from one oocyte retrieval was 1 (range 1–7). Finally, endometrium preparation with estradiol was used in more FET cycles in the antagonist group 71/275 (25.8%) compared to 48/288 (16.7%) in the agonist group (OR: 1.60; 95% CI: 1.06–2.43; $P = 0.02$) (Table III).

Women in the antagonist group were more likely to have a live birth following their first FET cycle 44/534 (8.2%) compared to the agonist group 25/516 (4.8%) (OR: 1.77; 95% CI: 1.07–2.74; $P = 0.03$). However, this difference disappeared after inclusion of additional FET cycles (Table IV). The LBRs per FET cycle with embryos thawed were higher in the antagonist group compared with the agonist group 64/330 (19.4%) and 43/355 (12.1%) (OR: 1.74; 95% CI: 1.14–2.66; $P = 0.01$), respectively. Of all FET cycles with a frozen–thawed embryo transfer, a total of 64/275 (23.3%) cycles resulted in live births in the antagonist group versus 42/288 (14.6%) in the agonist group (OR: 1.75; 95% CI: 1.13–2.71; $P = 0.01$) (Table IV).

In a subsequent regression analyses with embryo transfer day and endometrium preparation as the independent variables, we found no impact on the total LBRs from FET for embryo transfer day (OR: 0.80; 95% CI 0.38–1.66; $P = 0.55$). But for endometrium preparation, we found a significant effect (OR = 0.53; 95% CI: 0.29–0.98; $P = 0.04$) (data not shown in table). Substituted FET cycles were correlated with lower total FET LBRs. Overall the number of women with a second live birth was $n = 11$ and $n = 20$ for GnRH-antagonist and GnRH-agonist, respectively, when viewing complete cycles (fresh and frozen–thawed cycles from the first oocyte retrieval).

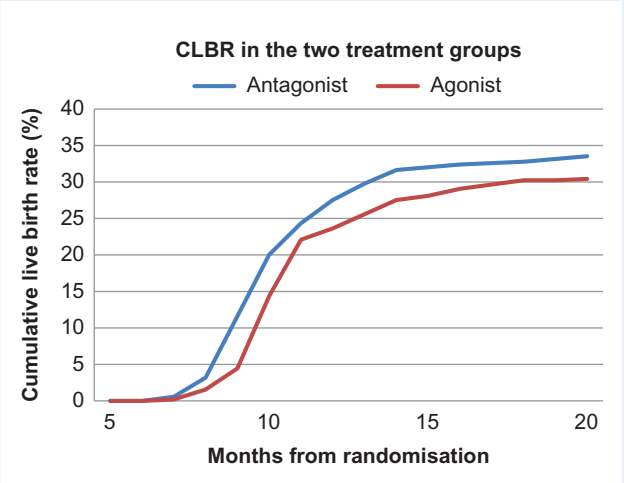

Figure 2 Cumulative live birth rates (CLBRs) in the two treatment groups GnRH-antagonist versus GnRH-agonist, including all first deliveries during a minimum of 2-year follow-up. A competing risk method has been used to test for difference between the treatment groups, Gray's test $P = 0.18$.

Prognostic covariate analyses

In the pooled Cox proportional hazard model for both the antagonist and agonist groups, the following independent variables had a significant influence on the CLBR; women with BMI >30 kg/m^2 had a lower chance of a live birth (adjusted hazard ratio (aHR): 0.62; 95% CI: 0.40–0.96; $P = 0.03$). Women with 10–15 and >15 retrieved oocytes had an increased chance of live birth (aHR: 1.87; 95% CI: 1.13–3.08; $P = 0.01$ and aHR: 2.15; 95% CI: 1.24–3.71; $P < 0.01$, respectively) (Table V). Treatment protocol, female age and primary cause of infertility did not show any significance in the model, nor did female age, as a continuous variable, show any correlation with the CLBR (not shown in table). However, a significant interaction between age and BMI was found ($P < 0.01$), indicating that BMI does not have the same influence over different age groups. In the analysis of maximum likelihood estimates for the individual treatment groups, no independent variables had a significant influence on the model for the antagonist group, whereas for the agonist group BMI >30 kg/m^2 showed a lower chance of live birth (aHR: 0.36; 95% CI: 0.17–0.78; $P = 0.01$) (not shown in table).

Table III Treatment characteristics of subsequent FET cycles in women allocated to either GnRH-antagonist or GnRH-agonist treatment for first fresh ART cycle.

FET treatments	Antagonist group ($n = 534$)	Agonist group ($n = 516$)	*P*-value	OR (95% CI)
Patients with frozen embryos after fresh cycle of all allocated, *n*/*n* (%)	278/534 (52.1%)	274/516 (53.1%)	0.76	0.96 (0.75–1.23)
Number of patients who continued with FET cycles, *n* (%)	229/534 (42.9%)	230/516 (44.6%)	0.61	0.94 (0.73–1.20)
Total number of FET cycles where embryos where thawed, *n*	330	355		
Total number of FET cycles with transfer, *n*/*n* (%)	275/330 (83.3%)	288/355 (81.1%)	0.48	1.15 (0.78–1.70)
Blastocyst transfer, *n*/*n* (%)	35/275 (12.7%)	30/288 (10.4%)	0.20	1.42 (0.83–2.44)
Day-2 embryo transfer, *n*/*n* (%)	240/275 (87.3%)	258/288 (89.6%)	0.20	0.70 (0.41–1.21)
Mean number of blastocysts transferred in FET cycles, mean (SD)	1.1 (0.2)	1.0 (0.2)	0.71	
Mean number of Day-2 embryos transferred in FET cycles, mean (SD)	1.5 (0.5)	1.5 (0.5)	0.66	
DET, *n*/*n* (%)	123/240 (51.3%)	127/258 (49.2%)	0.67	1.08 (0.76–1.54)
SET, *n*/*n* (%)	117/240 (48.8%)	131/258 (50.8%)	0.67	0.92 (0.65–1.32)
Number of stimulated cycles (endometrium preparation), *n*/*n* (%)	71/275 (25.8%)	48/288 (16.7%)	0.02	1.60 (1.06–2.43)

P-value, OR and 95% CI correspond to tests for difference between the two groups using Cochran–Mantel–Haenszel tests. The tests are performed controlling for the stratification variables (IVF clinic, age group and fertilization procedure (IVF/ICSI)). DET, double embryo transfer; SET, single embryo transfer.

Table IV Total reproductive outcome of subsequent FET cycles in women allocated to either GnRH-antagonist or GnRH-agonist treatment for first fresh ART cycle.

	Reproductive outcome	Antagonist group ($n = 534$)	Agonist group ($n = 516$)	*P*-value	OR (95% CI)
FET 1	Positive p-hCG, *n* (%)	68 (12.7%)	45 (8.7%)	0.03	1.54 (1.04–2.30)
	Ongoing pregnancy, *n* (%)	45 (8.4%)	27 (5.2%)	0.04	1.67 (1.02–2.74)
	Abortion <12 weeks/>12 weeks of gestation, *n* (%)/*n* (%)	24 (4.5%)/0	18 (3.5%)/1 (0.2%)	NS	
	Live birth, *n* (%)	44 (8.2%)	25 (4.8%)	0.03	1.77 (1.07–2.94)
FET 2	Positive p-hCG, *n* (%)	20 (3.7%)	21 (4.1%)	0.75	0.91 (0.49–1.69)
	Ongoing pregnancy, *n* (%)	16 (3.0%)	18 (3.5%)	0.67	0.86 (0.43–1.71)
	Abortion <12 weeks/>12 weeks of gestation, *n* (%)/*n* (%)	6 (1.1%)/0	6 (1.2%)/0	NS	
	Live birth, *n* (%)	14 (2.6%)	14 (2.7%)	0.94	0.97 (0.46–2.06)
≥FET 3	Positive p-hCG, *n* (%)	10 (1.9%)	12 (2.3%)	0.62	0.81 (0.35–1.88)
	Ongoing pregnancy, *n* (%)	8 (1.5%)	9 (1.7%)	0.77	0.86 (0.33–2.26)
	Abortion <12 weeks/>12 weeks of gestation, *n* (%)/*n* (%)	2 (0.4%)/0	3 (0.6%)/1 (0.2%)	NS	
	Live birth, *n* (%)	5 (0.7%)	5 (1.0%)	0.96	0.97 (0.28–3.38)
Total FET cycles	Positive p-hCG per all randomized, *n* (%)	98/534 (18.4%)	78/516 (15.1%)	0.16	1.26 (0.91–1.75)
	Ongoing pregnancy per all randomized, *n* (%)	69/534 (12.9%)	54/516 (10.5%)	0.22	1.27 (0.87–1.85)
	Live birth per all randomized, *n* (%)	63/534 (11.8%)	43/516 (8.3%)	0.06	1.48 (0.98–2.23)
	Live birth per FET cycle with embryo thawing, *n*/*n* (%)	64/330 (19.4%)	43/355 (12.1%)	0.01	1.74 (1.14–2.66)
	Live birth per FET cycle with embryo transfer, *n*/*n* (%)	64/275 (23.3%)	42/288 (14.6%)	0.01	1.75 (1.13–2.71)

P-value, OR and 95% CI correspond to tests for difference between the two groups using Cochran–Mantel–Haenszel tests. The tests are performed controlling for the stratification variables (IVF clinic, age group and fertilization procedure (IVF/ICSI)). Twins are counted as one live birth. All pregnancies are counted in this table, showing the total reproductive outcome, thus patients can be represented more than once. FET, frozen embryo transfer; NS, not significant.

Female age and CLBR

Stratification according to female age showed an impact of age on the CLBR in the antagonist group, varying from 21/93 (22.6%) in the oldest age group >36 years, 92/278 (33.1%) in the age group 30–36 years and 69/163 (42.3%) in the youngest age group <30 years ($P < 0.01$) (Fig. 3), but showed no effect in the agonist group, where the corresponding figures were 26/86 (30.2%), 85/287 (29.6%) and 50/143 (35.0%) in the agonist group ($P = 0.52$). When comparing CLBR in each separate age stratum between the antagonist and agonist groups no differences were observed.

BMI and CLBR

Stratification according to BMI showed no impact of BMI on the CLBR in the antagonist group, varying from 44/146 (30.2%) in the overweight women with BMI 25–30 kg/m^2 to 115/313 (36.7%) in the normal BMI group with BMI <25 kg/m^2 ($P = 0.30$) (Fig. 4). In the agonist group, the CLBRs differed significantly between the BMI groups, from 10/83 (12.0%) in the obese women with BMI >30 kg/m^2 to 46/122 (37.7%) in the group of overweight women ($P < 0.01$). When comparing CLBR in each separate BMI stratum between the antagonist and agonist groups, we found a significantly higher CLBR in the obese women treated with the antagonist protocol 30.7% (23/75) compared to 12.0% (10/83) in the agonist protocol ($P = 0.02$).

Number of oocytes and CLBR

Stratification according to number of retrieved oocytes showed an impact on the CLBR in both treatment groups, with the lowest CLBR in the subgroup with 1–3 retrieved oocytes and the highest CLBR in the subgroup with >15 retrieved oocytes, varying from 17/82 (20.7%) to 15/58 (43.1%) in the antagonist group ($P < 0.01$) and from 8/51 (15.7%) to 41/81 (50.6%) in the agonist group ($P < 0.01$) (Fig. 5). When comparing CLBR in each separate oocyte stratum between the antagonist and agonist groups, we found no significant differences.

Diagnosis of infertility and CLBR

Stratification according to the primary cause of infertility showed no impact on the CLBR in either treatment group. The lowest CLBR was found in the subgroup with endometriosis, 3/13 (23.1%) in the antagonist group and 2/13 (15.4%) in the agonist group. The highest CLRBs were found in the subgroup with male infertility in the antagonist group and in the subgroup with tubal factor in the agonist group, 92/229 (40.2%) and 29/68 (42.6%), respectively (Fig. 6).

When comparing CLBR in each separate diagnosis stratum between the antagonist and agonist groups, we found a significantly higher CLBR in couples with male factor in the antagonist group (40.2% versus 30.0%) ($P = 0.03$) while no differences were found for the other diagnoses.

Discussion

The main finding of this study was that the CLBR after the first oocyte retrieval including fresh and all subsequent frozen–thaw cycles were comparable for the GnRH-antagonist and GnRH-agonist groups, with 34.1% and 31.2% achieving at least one live birth. Although fewer

Table V Crude and aHR for cumulative live birth rate (CLBR) of both women treated with GnRH-antagonist and GnRH-agonist treatment ($n = 1050$). Adjustments were made for the following covariates; age, BMI, the number of retrieved oocytes and the primary infertility diagnosis.

Independent covariates	Covariate strata	Crude hazard ratio (95% CI)	*P*-value	aHR** (95% CI)	*P*-value
Treatment protocol	GnRH agonist	1		1	
	GnRH antagonist	1.18 (0.93–1.49)	0.18	1.22 (0.97–1.54)	0.10
Age	<30 years	1		1	
	30–36 years	0.81 (0.63–1.05)	0.11	0.89 (0.68–1.17)	0.39
	>36 years	0.71 (0.48–1.06)	0.09	0.92 (0.61–1.41)	0.71
BMI	<25 kg/m^2	1		1	
	25–30 kg/m^2	0.90 (0.68–1.18)	0.43	0.95 (0.72–1.25)	0.71
	>30 kg/m^2	0.55 (0.36–0.84)	<0.01	0.62 (0.40–0.96)	0.03
Number of retrieved oocytes	1–3 oocytes	1		1	
	4–9 oocytes	1.57 (0.97–2.53)	0.07	1.47 (0.90–2.41)	0.12
	10–15 oocytes	2.00 (1.24–3.25)	<0.01	1.87 (1.13–3.08)	0.01
	>15 oocytes	2.35 (1.40–3.92)	<0.01	2.15 (1.24–3.71)	<0.01
Primary infertility diagnosis	Unexplained	1		1	
	Anovulatory	0.97 (0.59–1.58)	0.89	0.86 (0.52–1.42)	0.54
	Tubal	1.26 (0.84–1.89)	0.26	1.27 (0.84–1.90)	0.25
	Endometriosis	0.57 (0.18–1.80)	0.34	0.54 (0.17–1.70)	0.29
	Other causes	0.65 (0.34–1.24)	0.19	0.74 (0.38–1.45)	0.39
	Male	1.22 (0.91–1.65)	0.19	1.17 (0.86–1.59)	0.31

P-values correspond to tests for difference in a cox regression analysis with cumulative LBR as the outcome (dependent) variable. **Adjusted for the explanatory (independent) variables; treatment group, age group, BMI group, number of oocyte group and diagnosis group. aHR, adjusted hazard ratio.

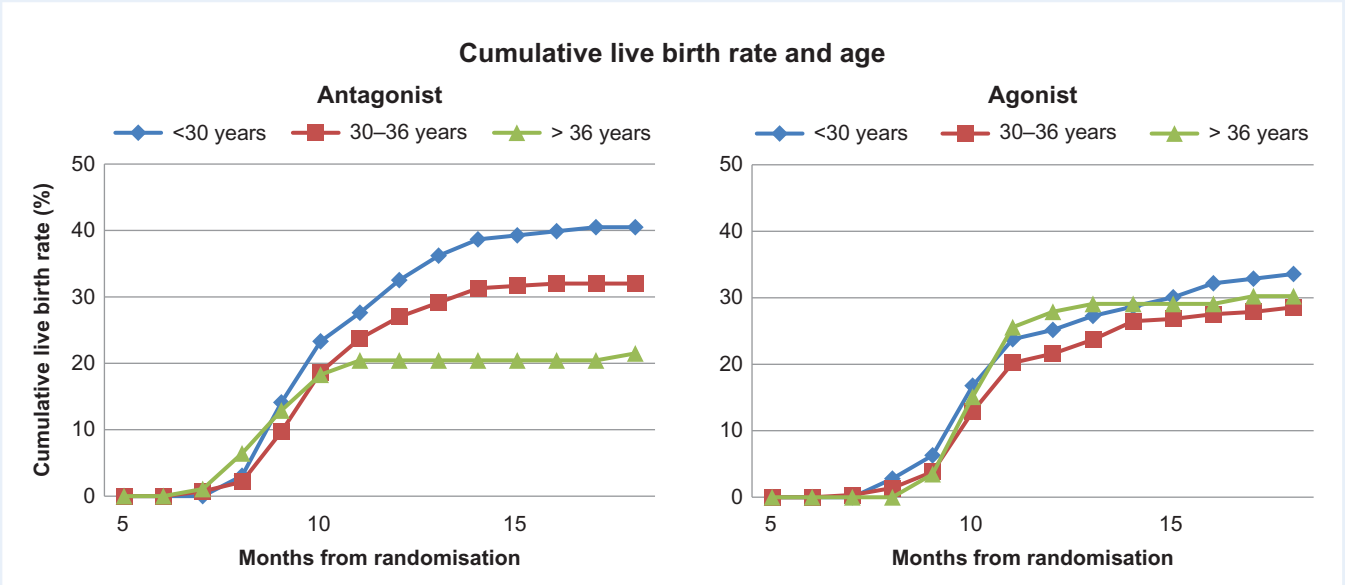

Figure 3 CLBR, stratified for age in three groups <30 years, 30–36 years and >36 years. The results for the GnRH-antagonist group are shown to the left and results for the GnRH-agonist group are shown to the right. The distribution differed significantly in the antagonist group ($P < 0.01$), but not in the agonist group ($P = 0.52$).

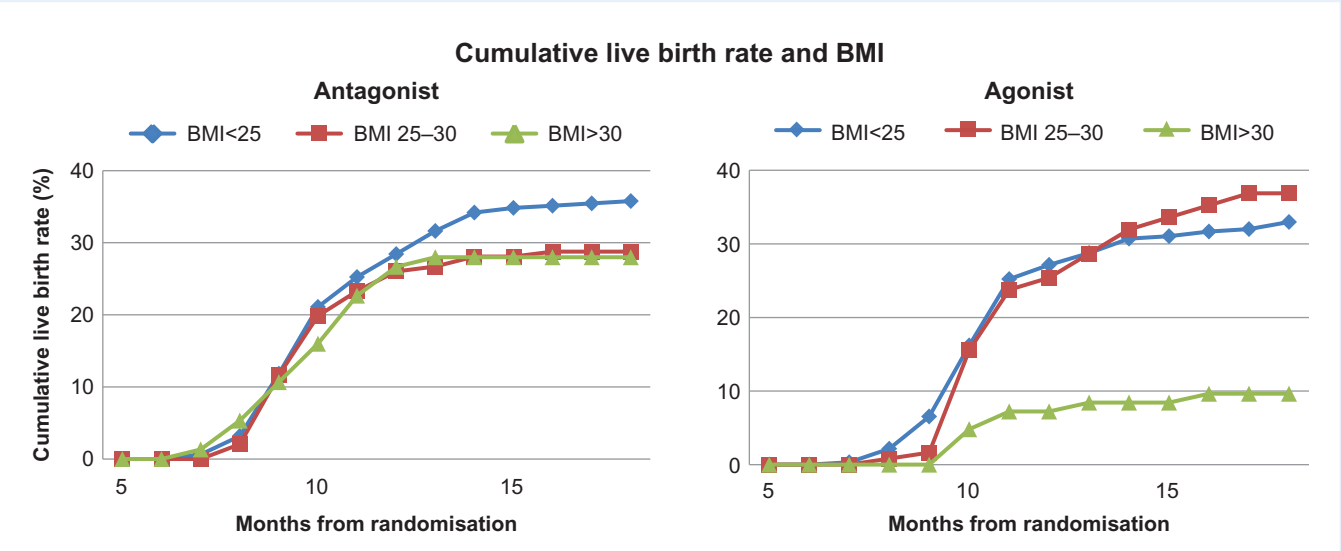

Figure 4 CLBR, stratified for BMI in three groups <25, 25–30 and >30. The results for the GnRH-antagonist group are shown to the left and results for the GnRH-agonist group are shown to the right. The distribution in the antagonist group were similar ($P = 0.30$), but differed significantly in the agonist group ($P < 0.01$).

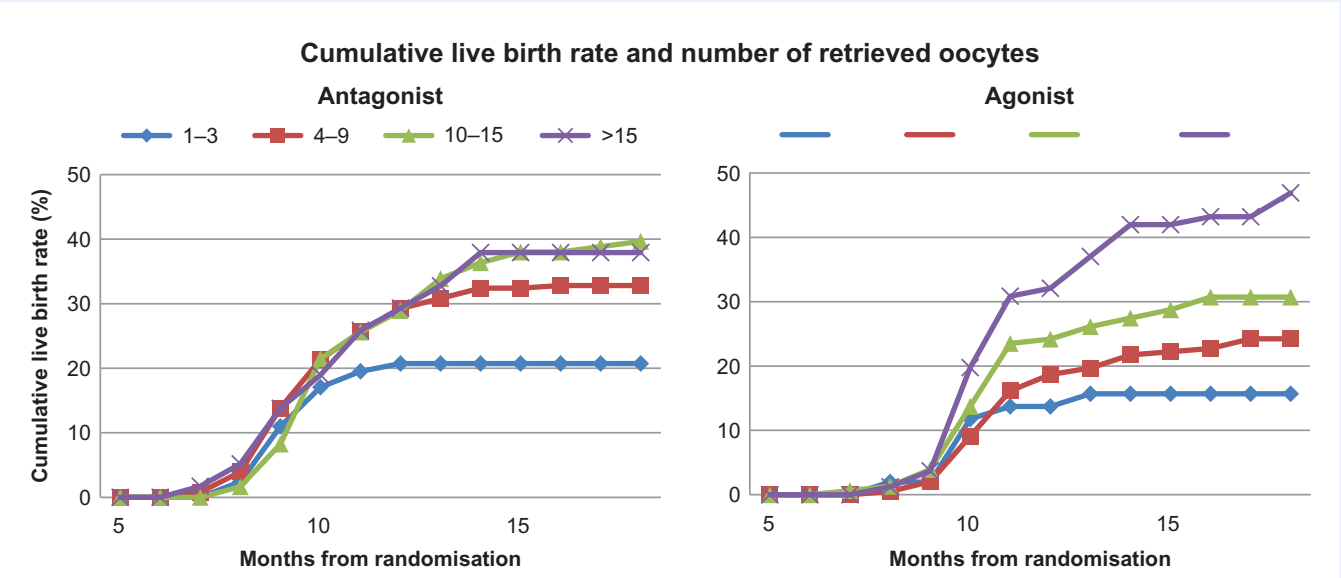

Figure 5 CLBRs, stratified for number of retrieved oocytes in four groups 1–3, 4–9, 10–15 and >15 oocytes. The results for the GnRH-antagonist group are shown to the left and results for the GnRH-agonist group are shown to the right. The distribution differed significantly in both the antagonist group ($P < 0.01$) and the agonist group ($P < 0.01$).

oocytes were retrieved initially in the GnRH-antagonist group compared to the GnRH-agonist group (8.4 versus 10.1, $P < 0.01$) (Toftager *et al.*, 2016), this did not influence the CLBR. Time to pregnancy and live birth was significantly shorter in the GnRH-antagonist group compared to the agonist group, which correlates well with the duration of the GnRH-antagonist treatment being shorter.

In the FET cycles, significantly higher LBRs per embryo thawing (19.4% versus 12.1%) and per frozen–thawed embryo transfer (23.3% versus 14.6%) were seen in the antagonist group compared to the agonist group. The GnRH-agonist protocol also seemed to be less effective in obese women.

Strengths and limitations

This is to our knowledge the first RCT comparing CLBR in GnRH-antagonist and agonist treatment. Furthermore, we included a relatively

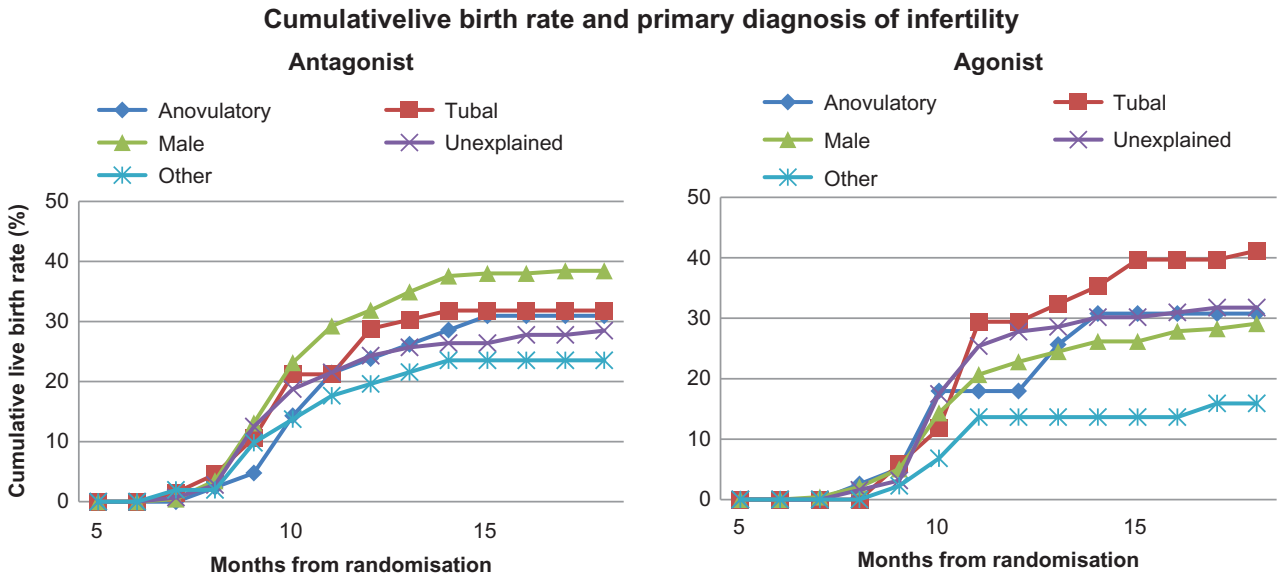

Figure 6 CLBRs, stratified by primary diagnosis of infertility in six groups. The results for the GnRH-antagonist group are shown to the left and results for the GnRH-agonist group are shown to the right. The distribution were similar in both the antagonist group ($P = 0.14$) and the agonist group ($P = 1.3$).

unselected population of women referred for their first ART cycle within the age range of 20–39 years. Hence, these results can be extrapolated to the general population seeking ART treatment within the above age range. All analyses were performed on intention-to-treat based principles, and the results were reported according to the CONSORT statements. As previous described, the two study groups were similar at baseline making risk of bias unlikely (Toftager *et al.*, 2016). The duration of the study period may be a limitation with new methods being developed during the trial, such as blastocyst culture and vitrification that were introduced halfway through the trial period; however, we consider the effect to be similar in both treatment arms and thus less likely to cause bias. The duration of the trial allowed women to use all their cryopreserved embryos within the trial period, except for only 10 women with remaining frozen embryos and no delivery at the end of the trial.

We performed a thorough follow-up with complete information on all patients and none of the patients were lost to follow-up. It is, however, important to note that the study was powered to detect a difference in severe OHSS and not in cumulative LBR.

Previous studies

The presented CLBR in this study was based on a large RCT where the LBRs from the first fresh ART cycle including spontaneously conceived pregnancies were similar: (22.8%) in the antagonist group and (23.8%) in the agonist group (OR: 0.95; $P = 0.70$). The shares of women with cryopreserved embryos were similar in the antagonist and agonist group: (52.1%) versus (53.1%), and there were no difference in mean number of cryopreserved embryos (3.2 versus 3.5). (Toftager *et al.*, 2016).

Mainly, retrospective cohort and large-scale retrospective registry studies have addressed the CLBR, but none have distinguished between different treatment protocols. A Belgian retrospective national cohort study including 12 869 patients who started first ART treatment with a minimum of 1 year follow-up found the CLBR after one complete ART cycle to be 29.6%; although slightly lower, this is in accordance with our results (De Neubourg *et al.*, 2016).

A UK population-based observational cohort study of 178 898 women with CLBR reported for two consecutive decades (McLernon *et al.*, 2016). The CLBR after one complete cycle was 19.1% in the years 1992–1998, increasing to 28.5% in the years 1999–2007. In a retrospective cohort study of 6164 patients undergoing 14 248 cycles in Boston, MA, the LBR after first fresh ART cycle was 24.5%. The CLBR increased to 51% after six cycles of either fresh or frozen–thawed embryo transfers, when the conservative approach was used. The authors did not present CLBR for the first complete cycle (Malizia *et al.*, 2009).

Cumulative LBRs

A highly relevant discussion regarding uniform criteria for presenting CLBR was recently published by Maheshwari *et al.*, 2015. Several different methods have been used to estimate the CLBR, some include all live births from one ART cycle (Li *et al.*, 2014), while others include only first live births in the numerator depending on when the woman is decided to be censored (Thurin-Kjellberg *et al.*, 2009, Luke *et al.*, 2012). There is no consensus on the preferred method and there are advantages and limitations to both approaches. Since few women delivered more than once based on their first oocyte retrieval in the current trial, we considered that women should be censored after their first live birth, hence only including the first live birth in the numerator. Previously used denominators could either be all women referred for IVF treatment, all who initiated ovarian stimulation or all who had undergone oocyte retrieval. To make the results relevant to all women referred for their first ART treatment, we used all women referred for ART as the denominator. Further, it is important to

determine the number of IVF treatments over which the CLBR will be estimated and the time period over which treatment is provided. In this case, we have defined the number of treatments as one complete cycle including all fresh and frozen–thawed embryo transfer cycles from one oocyte retrieval, and the time period was 2–5 years. Different methods of statistical analyses have also been used in the past; crude rates, conditional rates, life-table analysis, both optimistic and conservative estimates and competing risk analysis. Classic life-table analyses are known to overestimate the CLBR as in the optimistic Kaplan–Meier method, it is assumed that women who do not return for subsequent FER cycles have the same chance of a pregnancy resulting in a live birth as those who returned for treatment. An alternative approach is the conservative method assuming that patients who do not return for subsequent FET cycles had no chance of a pregnancy resulting in a live birth. In our case, however, only patients with cryopreserved embryos were eligible to return for treatment. This design made the competing risk method relevant, where spontaneous pregnancy and use of all frozen embryos is a competing risk to the outcome of live birth after treatment.

Effect of covariates on CLBR

The evaluation of prognostic factors showed that the CLBR was higher for women younger than 30 years of age and decreased with increasing age when using the GnRH-antagonist protocol. This was not seen in the GnRH-agonist protocol, where the CLBR remained constant, around 30% for the different age groups. Unexpectedly, age had no influence on the CLBR in the pooled Cox regression, including both GnRH-antagonist and GnRH agonist, and using age as a continuous independent variable showed similar results. This finding may be due to all women being in a rather narrow age range with no women being older than 40 years of age. Furthermore, age showed an impact on CLBR in the antagonist group, but not in the agonist group. The long agonist protocol may have a positive impact on the CLBR in women above 36 years of age, due to the robustness of the agonist protocol ensuring a similar follicular recruitment and minimizing follicular asynchrony. The results suggest the use of the short protocol for women below 36 years of age, and especially women at risk of OHSS and using the long protocol for women above 36 years of age (Lainas *et al.*, 2010, Al-Inany *et al.*, 2016, Toftager *et al.*, 2016).

Intriguingly, our results showed a significant reduction in the CLBR for obese women when the long agonist protocol was used, and further studies are needed to clarify potential benefits of the antagonist protocol in obese women. The majority of previous studies do not distinguish between treatment protocols, except one retrospective study of 463 women by Marci *et al.*, 2012. In both the antagonist and agonist groups, they found the number of clinical pregnancies to be higher in patients with BMI <25 kg/m^2 compared to patients with BMI >25 kg/m^2 (Marci *et al.*, 2012). The results from a large American SART registry study, including 45 163 ART embryo transfers, suggested an impaired embryo quality in obese women (Luke *et al.*, 2011) and other studies have suggested that infertile have an exaggerated inflammatory immune responses (Christiansen, 2013). This combined with the knowledge that obese patients are in a chronic inflammatory state, will further increase this inflammatory response, increasing the known risks for adverse reproductive outcomes. However, this does not explain the difference between the protocol arms found in the present study.

All subgroup analyses for covariate's effect on the CLBR were based on *post hoc* analyses with multiple strata and should be interpreted with caution. However, it would be interesting to investigate these secondary findings further.

Conclusion

This study is the first RCT comparing CLBRs in short GnRH-antagonist protocol with long GnRH-agonist protocol. After one complete cycle, we found comparable CLBRs in both groups, despite significantly more oocytes were retrieved in the long agonist protocol. Furthermore, time-to-pregnancy was shorter in the GnRH-antagonist group and the GnRH-agonist protocol was less effective in obese women. The GnRH-antagonist protocol is as effective as the GnRH-agonist protocol with lower OHSS risk and should be the first choice of treatment for ART. Subgroups such as women older than 36 years may still benefit from the GnRH-agonist protocol.

The results provide us with a tool to inform our patients of the prognosis after the first oocyte retrieval with GnRH-antagonist and GnRH-agonist protocols.

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Authors' roles

M.T.: design of the study, acquisition of data, analysis and interpretation of data, drafting the article. T.B.: conception and design of the study, acquisition of data, revising the article. J.B., L.P., A.Z., K.L.: acquisition of data, revising the article. L.N.: revising the article, analysis and interpretation of data. A.P.: acquisition of data, analysis and interpretation of data, revising the article. All authors approved the final version of the manuscript.

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Conflict of interest

The funders had no influence on the data collection, analyses or conclusions of the study. There are no conflict of interests to declare.

References

Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev* 2016;**4**:CD001750.

Christiansen OB. Reproductive immunology. *Mol Immunol* 2013;**55**:8–15.

de Mouzon J, Goossens V, Bhattacharya S, Castilla JA, Ferraretti AP, Korsak V, Kupka M, Nygren KG, Nyboe Andersen A, European

Ivf-monitoring Consortium ftESoHR *et al*. Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE. *Hum Reprod* 2010;**25**:1851–1862.

De Neubourg D, Bogaerts K, Blockeel C, Coetsier T, Delvigne A, Devreker F, Dubois M, Gillain N, Gordts S, Wyns C. How do cumulative live birth rates and cumulative multiple live birth rates over complete courses of assisted reproductive technology treatment per woman compare among registries? *Hum Reprod* 2016;**31**:93–99.

Jones HW Jr, Jones D, Kolm P. Cryopreservation: a simplified method of evaluation. *Hum Reprod* 1997;**12**:548–553.

Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, Kolibianakis EM. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). *Hum Reprod* 2010;**25**:683–689.

Li HW, Lee VC, Lau EY, Yeung WS, Ho PC, Ng EH. Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. *J Assist Reprod Genet* 2014;**31**:205–211.

Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R, SART Writing Group. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod* 2011;**26**:245–252.

Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, Lobo RA, Leach RE, Stern JE. Cumulative birth rates with linked assisted reproductive technology cycles. *N Engl J Med* 2012;**366**:2483–2491.

Maheshwari A, McLernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? *Hum Reprod* 2015;**30**:2703–2707.

Malizia BA, Hacker MR, Penzias AS. Cumulative live-birth rates after in vitro fertilization. *N Engl J Med* 2009;**360**:236–243.

Marci R, Lisi F, Soave I, Lo Monte G, Patella A, Caserta D, Moscarini M. Ovarian stimulation in women with high and normal body mass index: GnRH agonist versus GnRH antagonist. *Gynecol Endocrinol* 2012;**28**:792–795.

McLernon DJ, Maheshwari A, Lee AJ, Bhattacharya S. Cumulative live birth rates after one or more complete cycles of IVF: a population-based study of linked cycle data from 178,898 women. *Hum Reprod* 2016;**31**:572–581.

Moragianni VA, Penzias AS. Cumulative live-birth rates after assisted reproductive technology. *Curr Opin Obstet Gynecol* 2010;**22**:189–192.

Roque M, Lattes K, Serra S, Sola I, Geber S, Carreras R, Checa MA. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. *Fertil Steril* 2013;**99**:156–162.

Thurin-Kjellberg A, Olivius C, Bergh C. Cumulative live-birth rates in a trial of single-embryo or double-embryo transfer. *N Engl J Med* 2009;**361**:1812–1813.

Toftager M, Bogstad J, Bryndorf T, Lossl K, Roskaer J, Holland T, Praetorius L, Zedeler A, Nilas L, Pinborg A. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. *Hum Reprod* 2016;**31**:1253–1264.

Viardot-Foucault V, Tai BC, Chen ZJ, Lim GH, Loh SF, Tan HH, Nadarajah S, Chan JK. Estimating cumulative live-birth rates after IVF treatment with Kaplan-Meier and competing risk methods. *Eur J Obstet Gynecol Reprod Biol* 2015;**192**:41–46.