Conditional and cumulative live birth rates after blastocyst transfer

Høyer, Sidse; Kesmodel, Ulrik Schiøler; Aagaard, Jørn

Published in:
European Journal of Obstetrics and Gynecology and Reproductive Biology

DOI (link to publication from Publisher):
10.1016/j.ejogrb.2021.03.037

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

European Journal of Obstetrics & Gynecology and Reproductive Biology 261 (2021) 46–51

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Conditional and cumulative live birth rates after blastocyst transfer

Sidse Høyer[a,*], Ulrik Schiøler Kesmodel[a,b], Jørn Aagaard[a]

[a] Aagaard Fertility Clinic, Hedeager, 35 8200, Aarhus, Denmark
[b] Department of Obstetrics and Gynecology, Aalborg University Hospital, 9000, Aalborg, Denmark

ARTICLE INFO

Article history:
Received 12 January 2021
Received in revised form 24 March 2021
Accepted 28 March 2021

Keywords:
Cumulative live birth rate
Live birth rate
IVF
Blastocyst transfer

ABSTRACT

Objective: We aimed to investigate live birth rate (LBR), cumulative live birth rate (CLBR) for consecutive fresh and frozen-thawed in vitro fertilization (IVF) cycles, and CLBR after an entire IVF programme involving multiple ovarian stimulations using blastocyst transfer only.
Study design: From January 1 st 2014 to December 31 st 2018, we included women aged 18–45 years who initiated IVF or intracytoplasmic sperm injection at Aagaard Fertility Clinic, Denmark. The primary outcome was live birth, and secondary outcomes were a positive hCG blood test and ongoing pregnancy confirmed by ultrasonography. All proportions were estimated for initiated and transferred cycles with 95 % confidence intervals (CI). We used a conservative strategy, assuming that none of the women who did not return for further treatments had a live birth.
Results: 871 women contributed 2236 initiated/1670 transferred fresh and/or frozen-thawed cycles. LBRs for first fresh cycles were 22.8 % (95 %-CI: 19.8–26.0) and 35.7 % (95 %-CI: 31.4–40.2) for initiated and transferred cycles, respectively. LBRs for first frozen-thawed cycles were 30.6 % (95 %-CI: 26.4–35.1) and 31.7 % (95 %-CI: 27.4–36.3) for initiated and transferred cycles, respectively. CLBRs for consecutive cycles were 18.2 % (95 %-CI: 16.2–20.3) for fresh initiated cycles, 29.7 % (95 %-CI: 26.6–32.9) for fresh transferred cycles, 25.5 % (95 %-CI: 22.6–28.5) for frozen-thawed initiated cycles, and 26.4 % (95 %-CI: 23.5–29.6) for frozen-thawed transferred cycles. For 436 women who contributed with an entire IVF programme we found a CLBR of 64.0 % (95 %-CI: 59.3–68.5).
Conclusion: Compared to other studies of CLBR after multiple ovarian stimulations using cleavage stage transfer, our study presents a considerable effect in the IVF success rate when using blastocyst transfer only. In a clinical setting, transfer of blastocysts seems to be a viable method.

Introduction

Globally, infertility is estimated to affect up to 15 % of couples of reproductive age [1,2]. In developed countries it has been estimated that an average of 56 % of couples seek medical care for their infertility problems [1], and even if substantially fewer end up receiving treatment, more than a half million babies are born each year by use of assisted reproductive technology (ART) [3]. The most frequent fertilization techniques are in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) [4]. Although there has been a decrease in the number of embryos transferred per cycle, one study indicates an improved cumulative IVF success rate over the last decade [5].

Previously, most IVF studies have reported a 'per-cycle' probability (sometimes referred to as 'conditional rate') of live birth in fresh and frozen-thawed cycles, respectively [6,7]. However, from a patient perspective it is more relevant to know the cumulative chance of having a child by continuing treatment over an entire IVF programme involving all fresh and frozen-thawed IVF treatments [7,8]. Therefore, recent studies have evaluated the cumulative live birth rate (CLBR) rather than the conditional live birth rate (LBR). Several studies estimated CLBR from a single ovarian stimulation [9–11] or utilized embryos at cleavage stage (day 2 or 3 transfer) instead of embryos at the blastocyst stage (day 5 or 6 transfer) [8,12,13]. Although many fertility clinics still perform cleavage stage embryo transfer to avoid cycle cancellation in case of few available embryos, several studies have shown significantly higher LBR after blastocyst transfer rather than cleavage stage transfer [14,15].

The aim of this study was to investigate conditional LBR, CLBRs for consecutive fresh and frozen-thawed IVF cycles, and CLBR after multiple ovarian stimulations using blastocyst transfer at a private Danish fertility clinic.

* Corresponding author.
E-mail addresses: sidse.hoeyer@hotmail.com (S. Høyer), u.kesmodel@rn.dk (U.S. Kesmodel), jaagaard03@gmail.com (J. Aagaard).

https://doi.org/10.1016/j.ejogrb.2021.03.037

Methods

Study population

This prospective cohort study included women referred for ART treatment at Aagaard Fertility Clinic in Aarhus, Denmark. All women had fresh and/or frozen-thawed IVF (including ICSI) cycles. Women were aged 18–45 years at the time of their first treatment and enrolled regardless of the cause of infertility. Initiated treatments were recorded over a 5-year period from January 1 st 2014 to December 31 st 2018, and all women were followed until the end of their treatment, delivery, or the end of the study period (hence, follow up time may proceed into 2019). Exclusion criteria (Fig. 1) were: >2 embryos transferred, protocols with preimplantation genetic testing (PGT), or conversion within a cycle from intrauterine insemination (IUI) to IVF. As most women are offered/buy IVF cycles in packages of three, fresh IVF cycles beyond the 3rd cycle were excluded (cycles 1–3 included). In case of dual stimulation with two oocyte aspirations in one cycle, only results of the first aspiration were included. For the entire IVF programme, we excluded women who re-enrolled for treatment of a second child (IVF cycles for the first child included).

Protocols

All women who received cycle transfer had day 5 or day 6 transfer of embryos. Of all fresh embryo transfers, the majority had short antagonist protocols (97.2 %), whereas few had long agonist protocols (2.8 %). Additional embryos were frozen and cryopreserved using standardized methods at day 5 or 6. A later frozen-thawed embryo transfer (FET) was performed in either natural cycle or estrogen-substituted cycles. Of 1670 cycles, 1437 (86.0 %) were single embryo transfer (SET) and 233 (14.0 %) were double embryo transfer (DET). Homologous semen was used in 1381 cycles (82.7 %), whereas donor semen was used in 289 cycles (17.3 %). The reasons for use of donor semen were single marital status/female partner (83.7 %) or severe male infertility (16.3 %). There were no criteria for use of blastocysts from one complete cycle (all available blastocysts from one fresh cycle including eventual frozen-thawed cycles) before proceeding to the next ovarian stimulation.

Reproductive outcomes

The primary outcome was delivery of a living child. Live birth was confirmed by personal follow-up. In case of no response, women were contacted by email or telephone at least two times, whereafter non-responders were categorized as lost to follow-up. Secondary outcomes were a positive hCG at two weeks after embryo transfer and an ongoing pregnancy at gestational week 7–9. The hCG test was defined positive if hCG > 10 IU/L, whereas ongoing pregnancy was confirmed by heartbeat using ultrasonography.

Statistics

Descriptive statistics were computed for women initiating their first fresh IVF cycle. Baseline characteristics included age ($\leq$ 30, 31–35, 36–40 and $\geq$ 41 years), body mass index (BMI) (continuous), number of cigarettes per day (continuous), and number of units of alcohol consumed (continuous). For each cycle-specific fresh and frozen-thawed cycle, we estimated conditional rates of positive hCG, ongoing pregnancy and live birth for both initiated and transferred treatments. Also, cumulative rates of all reproductive outcomes were estimated for consecutive fresh and frozen-thawed cycles, respectively. Women contributed with an entire IVF programme if they had a live birth (irrespective of number of cycles) or three ovarian stimulations including three fresh IVF cycles and all additional frozen-thawed cycles. Cumulative rates of all reproductive outcomes were calculated using women as the denominator. Once a woman contributed with three ovarian stimulations or a live birth, she did not contribute further to the cumulative rates estimated for the entire IVF programme. All proportions were evaluated with 95 % confidence interval (CI). For all cumulative rates, we used the conservative strategy, assuming that none of the women who did not return for further treatments had a live birth. All analyses were performed using Stata software version 14.0.

Results

Characteristics of study population and protocols

In total, 871 women contributed 2236 initiated fresh and/or frozen-thawed cycles, irrespective of cycle number. Of those cycles, 1376 (61.5 %) were fresh IVF cycles and 860 (38.5 %) were frozen-thawed cycles (Fig. 1). For transferred cycles only, 842 (50.4 %) and 828 (49.6 %) were fresh and FET cycles, respectively. For the 534 fresh IVF cycles without embryo transfer, the reasons were a freeze all strategy (45.7 %), no follicular development (1.9 %), no oocytes at

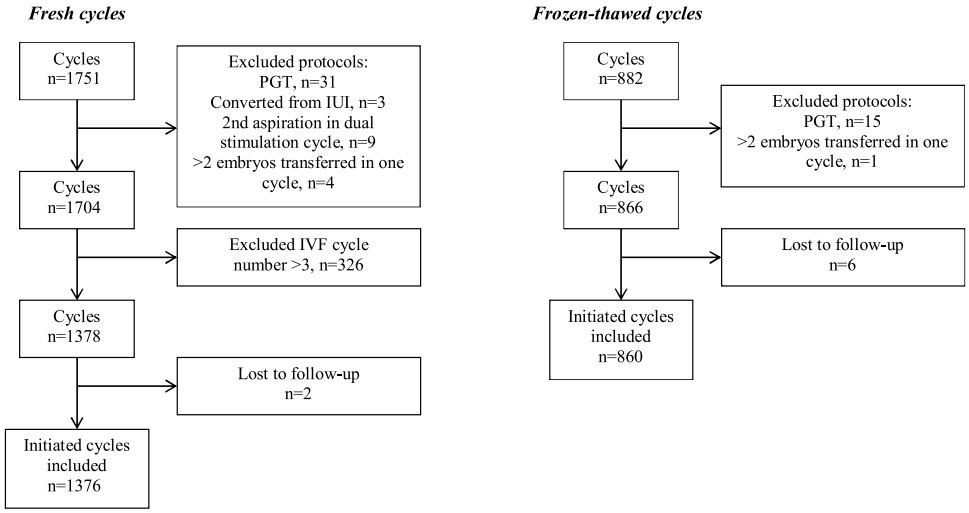

Fig. 1. Flow chart of included IVF cycles, Denmark, 2014-2018.

aspiration (6.0 %), no fertilization (15.2 %), no blastocyst for transfer (30.3 %), or other complications e.g. insufficient endometrial thickness, spontaneous bleeding, or risk of ovarian hyperstimulation (0.9 %). For the 32 frozen-thawed cycles without embryo transfer, the reasons were no blastocyst for transfer (84.4 %) or other complications such as insufficient endometrial thickness or spontaneous bleeding (15.6 %). In total, 436 women contributed with an entire IVF programme, and all the women received at least one embryo transfer in the programme.

Within the study period, 742 women initiated their first fresh IVF cycle, while the remaining 129 women only initiated subsequent cycles during the study period, the first cycle being carried out before the pre-defined study period. Of the 742 women, 473 (63.7 %) received embryo transfer within this cycle. The remaining 269 (36.6 %) did not receive embryo transfer due to a freeze all strategy (42.8 %), no follicular development (1.5 %), no oocytes at aspiration (5.2 %), no fertilization (19.0 %), no blastocyst for transfer (30.1 %), or other complications e.g. insufficient endometrial thickness, spontaneous bleeding, or risk of ovarian hyperstimulation (1.5 %). Baseline characteristics of the 742 women can be seen in Table 1. Briefly, the age distribution was 17.4 %, 32.6 %, 29.9 % and 20.1 % for ≤ 30, 31–35, 36–40 and ≥ 41 years, respectively. Younger age was positively associated with receiving embryo transfer, use of homologous semen, and proportion of positive hCG test, confirmed heartbeats, and live births. On the other hand, women of older age had fewer oocytes retrieved and thus, were more likely to proceed to second and third fresh IVF cycle after an unsuccessful first fresh IVF cycle. Other baseline characteristics were comparable across age categories (Table 1).

Reproductive outcome

For women having their first fresh IVF treatment, the conditional live birth rate was 22.8 % (95 %-CI: 19.8–26.0) for initiated cycles and 35.7 % (95 %-CI: 31.4–40.2) for transferred cycles (Table 2). Furthermore, women having their first frozen-thawed embryo treatment had 30.6 % (95 %-CI: 26.4–35.1) and 31.7 % (95 %-CI: 27.4–36.3) per-cycle chance of a live birth for the initiated and transferred cycles, respectively (Table 3). Compared to the first cycles, a decline in LBR was seen in all subsequent cycles. In addition, CLBRs of all initiated cycles were 18.2 % (95 %-CI: 16.2–20.3) and 25.5 % (95 %-CI: 22.6–28.5) for fresh and frozen-thawed cycles, respectively (Table 4). For all transferred cycles, CLBRs were 29.7 % (95 %-CI: 26.6–32.9) for fresh cycles and 26.4 % (95 %-CI: 23.5–29.6) for FET cycles. For the 436 women completing an entire IVF programme, involving up to 3 fresh cycles and all frozen-thawed cycles, a total of 279 women had at least one live birth corresponding to a CLBR of 64.0 % (95 %-CI: 59.3–68.5). Among the 279 women, 177 (63.4 %) had a live birth from embryo transfer in the first fresh cycle, whereas 19.4 %, 5.4 % and 11.8 % had a live birth from embryo transfer in the second fresh cycle, third fresh cycle and any frozen cycle, respectively (data not shown).

Similarly, the highest cumulative rates of positive hCG and confirmed heartbeat were found among women contributing with an entire IVF programme (cumulative rates: 76.1 % (95 %-CI: 71.9–80.1) for a positive hCG and 68.8 % (95 %-CI: 64.2–73.1) for confirmed heartbeat). For conditional estimates, the highest rate of positive hCG was found among the first FET cycles (conditional rate: 50.6 % (95 %-CI: 45.8–55.3)), whereas the highest rate of confirmed heartbeat was found among the first fresh transferred cycles (conditional rate: 40.8 % (95 %-CI: 36.3–45.4)).

Discussion

For conditional rates, we found the highest LBR among the first fresh transferred cycles, followed by the first FET cycles. The decline in LBR in all subsequent cycles is consistent with an accumulation of less fertile women in later cycles. For transferred consecutive cycles, all cumulative reproductive outcomes were slightly higher for fresh cycles compared to FET cycles. This may be explained by several cycles (up to 10 cycles) in the FET analysis compared to maximum three cycles per woman in the fresh IVF analysis. Thus, fresh and frozen-thawed embryo transfers are most likely equal in their success rate. However, when considering initiated treatments, significantly higher CLBR are found among frozen-thawed cycles compared to fresh cycles. Therefore, the awareness of the defined CLBR is important when dealing with these kinds of studies [7]. In our study, all women who initiated an entire IVF programme also had at least one embryo transfer and the chance of a live birth was 64.0 %. Few other studies investigated CLBR for multiple cycles of ovarian stimulations. One prediction model study found a CLBR of 43.0 % over 6 complete cycles [16]. Another retrospective cohort study estimated a CLBR of 54.1 % over

Table 1
Baseline characteristics of 742 women, who initiated first fresh IVF cycle, by age. Denmark 2014-2018.

Characteristics	Total	Female age			
		≤30 years	31–35 years	36–40 years	≥41 years
Number of women, N (%)	742	129 (17.4)	242 (32.6)	222 (29.9)	149 (20.1)
Received embryo transfer (%)	473 (63.7)	91 (70.5)	172 (71.1)	138 (62.2)	72 (48.3)
2 transferred eggs (%)[1]	62 (13.1)	14 (15.4)	18 (10.5)	21 (15.2)	9 (12.5)
Mean number of retrieved eggs	9.0	10.1	9.9	8.8	6.8
Short antagonist protocol (%)	721 (97.2)	126 (97.7)	235 (97.1)	211 (95.1)	149 (100)
Median BMI (IQR)	23.2 (20.8–26.1)	21.6 (20.0–24.2)	23.6 (20.5–27.1)	23.8 (21.5–26.5)	23.1 (21.5–25.7)
BMI missing (%)	393 (53.3)	63 (48.1)	125 (51.0)	116 (51.3)	97 (64.2)
Smoking ≥1 cigarette/day (%)	19 (5.4)	2 (2.9)	8 (6.7)	8 (7.3)	1 (1.8)
Smoking missing (%)	389 (52.4)	60 (46.5)	122 (50.4)	113 (50.9)	94 (63.1)
Median alcohol, drinks/week (IQR)	1 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	1 (0–3)
Alcohol missing (%)	387 (52.2)	60 (46.5)	121 (50.0)	112 (50.5)	94 (63.1)
Semen source, male partner (%)	606 (81.7)	124 (96.1)	213 (88.0)	161 (72.5)	108 (72.5)
Positive hCG (%)	235 (31.7)	57 (44.2)	94 (38.8)	70 (31.5)	14 (9.4)
≥1 heartbeats (%)	193 (26.0)	52 (40.3)	78 (32.2)	50 (22.5)	13 (8.7)
≥1 live births (%)	169 (22.8)	49 (38.0)	70 (28.9)	40 (18.0)	10 (6.7)
Miscarriage (%)	66 (8.9)	8 (6.2)	24 (9.9)	30 (13.5)	4 (2.7)
Started IVF/2. Cycle[2] (%)	375 (50.4)	48 (37.2)	106 (43.8)	115 (51.8)	105 (70.5)
Started IVF/3. Cycle[2] (%)	221 (28.4)	18 (14.0)	47 (19.4)	74 (33.3)	72 (48.4)

[1]Of women who received embryo transfer.
[2]Of women who initiated 1st cycle within the study period.

Table 2
Conditional rates of positive hCG, heartbeat and live birth for fresh IVF cycles, Denmark, 2014-2018.

Initiated treatment	Women (N)	hCG[a] (N)	Heartbeat[b] (N)	Live birth (N)	Proportion (%)	95 % CI (%)
1st fresh cycle	742	235	–	–	31.7	28.3–35.2
		–	193	–	26.0	22.9–29.3
		–	–	169	22.8	19.8–26.0
2nd fresh cycle	398	113	–	–	28.4	24.0–33.1
		–	77	–	19.3	15.6–23.6
		–	–	61	15.3	11.9–19.2
3rd fresh cycle	236	29	–	–	12.3	8.4–17.2
		–	23	–	9.7	6.3–14.3
		–	–	20	8.5	5.3–12.8
Transferred treatment	**Women (N)**	**hCG[a] (N)**	**Heartbeat[b] (N)**	**Live birth (N)**	**Proportion (%)**	**95 % CI (%)**
1st fresh cycle	473	235	–	–	49.7	45.1–54.3
		–	193	–	40.8	36.3–45.4
		–	–	169	35.7	31.4–40.2
2nd fresh cycle	237	113	–	–	47.7	41.2–54.2
		–	77	–	32.5	26.6–38.9
		–	–	61	25.7	20.3–31.8
3rd fresh cycle	132	29	–	–	22.0	15.2–30.0
		–	23	–	17.4	11.4–25.0
		–	–	20	15.2	9.5–22.4

[a] hCG: Positive hCG defined as >10 IU/L.
[b] Heartbeat: Ongoing pregnancy defined as a viable pregnancy at ultrasound at gestational week 7–9.

Table 3
Conditional rates of positive hCG, heartbeat and live birth for frozen-thawed IVF cycles, Denmark, 2014-2018.

Initiated treatment	Women (N)	hCG[a] (N)	Heartbeat[b] (N)	Live birth (N)	Proportion (%)	95 % CI (%)
1st frozen-thawed cycle	457	223	–	–	48.8	44.1–53.5
		–	163	–	35.7	31.3–40.3
		–	–	140	30.6	26.4–35.1
2nd frozen-thawed cycle	219	73	–	–	33.3	27.1–40.0
		–	54	–	24.7	19.1–30.9
		–	–	43	19.6	14.6–25.5
3rd frozen-thawed cycle	90	31	–	–	34.4	24.7–45.2
		–	24	–	26.7	17.9–37.0
		–	–	20	22.2	14.1–32.2
Transferred treatment	**Women (N)**	**hCG[a] (N)**	**Heartbeat[b] (N)**	**Live birth (N)**	**Proportion (%)**	**95 % CI (%)**
1st FET cycle	441	223	–	–	50.6	45.8–55.3
		–	163	–	37.0	32.4–41.7
		–	–	140	31.7	27.4–36.3
2nd FET cycle	209	73	–	–	34.9	28.5–41.8
		–	54	–	25.8	20.0–32.3
		–	–	43	20.6	15.3–26.7
3rd FET cycle	86	31	–	–	36.0	26.0–47.1
		–	24	–	27.9	18.8–38.6
		–	–	20	23.3	14.8–33.6

[a] hCG: Positive hCG defined as >10 IU/L.
[b] Heartbeat: Ongoing pregnancy defined as a viable pregnancy at ultrasound at gestational week 7–9.

7 complete cycles [9]. However, in both studies the majority received cleavage stage embryo transfer (82.0 % (in first complete cycle) and 85.6 % (in all complete cycles), respectively). On the other hand, more studies reported CLBR using blastocyst transfer after a single ovarian stimulation (CLBR ranging from 25.5%–65.3%) [11,17,18], whereas other studies reported similar CLBR but in a freeze all strategy only (CLBR ranging from 55.0%–66.7%) [19–21].

Strengths and limitations

The main strength of our study is the nearly complete follow-up of all relevant fresh and frozen-thawed cycles with <0.5 % lost to follow-up. We considered both initiated and transferred cycles when providing estimates of conditional LBR, consecutive CLBR for fresh and frozen-thawed cycles, and CLBR for an entire IVF programme. Many couples who decide whether or not to begin IVF treatment will consider the costs, complications and emotional distress followed by potentially repeated treatments. Thus, using initiated cycles as the denominator may present the most relevant estimate in a clinical setting [22]. By taking several IVF outcomes into account, our study is comparable to other IVF studies and likewise contributes with further aspects to the research of IVF studies.

In all analyses, we used a conservative strategy, which may have underestimated the CLBR compared to an optimistic strategy, assuming that women who discontinued treatment had the same chance of a live birth as women continuing treatment. However, the optimistic approach has been criticized for overestimating CLBR, which may cause unrealistic information when counseling patients about their IVF success rate [7,23].

Finally, our data did not include information on previous history of ART. It is possible that a fair proportion of women in our population received ART before entering this study (e.g. from public Danish fertility clinics covered by public healthcare).

Table 4
Cumulated rates of positive hCG, heartbeat and live birth, Denmark, 2014-2018.

Treatment	Cycles (N)	hCG[a] (N)	Heartbeat[b] (N)	Live birth (N)	Proportion (%)	95 % CI (%)
All initiated fresh cycles	1376	377	–	–	27.4	25.1–29.8
		–	293	–	21.3	19.2–23.6
		–	–	250	18.2	16.2–20.3
All transferred fresh cycles	842	377	–	–	44.8	41.4–48.2
		–	293	–	34.8	31.6–38.1
		–	–	250	29.7	26.6–32.9
All initiated frozen-thawed cycles	860	354	–	–	41.2	37.9–44.5
		–	260	–	30.2	27.2–33.4
		–	–	219	25.5	22.6–28.5
All transferred frozen-thawed cycles	828	354	–	–	42.8	39.4–46.2
		–	260	–	31.4	28.3–34.7
		–	–	219	26.4	23.5–29.6

Treatment	Women (N)	hCG[a] (N)	Heartbeat[b] (N)	Live birth (N)	Proportion (%)	95 % CI (%)
Entire IVF programme[c]	436	332	–	–	76.1	71.9–80.1
		–	300	–	68.8	64.2–73.1
		–	–	279	64.0	59.3–68.5

[a] hCG: Positive hCG defined as >10 IU/L.
[b] Heartbeat: Ongoing pregnancy defined as a viable pregnancy at ultrasound at gestational week 7–9.
[c] Includes initiated fresh IVF cycles for up to 3 ovarian stimulations and all frozen-thawed IVF cycles. All females had at least one embryo transfer.

Consequently, our study population is likely to consist of less fertile women compared to other IVF studies, which potentially underestimates our findings of LBR and CLBR.

Perspectives

To fulfill the patients` wish to reduce the time to pregnancy and to reduce the miscarriage rate, transfer of blastocysts is becoming increasingly common in ART. Based on our results, this procedure seems to be a viable method when using CLBR as the outcome. Until now the morphological assessment of blastocysts has been used. Although development appears linked to viability, the assessment of morphology alone remains subjective and hard to quantify [24]. Implementation of artificial intelligence, genetic analyses and metabolic functions, will in the near future be important subjects in the endeavor to select the best blastocyst for transfer. To be able to culture an embryo to the blastocyst stage is therefore likely to become mandatory for the upcoming research/treatment.

Conclusion

In summary we evaluated LBRs and CLBRs at a Danish fertility clinic, where only transfer of blastocysts was used in the IVF procedure. Of particular interest, we found a CLBR of 64.0 % after multiple ovarian stimulations. Compared to other studies of CLBR after multiple ovarian stimulations using cleavage stage transfer, our study presents a considerable effect on the IVF success rate when using blastocyst transfer.

Authors' contributions

All authors designed the study, interpreted the results, reviewed the manuscript and approved the final version. SH took the lead in writing the manuscript and conducted the statistical analyses.

Availability of data and materials

The dataset generated and analysed during the current study is not publicly available due to its content of confidential personal health related information, but data may be available from the corresponding author on reasonable request provided permission to do so is granted from relevant authorities.

Funding

External funding was not used for this study.

Ethics approval

According to Danish legislation, no ethical approval was required for this study.

Consent for publication

According to Danish legislation, quality assessment studies do not require personal informed consent.

Declaration of Competing Interest

All authors were employees at Aagaard Fertility Clinic.

Acknowledgements

We are grateful to all the women who participated. Also, we thank the staff at Aagaard Fertility Clinic for their assistance in data collection.

References

[1] Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 2007;22(6):1506–12.
[2] Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril 2013;99(5)1324-31.e1.
[3] European Society of Human Reproduction and Embryology. More than 8 million babies born from IVF since the world's first in 1978: european IVF pregnancy rates now steady at around 36 percent, according to ESHRE monitoring. ScienceDaily 2018.
[4] European Society of Human Reproduction and Embryology. ART (assisted reproductive technology) fact sheet. 2016.
[5] Wade JJ, MacLachlan V, Kovacs G. The success rate of IVF has significantly improved over the last decade. Aust N Z J Obstet Gynaecol 2015;55(5):473–6.
[6] Nyboe Andersen A, Goossens V, Bhattacharya S, Ferraretti AP, Kupka MS, de Mouzon J, et al. Assisted reproductive technology and intrauterine inseminations in Europe, 2005: results generated from European registers by ESHRE: ESHRE. The European IVF Monitoring Programme (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod 2009;24(6):1267–87.
[7] Maheshwari A, McLernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? Hum Reprod 2015;30(12):2703–7.

[8] Malizia BA, Dodge LE, Penzias AS, Hacker MR. The cumulative probability of liveborn multiples after in vitro fertilization: a cohort study of more than 10,000 women. Fertil Steril 2013;99(2):393–9.
[9] De Neubourg D, Bogaerts K, Blockeel C, Coetsier T, Delvigne A, Devreker F, et al. 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(1):93–9.
[10] Toftager M, Bogstad J, Lossl K, Praetorius L, Zedeler A, Bryndorf T, et al. 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. Hum Reprod 2017;32(3):556–67.
[11] De Vos A, Van Landuyt L, Santos-Ribeiro S, Camus M, Van de Velde H, Tournaye H, et al. Cumulative live birth rates after fresh and vitrified cleavage-stage versus blastocyst-stage embryo transfer in the first treatment cycle. Hum Reprod 2016;31(11):2442–9.
[12] Chen ZJ, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med 2016;375(6):523–33.
[13] Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. N Engl J Med 2004;351:2392–402.
[14] Papanikolaou EG, D'Haeseleer E, Verheyen G, Van de Velde H, Camus M, Van Steirteghem A, et al. Live birth rate is significantly higher after blastocyst transfer than after cleavage-stage embryo transfer when at least four embryos are available on day 3 of embryo culture. A randomized prospective study. Hum Reprod 2005;20(11):3198–203.
[15] Glujovsky D, Farquhar C, Quinteiro Retamar AM, Alvarez Sedo CR, Blake D. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev 2016;(6):CD002118.
[16] McLernon DJ, Steyerberg EW, Te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population based study of linked cycle data from 113 873 women. BMJ 2016;355:i5735.
[17] De Croo I, Colman R, De Sutter P, Tilleman K. Blastocyst transfer for all? Higher cumulative live birth chance in a blastocyst-stage transfer policy compared to a cleavage-stage transfer policy. Facts Views Vis Obgyn 2019;11(2):169–76.
[18] Abuzeid O, Deanna J, Abdelaziz A, Joseph S, Abuzeid Y, Salem W, et al. The impact of single versus double blastocyst transfer on pregnancy outcomes: a prospective, randomized control trial. Facts Views Vis Obgyn 2017;9(4):195–206.
[19] Ozgur K, Bulut H, Berkkanoglu M, Donmez L, Coetzee K. Prediction of live birth and cumulative live birth rates in freeze-all-IVF treatment of a general population. J Assist Reprod Genet 2019;36(4):685–96.
[20] Vlaisavljevic V, Kovacic B, Knez J. Cumulative live birth rate after GnRH agonist trigger and elective cryopreservation of all embryos in high responders. Reprod Biomed Online 2017;35(1):42–8.
[21] Zaca C, Bazzocchi A, Pennetta F, Bonu MA, Coticchio G, Borini A. Cumulative live birth rate in freeze-all cycles is comparable to that of a conventional embryo transfer policy at the cleavage stage but superior at the blastocyst stage. Fertil Steril 2018;110(4):703–9.
[22] Heijnen EM, Macklon NS, Fauser BC. What is the most relevant standard of success in assisted reproduction? The next step to improving outcomes of IVF: consider the whole treatment. Hum Reprod 2004;19(9):1936–8.
[23] Daya S. Life table (survival) analysis to generate cumulative pregnancy rates in assisted reproduction: are we overestimating our success rates? Hum Reprod 2005;20(5):1135–43.
[24] Paternot G, Wetzels AM, Thonon F, Vansteenbrugge A, Willemen D, Devroe J, et al. Intra- and interobserver analysis in the morphological assessment of early stage embryos during an IVF procedure: a multicentre study. Reprod Biol Endocrinol 2011;9:127.