ECRONICON OPEN ACCESS

EC GYNAECOLOGY
Research Article

How Do Live Birth and Cumulative Live Birth Rate in IVF Cycles Change with the Number of Oocytes Retrieved?

Carlotta Zacà, Valentina Spadoni, Gilda Patria, Monica Cattoli, Maria Antonietta Bonu and Andrea Borini*

9. Baby Centre for Reproductive Health, Via Dante 15, I-40125 Bologna, Italy

***Corresponding Author:** Andrea Borini, 9. Baby Centre for Reproductive Health, Via Dante 15, I-40125 Bologna, Italy.

Received: October 19, 2016; **Published:** January 06, 2017

Abstract

Background: There is a strong relationship between the number of oocytes retrieved and success rate, in fact the number of oocytes retrieved is considered to be an important prognostic variable, a robust surrogate outcome for clinical success for IVF treatment.

Methods: A retrospective study was performed on 6268 women undergoing a total of 8142 completed IVF cycles conducted between 2009 and 2013, in which at least one oocyte was retrieved. Cycle data was stratified according to the number of oocytes retrieved and the woman's age.

Findings: There is a strong relationship between the number of oocytes retrieved and success rate. Generally speaking, the IVF birth rate (LBR) per cycle increases up to retrieval of 15 oocytes and subsequently decreases. Differently, our data shows that live birth rate LBR per transfer and cumulative LBR do not decrease when more than 15-16 oocytes are retrieved (a slight increase constituting a plateau was reported).

Conclusion: Data analysis suggests that it's important to optimise the quantity of oocytes in order to maximise the chances of success. However, the optimal number of retrieved oocytes is around 15-16, it allows us to have a adequate number of embryos to select for transfer or to cryopreserve and thaw into a subsequent cycles. This information is helpful to clinicians for linking the predicted number of oocytes to the cumulative likelihood of live birth.

Keywords: *IVF; Number of Oocytes; Cumulative Live Birth; Live Birth Rate; Ovarian Response*

Introduction

Ovarian stimulation is an essential component of assisted reproductive technology (ART).

In the early 1980s, in order to increase IVF pregnancy rates, controlled ovarian hyperstimulation (COH) was introduced to stimulate multiple follicle development, in order to obtain multiple oocytes to be picked up at retrieval [1].

For positive IVF cycle outcome, it is essential to optimise the choice of ovarian stimulation protocols, to obtain the greatest possible oocyte and embryo quality as well as quantity. For this reason, it is important to personalise stimulation taking into account the patient's age, ovarian reserve and hormonal status.

Given that the number of oocytes retrieved is considered to be an important prognostic variable, a robust surrogate outcome for clinical success for IVF treatment, protocols aim to optimise this outcome [2,3]. Historically, low oocyte retrieval after follicular aspiration has been associated with diminished outcomes, often attributed to ovarian aging [4].

Previous works, in which few IVF cycles were analysed and/or just one centre was considered, investigated the relationship between the number of oocytes retrieved and pregnancy rates or live birth rate (LBR) following IVF fresh cycles [1,5-11]. One interesting paper, published by Sunkara., *et al*. [2], includes an analysis of more than 400.000 IVF cycles from the national Assisted Reproductive Technology (ART) registry in the United Kingdom. This study analysed the relationship between the number of eggs retrieved and the LBR in a fresh IVF cycle, across all female age groups. However, the authors did not take into account the impact of frozen-thawed cycles on cumulative rates. To determine the significant meaning of the "number of retrieved oocytes" is essential to consider in addition to the chance of live birth on fresh cycle the probability of live birth added after thawing cycles.

One study [3] focused on the correlation between the number of oocytes retrieved and the LBR both per fresh stimulation cycle and cumulatively for fresh and frozen cycles. However, this study is limited by the fact that only young, slim patients were recruited, and that the correlation was performed on just four oocyte count groups.

We performed our study in order to better understand the real contribution of number of retrieved oocytes. The aim was to determine the relationship between the number of oocytes retrieved and live birth rate (LBR) in fresh and in cumulative IVF cycles by including the outcome following the warming of all frozen oocytes and embryos generated by a single ovarian stimulation cycle.

However, the strongest factor in predicting the likelihood of pregnancy after IVF treatment is patient age [9,12]. Increase in patient age is associated with a reduction in ovarian reserve, as a stimulation response worsens the quality of both oocytes and embryos, decreases the implantation rate and increases the miscarriage rate. Consequently, we also stratified data into four female age groups, in order to evaluate the data trend.

Materials and Methods

Patients

A retrospective study was conducted on all the IVF cycles performed between May 2009 and June 2013 in three different centres. The study involved 6268 women undergoing a total of 8142 completed IVF cycles, of which 3244 were conventional IVF cycles (39.8%) and 4898 ICSI cycles (60.2%) (Table 1). For the analysis we only considered data from completed cycles, i.e. treatments resulting into a successful pregnancy and treatments resulting into not pregnancy with ended availability of cryopreserved oocytes or embryos. When the patient's pregnancy resulted in a miscarriage; we considered the thawing of both oocytes and embryos performed subsequently by the patient and, consequently, also potential pregnancies.

In order to obtain cumulative results, the freezing/thawing cycle was not considered as an additional treatment, but included in the relevant fresh cycle.

In 8142 completed cycles, 401 oocyte thawing cycles and 2192 embryo thawing cycles were reported. Women over 45 and PGS cycles was not included in the study. In our population 8 patients underwent to a voluntary abortion. Average patient age at the start of treatment was 36.8 ± 4.2 years.

In vitro Fertilization; Fresh and Frozen Embryo transfer

To obtain a multiple follicle result, all patients were treated with exogenous gonadotropin. Standard formulations of either recombinant FSH or hMG were used for stimulation; with initial dosing ranging from 100 UI to 450 UI per day, according to hormonal and anthropometric parameters. The drug dose was adjusted according to the individual follicular response. GnRH analogues were used to avoid an LH spontaneous surge. An ampoule of human chorionic gonadotropin was given to the patient to trigger ovulation and 35-36 hours after hCG, the oocytes were trans-vaginally retrieved. The oocytes were inseminated by conventional IVF in 3244 cycles (39.8%) and ICSI in 4898 cycles (60.2%), according to standard techniques.

Conventional IVF was carried out 4-5 hours after oocyte pick-up and oocyte was inseminated with a final motile sperm concentration of 200000-300000/ml. On the contrary, before proceeding with ICSI, the cumulus cells were removed from the oocytes after 3-4 h of incubation in hyaluronidase at a concentration of 80 IU/ml [14], after which the oocytes were injected as described previously [15]. Fertilisation was checked 14 - 18 hours later and confirmed by the presence of two pronuclei. Embryo transfer (ET) was carried out 2, 3 or 5 days after oocyte pick-up; the number of embryos to be transferred was decided according to patient needs and national guidelines. Surplus oocytes or embryos were cryopreserved [16], as agreed with the patient. Endometrial preparation for the thawing cycles was performed in all women as previously described [17].

In artificial cycle freezing ET (FET), estrogen and progesterone were administered in a sequential regimen which aims to mimick the endocrine exposure of the endometrium in the normal cycle. Initially, estradiol was given in order to cause proliferation of the endometrium, while suppressing the development of the dominant follicle. This was continued until the endometrium was observed to be 7–9 mm thick at ultrasound, then progesterone was added to initiate secretory changes [18]. The physiological mid-cycle shift from estrogen to progesterone was thus emulated [19-20]. The timing of embryo thawing and transfer was planned according to the moment of progesterone supplementation.

Data collection

The data from our database includes patient characteristics such as age, diagnosis, previous IVF treatments and the parameters of each cycle (conventional IVF or ICSI, number of cryopreserved embryos, number of thawed oocytes or embryos, number of transferred embryos, number of implanted embryos, subsequent clinical pregnancy, miscarriage and live birth). The aim of this retrospective study was to analyse the relationship between the number of retrieved oocytes and LBR in both fresh and cumulative cycles. The cumulative outcome was calculated including the thawing of all frozen oocytes and embryos generated from a single ovarian stimulation cycle.

The large number of treatments analysed allowed us to stratify the data and evaluate the relationship between the number of oocytes retrieved and LBR in fresh and in cumulative IVF cycles in the various age groups (Group 1: patients ≤ 34 years, Group 2: patients 35-38 years, Group 3: patients 39 - 42 years and Group 4: patients 43 - 45 years).

Institutional review board approval was not required because all patients in this study underwent routine IVF cycle and no additional intervention was performed.

Statistical Analysis

The cycles we analysed were first classified according to the number oocytes retrieved and then stratified into age groups. The differences observed between groups were analysed by means of nonparametric statistics ("Chi-Square Test" χ^2). $P < 0.05$ was considered statistically significant. To describe the relationship between sensitivity and specificity of the retrieved oocytes number in predicting the cumulative LBR, receiver operating characteristic (ROC) curves were designed. The association between the number of oocytes and the chance of cumulative LBR was calculated by logistic regression. Data analysis was performed using the Statistical Package for Social Sciences version 16.0 (SPSS Inc., USA).

Results and Discussion

Our study includes data from 6268 women undergoing a total of 8142 cycles. The characteristics of the cycles analysed are given in table 1. 28.1% of all cycles were conducted on women younger than 34, 32.7% on women between 35 and 38, 33.0% on women between 39 and 42 and a mere 6.2% on women aged 43 - 45.

Overall, the LBR per cycle was 16.5 % and cumulative LBR per cycle was 20.0 %. Maternal age was found to be an important factor in predicting IVF cycle outcome (Table 1). We considered different age groups: LBR and cumulative LBR drop significantly with an increase in the woman's age (LBR and cumulative LBR were 23.5% and 29.8%, in group 1; 19.5% and 23.6% in group 2; 9.9% and 11.2% in group 3; 3.8% and 3.8% in group 4, respectively) (Table 1).

The median number of eggs retrieved in all cycles was 7.9 ± 4.9 (Table 1) and the distribution of these in relation to treatment has a Gaussian trend (Figure 1). There was a negative correlation between age and oocyte yield; indeed, when stratified according to the woman's age, the number of oocytes retrieved decreases with an increase in the age of the patient (Table 1), however, the distribution of oocytes retrieved maintained a Gaussian trend in all 4groups (Figure 1).

	All cycles	**Group 1 ≤ 34 years**	**Group 2 35-38 years**	**Group 3 39-42 years**	**Group 4 43 - 45 years**
No. of completed cycles	8142	2290 (28.1)	2662 (32.7)	2685 (33.0)	505 (6.2)
No.of thawing oocytes cycles	401	179	162	60	0
No.of thawing embryos cycles	2192	937	769	450	36
Patients	6268	1890	2059	1956	363
Age (m±sd)	36.8 ± 4.2	31.4 ± 2.5	36.6 ± 1.1	40.4 ± 1.1	43.6 ± 0.7
Treatment type					
IVF (%)	3244 (39.8)	795 (34.7)	999 (37.5)	1186 (44.2)	264 (52.3)
ICSI (%)	4898 (60.2)	1495 65.3)	1663 62.5)	1499 (55.8)	241 (47.7)
Fresh cycle					
Pregnancies	1818	648	694	426	42
Live birth	1342	538	520	265	19
Newborn	1639	673	642	304	20
Live birth/cycle (%)	16.5	23.5	19.5	9.9	3.8
Cumulative cycle (fresh cycles + warming cycles)					
Pregnancies	2254	849	863	486	43
Live birth	1628	682	627	301	19
Newborn	1964	837	766	341	20
Cumulative live birth/cycle (%)	20.0	29.8	23.6	11.2	3.8
Miscarriage					
No. of Miscarriage	605	166	233	183	22
Miscarriage rate (%)	26.8	18.6	26.2	36.4	50.0
No. of voluntary abortion	8	1	3	2	2
Oocytes retrieved					
Oocytes retrieved (m ± sd)	7.9 ± 4.9	9.5 ± 5.1	8.4 ± 4.8	6.6 ± 4.4	5.1 ± 3.8

Table 1: *Characteristics of the cohort.*

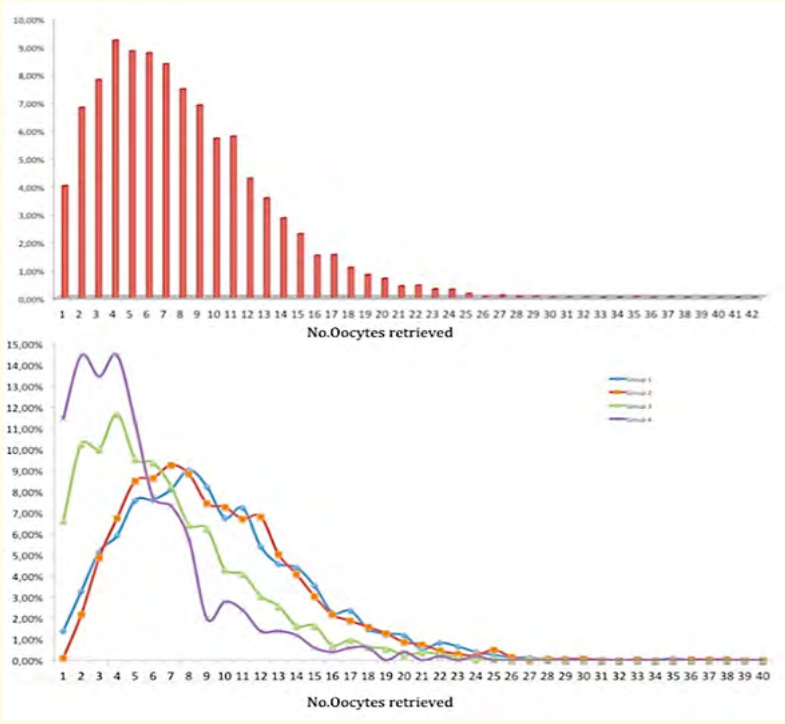

Figure 1: *Number of oocytes retrieved.*

There is a strong relationship between the number of oocytes retrieved and LBR and cumulative LBR. In the overall analysis, the LBR per cycle increases when up to 15 oocytes were retrieved and subsequently decreased. This trend is probably due to the high percentage of cycles in which all embryos/oocytes are cryopreserved when more than 15 oocytes are retrieved. In order to verify the effective reduction of live birth probability in fresh cycles we calculated the LBR/transfer. In actual fact, the LBR/transfer does not decrease when more than 15-16oocytes are retrieved, rather it slightly increase to form a plateau (Figure 2).

On the other hand, considered the additional live birth obtained by thawing of cryopreserved oocytes and embryos, the probability per patients to get a live birth in a single ovarian stimulation cycle was significantly increased compared to the probability given by a fresh cycle per se (Figure 2). Overall, cumulative LBR also increased when more than 15 oocytes were retrieved, however, this increase was so slight it constituted a plateau ($p = 0.502$).The same association when more than 15 oocytes were retrieved between the number of eggs retrieved and cumulative LBR was also observed in patient age groups1, 2 and 3 (Group 1: $p = 0.520$; Group 2: $p = 0.207$; Group 3: $p = 0.435$).

In older patients (Group 4), due to the low number of cycles analysed, we only created 3 oocyte count groups; in these groups, the likelihood of live birth was seen to increase slightly and non-significantly, with the number of oocytes retrieved ($p = 0.294$). ROC curves were constructed to examine retrieved oocytes number as predictor of cumulative LBR. The area under ROC curve (AUC) was 0.691 (Figure 3), however, retrieved oocytes number did not accurately predict cumulative LBR and the information it will provide for any one patient is limited.

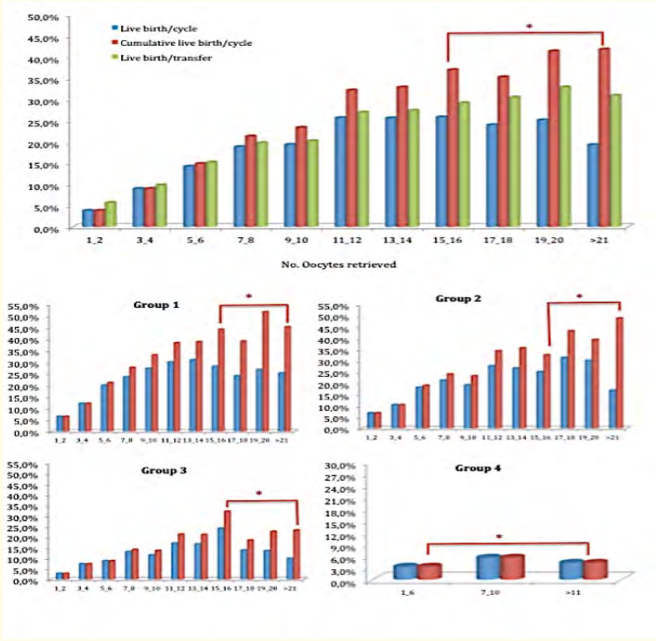

Figure 2: *Association between oocyte number and live birth per cycle and cumulative live birth rate per cycle. Overall association and stratification by age group (Group 1: ≤ 34 years; Group 2: 35 - 38 years; Group 3: 39 - 42 years; Group 4: 43 - 45 years). * p value is not statistically significant.*

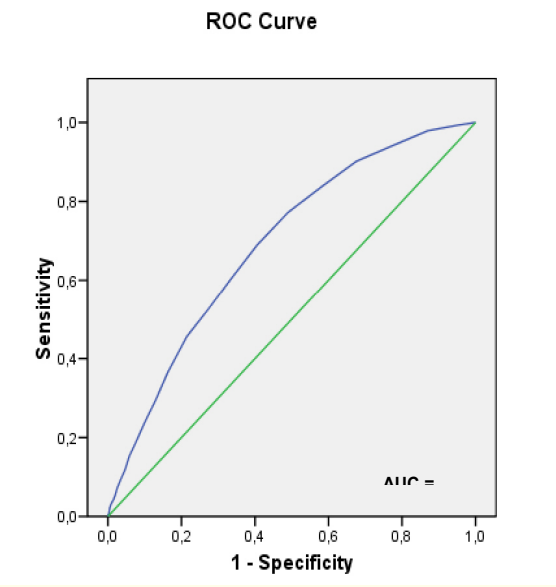

Figure 3: *Receiver operating characteristic curve for retrieved oocytes number as predictor of cumulative live birth.*

In addiction, logistic regression analysis shows that the number of retrieved oocytes has significant impact on cumulative LBR ($p < 0.001$) and to increase of an retrieved oocyte the cumulative probability of cumulative LBR increases 112% (Table 2).

Variable	B	SE(B)	df	Sig.	Exp(B)
Oocytes retrieved	0.121	0.006	1	0.000	1.129

Table 2: *Logistic regression.*

Discussion

The main objective of individualising IVF treatment is to offer each and every woman the best treatment, tailored to suit her unique characteristics, in order to maximise the likelihood of pregnancy and eliminate the avoidable, treatment-induced risks of ovarian stimulation [21].

It has been shown that the availability of a good number of oocytes improves the likelihood of generating good quality embryos and, consequently, achieving successful pregnancy and live birth [10,22-23].

Despite this, given the cost, complexity, effects and stress associated with conventional ovarian stimulation regimens, some centres are interested in applying mild stimulation protocols in an attempt to make IVF treatment more patient-friendly, reduce the likelihood of complications (especially ovarian hyperstimulation syndrome) and lower costs [24,25].

As for ovarian stimulation and response (in terms of number of retrieved oocytes), previous studies have analysed the relationship with pre-implantation genetic screening.

According to literature, the frequency of aneuploidy in human oocytes is reported to range from 15.0 to 20.0% [26]; preliminary studies suggest that many factors might affect the incidence of embryo aneuploidy, among these the maternal age is certainly the most significant, but also the ovarian stimulation protocols employed in IVF, patient's estradiol (E2) levels, the number of oocytes retrieved and number of follicles [27-29,42]. However, the studies published report contradictory results on this topic.

The number of oocytes could also be considered a surrogate of embryo quality, as a greater number of oocytes retrieved reflects a higher number of embryos available and one or two good-quality embryos are more likely to be obtained for fresh ET [36,37]. Moreover, Cai., *et al*. [35] demonstrated that embryo quality and quantity are two of the most important predictors of fresh and cumulative outcome in IVF/ICSI.

It is known that a low number of retrieved oocytes has been associated with diminished outcomes [4]; indeed McAvey., *et al*. [36] demonstrated that, in cycles in which five or fewer MII were obtained; a significantly lower likelihood of live birth was present. As a matter of fact, our findings state that patients with a low number of retrieved oocytes have poorer likelihoods in fresh cycles and a non-significant increase in the cumulative data.

One recent study published by Sunkara., *et al*. [37] also demonstrated that women with poor ovarian response (≤ 3 oocytes) have a higher risk of miscarriage following IVF treatment across all age groups. The majority of miscarriages are a result of embryo aneuploidy as a consequence of oocyte aneuploidy and the high miscarriage rate in poor responders probably reflects poor oocyte quality. Women who have a hyper-response to ovarian stimulation do not generally have a significantly higher risk of miscarriage [37].

Some studies have shown that in high responder patients, there is a drop in pregnancy or LBR per fresh cycle [2-3,35,38]. It has been seen that retrieval of >15 oocytes significantly increases the risk of OHSS without improving LB rate in fresh autologous IVF cycles [39].

In these patients, in order to prevent OHSS, the transfer is often avoided and all embryos are cryopreserved. In order to investigate the actual reduction in probability in this category, it is necessary to assess the percentage for transfer. On the basis of our data, we can stated that, by calculating the LBR per transfer, the likelihood of live birth in these patients does not decrease and the cumulative live birth rate per cycle does not drop (Figure II).

Kok., *et al*. [40] also stated that high responder patients with high number of retrieved oocytes have a greater fraction of immature oocytes, but their pregnancy outcome is not impaired. Some previous work focused on the relationship between eggs retrieved and pregnancy rate or live birth rate per fresh cycle following IVF [2,4-9,32-36,38].

The experience with the highest number of IVF cycles analysing the relationship between the number of eggs and IVF cycle outcome, was conducted by Sunkara., *et al*. [2]. The study is based on more than 400.000 IVF cycles from the national ART registry in the United Kingdom (from 1991 to 2008), but does not consider the impact of frozen–thawed cycles on the cumulative LBR, because the Human Fertilization and Embryology Authority (HFEA) data set does not allow the linkage of fresh and frozen cycles in the same woman. In this study, Sunkara concluded that, across all female age groups, there is a strong relationship between the number of eggs and live births, which in overall analysis rises with an increase in oocyte count up to ~15, forms a plateau between 15-20 eggs and steadily declines over 20 eggs.

Just one study, published by Ji., *et al*. [3], focused on fresh and cumulative LBR, however, this work is limited the fact that the study only recruited young; slim subjects and only considers four oocyte count groups (0-5, 6-10, 11-15 and >16 oocytes retrieved). Furthermore, having a small number of groups means that it is not possible to accurately assess likelihood in relation to ovarian response.

To correctly evaluate the potential of the number of oocytes retrieved, it is necessary to create groups composed of no more than one or two oocytes and to have a complete representation of IVF treatment. It is also important to consider, further to the pregnancies achieved from fresh transfer, those pregnancies obtained by thawing cycles of oocytes or embryos cryopreserved in that cycle. In our study, we created groups composed of two oocytes (1-2, 3-4, 5-6, 7-8, etc. oocytes retrieved) and each freezing/thawing cycle was not considered as an additional treatment, but was included in the relevant fresh cycle to obtain a given cumulative result from the fresh and thawing cycles. We only considered complete cycles resulting either in a pregnancy or finished oocytes or embryos cryopreserved in that treatment.

We obtained a strong correlation between the number of oocytes retrieved and cumulative LBR in both the overall analysis and the groups stratified by age (Figure 2). In the overall analysis, cumulative LBR increased up to the retrieval of 15-16 oocytes, after which we observed a small increase defining a plateau.

Besides the number of oocytes, the woman's age is one of the strongest factors in predicting the likelihood of pregnancy after IVF treatment [9,12]. Advancing age has a significant adverse effect on the outcome of IVF cycles, regardless of the oocyte count, indeed, in stratification by age LBR and cumulative LBR decrease significantly with an increase in the age of the patient: LBR decreases from 23.8% in younger patients to 3.8% in older ones and cumulative LBR decreases from 29.8% in patients aged ≤ 34 to 3.8 % in patients aged 43-45.

There is a negative relationship between age and the number of oocytes retrieved: in the stratification according to the woman's age, the number of oocytes retrieved decreases as the patient's age increases. In our data, the mean oocyte count is significantly lower in older women. As shown by our study results and by literature data, the number of oocytes retrieved is a predictive factor of IVF outcome.

In the light of this, it is important to optimise the quantity of oocytes retrieved in order to maximize the chances of success. Obtaining more embryos from one oocyte collection also increases the chance of cryopreservation and subsequent frozen embryo transfers and

reduces the need of repeated ovarian stimulation [10]. The optimal number of retrieved oocytes is around 15-16, it allows us to have a adequate number of embryos to select for transfer either in a fresh cycles or to cryopreserve and thaw into a subsequent cycles; also as reported in literature the retrieval of >15 oocytes significantly increases the risk of OHSS [39] According to the data collected in our study, by adding live birth from fresh cycles to live birth from thawing cycles, there is a significant increase in the chances a patient may have from a single ovarian stimulation cycle.

Conclusion

Our study is the first aiming to determine the relationship between the number of oocytes retrieved and LBR in fresh and in cumulative IVF cycles by including the outcome following warming of all frozen oocytes and embryos generated by a single ovarian stimulation cycle in a large group of heterogeneous patients. This information is helpful to clinicians when advising couples and for linking the number of oocytes predicted to cumulative live birth rate per cycle.

Acknowledgements

We thank Ms. Emma Drew her review of the article in English and Dr. Roberto Bolzani for his assistance in the statistical data analysis.

Conflict of Interest

We declare that we have no conflict of interest.

Bibliography

1. Qianfang Cai., *et al*. "Does the Number of Oocytes Retrieved Influence Pregnancy after Fresh Embryo Transfer?" *Plos one* 8.2 (2013): e56189.

2. Sunkara SK., *et al*. "Association between the number of eggs and live birthin IVF treatment: an analysis of 400 135 treatment cycles". *Human Reproduction* 26.7 (2011): 17680-1774.

3. Ji J., *et al*. "The optimum number of oocytes in IVF treatment: an analysis of 2455 cycles in China". *Human Reproduction* 28.10 (2013): 2728-2734.

4. Beckers NG., *et al*. "Women with regular menstrual cycles and a poor response to ovarian hyperstimulation for *in vitro* fertilization exhibit follicular phase characteristics suggestive of ovarian aging". *Fertility and Sterility* 78.2 (2002): 291-297.

5. Letterie G., *et al*. "The relationship of clinical response; oocyte number; and success in oocyte donor cycles". *Journal of Assisted Reproduction and Genetics* 22.3 (2005): 115-117.

6. KablyAmbe A., *et al*. "Comparative analysis of pregnancy rate/captured oocytes in an *in vitro* fertilization program". *Ginecologia Y Obstetricia De Mexico* 76.5 (2008): 256-260.

7. Molina Hita Ma del M., *et al*. "Correlation between the number of oocytes and the pregnancy rate in IVF-ICSI cycles". *Revista Iberoamericana de Fertilidad y Reproducción Humana* 25 (2008): 153-159.

8. Hamoda H., *et al*. "Outcome of fresh IVF/ICSI cycles in relation to the number of oocytes collected: a review of 4;701 treatment cycles". *Human Reproduction* 25 (2010): 147.

9. Yih MC., *et al*. "Egg production predicts a doubling of *in vitro* fertilization pregnancy rates even within defined age and ovarian reserve categories". *Fertility and Sterility* 83.1 (2005): 24-29.

10. Briggs R., *et al*. "Can you ever collect too many oocytes?" *Human Reproduction* 30.1 (2015): 81-87.

11. Baker VL., *et al*. "Association of number of retrieved oocytes with live birth rate and birth weight: an analysis of 231;815 cycles of *in vitro* fertilization". *Fertility and Sterility* 103.4 (2015): 938.e2.

12. Van Loendersloot LL., *et al*. "Predictive factors in *in vitro* fertilization (IVF): a systematic review and meta-analysis". *Human Reproduction Update* 16.6 (2010): 577-589.

13. Dal Prato L., *et al*. "Effect of reduced dose of triptorelin at the start of ovarian stimulation on the outcome of IVF: a randomized study". *Human Reproduction* 16.7 (2001): 1409-1414.

14. Borini A., *et al*. "Comparison of IVF and ICSI when only few oocytes are available for insemination". *Reproductive BioMedicine Online* 19.2 (2009): 270-275.

15. Borini A., *et al*. "Oocyte donation programme: results obtained with intracytoplasmic sperm injection in cases of severe male facto infertility or previous failed fertilization". *Human Reproduction* 11 (1996): 548-550

16. Bianchi V., *et al*. "Oocyte slow freezing using a 0.2-0.3 M sucrose concentration protocol: is it really the time to trash the cryopreservation machine?" *Fertility and Sterility* 97.5 (2012): 1101-1107.

17. Dal Prato L., *et al*. "Endometrial preparation for frozen-thawed embryo transfer with or without pretreatment with gonadotropin-releasing hormone agonist". *Fertility and Sterility* 77.5 (2002): 956-960.

18. El-Toukhy T., *et al*. "The relationship between endometrial thickness and outcome of medicated frozen embryo replacement cycles". *Fertility and Sterility* 89.4 (2008): 832-839.

19. Dor J., *et al*. "Endocrine and biological factors influencing implantation of human embryos following cryopreservation". *Gynecological Endocrinology* 5.3 (1991): 203-211.

20. Jaroudi KA., *et al*. "Artificial endometrial stimulation for frozen embryo replacement". *Fertility and Sterility* 55.4 (1991): 835-837.

21. La Marca A., and Sunkara SK. "Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice". *Human Reproduction Update* 20.1 (2014): 124-140.

22. Fauser BC., *et al*. "Multiple birth resulting from ovarian stimulation for subfertility treatment". *Lancet* 365.9473 (2005): 1807-1816.

23. Macklon NS., *et al*. "The science behind 25 years of ovarian stimulation for *in vitro* fertilization". *Endocrine Reviews* 27.2 (2006): 170-207.

24. Fauser BC., *et al*. "Minimal ovarian stimulation for IVF: appraisal of potential benefits and drawbacks". *Human Reproduction* 14.11 (1999): 2681-2686.

25. Verberg MFG., *et al*. "The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis". *Human Reproduction Update* 15.1 (2009): 5-12.

26. Haaf T., *et al*. "A high oocyte yield for intracytoplasmic sperm injection treatment is associated with an increased chromosome error rate". *Fertility and Sterility* 91.3 (2009): 733-738.

27. Munne S., *et al*. "Treatment-related chromosome abnormalities in human embryos". *Human Reproduction* 12.4 (1997): 780-784.

28. Katz-Jaffe MG., *et al*. "Chromosome 21 mosaic human preimplantation embryos predominantly arise from diploid conceptions". *Fertility and Sterility* 84.3 (2005): 634-643.

29. Soares SR., *et al*. "High frequency of chromosomal abnormalities in embryos obtained from oocyte donation cycles". *Fertility and Sterility* 80 (2003): 656-657.

30. Baart EB., *et al*. "Milder ovarian stimulation for *in vitro* fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial". *Human Reproduction* 22.4 (2007): 980-988.

31. Santana A., *et al*. "Number of oocytes retrieved and cycle outcome in preimplantation genetic diagnosis (PGD) patients for aneuploidy screening". *Reproductive BioMedicine Online* 16.3 (2008): s21.

32. Labarta E., *et al*. "Moderate ovarian stimulation does not increase the incidence of human embryo chromosomal abnormalities in *in vitro* fertilization cycles". *Journal of Clinical Endocrinology and Metabolism* 97.10 (2012): E1987-E1994.

33. Roberts SA., *et al*. "Modelling the impact of single embryo transfer in a national health service IVF programme". *Human Reproduction* 24.1 (2009): 122-131.

34. Roberts SA., *et al*. "Embryo and uterine influences on IVF outcomes: an analysis of a UK multicentre cohort". *Human Reproduction* 25.11 (2010): 2792-2802.

35. Cai QF., *et al*. "Factors predicting the cumulative outcome of IVF/ICSI treatment: a multivariable analysis of 2450 patients". *Human Reproduction* 26.9 (2011): 2532-2540.

36. McAvey B., *et al*. "How many eggs are needed to produce an assisted reproductive technology baby: is more always better?" *Fertility and Sterility* 96.2 (2011): 332-335.

37. Sunkara SK., *et al*. "Association between response to ovarian stimulation and miscarriage following IVF: an analysis of 124 351 IVF pregnancies". *Human Reproduction* 29.6 (2014): 1218-1224.

38. van der Gaast MH., *et al*. "Optimum number of oocytes for a successful first IVF treatment cycle". *Reproductive BioMedicine Online* 13.4 (2006): 476-480.

39. Steward RG., *et al*. "Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256;381 *in vitro* fertilization cycles". *Fertility and Sterility* 101.4 (2014): 967-973.

40. Kok JD., *et al*. "A high number of oocytes obtained after ovarian hyperstimulation for *in vitro* fertilization or intracytoplasmic sperm injection is not associated with decreased pregnancy outcome". *Fertility and Sterility* 85.4 (2006): 918-924.

41. Griffin DK. "The incidence; origin; and etiology of aneuploidy". *International Review of Cytology* 167 (1996): 263-296.

42. Munne S., *et al*. "Wide range of chromosome abnormalities in the embryos of young egg donors". *Reproductive BioMedicine Online* 12.3 (2006): 340-346.

Volume 3 Issue 5 January 2017