sciendo

10.2478/sjph-2019-0022 Zdr Varst. 2019;58(4):173-178

Reljič M, Gavrić Lovrec V. Predictive factors for live birth in autologous in vitro fertilization cycles in women aged 40 years and older.
Zdr Varst. 2019;58(4):173-178. doi: 10.2478/sjph-2019-0022.

PREDICTIVE FACTORS FOR LIVE BIRTH IN AUTOLOGOUS IN VITRO FERTILIZATION CYCLES IN WOMEN AGED 40 YEARS AND OLDER

NAPOVEDNI DEJAVNIKI ZA ŽIVOROJENOST V AVTOLOGNIH CIKLIH ZUNAJTELESNE OPLODITVE PRI ŽENSKAH, STARIH 40 LET IN VEČ

Milan RELJIČ[1], Vida GAVRIĆ LOVREC[1*]

[1]University Medical Centre Maribor, Department for Reproductive Medicine,
Ljubljanska ul. 5, 2000 Maribor, Slovenia

Received: Nov 7, 2018
Accepted: Aug 8, 2019

Original scientific article

ABSTRACT

Background: The aim of the study was to determine predictive factors for live birth after in vitro fertilization with autologous oocytes in women ≥40 years of age.

Methods: Authors conducted a retrospective analysis of in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles performed at the Department of Reproductive Medicine and Gynecologic Endocrinology, University Medical Centre Maribor, Slovenia between January 2006 and December 2015 in women aged 40 or more. The characteristics of patients and cycles were compared regarding live birth as the final outcome.

Results: A total of 1920 IVF/ICSI cycles with egg retrieval in women ≥40 years of age were performed leading to 1591 embryo transfers. The live birth rate per embryo transfer was 17.3% at 40, 11.6% at 41, 8.2% at 42, 7.9% at 43, 1.9% at 44 and 0.0% at ≥45 years of age. The multivariate logistic regression model showed that besides women's age (OR 0.66, 95% CI: 0.55–0.78), the number of previous cycles (OR 0.88, 95% CI: 0.82–0.95), number of good quality embryos on day 2 (OR 1.19, 95% CI: 1.05-1.36), number of embryos transferred (OR 1.57, 95% CI: 1.19–2.07) and day 5 embryo transfer (OR 2.21, 95% CI: 1.37–3.55) were also independent prognostic factors for live birth.

Conclusions: The chance of in vitro fertilization success in women ≥40 years of age should not be estimated only on the woman's age, but also on other predictive factors: number of previous cycles, number of good quality embryos on day 2, number of transferred embryos and blastocyst embry transfer.

Keywords:
in vitro fertilization,
late reproductive age,
pregnancy rate,
abortion rate,
live birth rate,
predictive factors

IZVLEČEK

Namen: *Namen raziskave je bil odkriti napovedne dejavnike za živorojenost po postopku zunajtelesne oploditve z lastnimi jajčnimi celicami pri ženskah, starih 40 let in več.*

Metode: *Avtorji so v retrospektivno analizo zajeli postopke zunajtelesne oploditve, ki so jih opravili na Oddelku za reproduktivno medicino in ginekološko endokrinologijo Univerzitetnega kliničnega centra Maribor od januarja 2006 do decembra 2015 pri bolnicah, starih 40 let ali več. Primerjali so značilnosti bolnic in postopkov, ki so se končali s porodom, s tistimi, kjer je bil postopek neuspešen.*

Rezultati: *Pri bolnicah, starih 40 let in več, so naredili 1.920 aspiracij foliklov, v 1.591 postopkih pa so prenesli zarodke v maternično votlino. Delež živorojenih na prenos zarodka je bil v starosti 40 let 17,3 %, v starosti 41 let 11,6 %, pri 42 let starih ženskah 8,2 %, v starosti 43 let 7,9 %, pri 44-letnih 1,9 % in 0,0 % v starosti ≥45 let. Multivariatni logistični regresijski model je pokazal, da so ob starosti ženske (RR 0,66, 95 % CI: 0,55-0,78) neodvisni napovedni dejavniki za porod še število predhodno opravljenih postopkov (RR 0,88, 95 % CI: 0,82-0,95), število kakovostnih zarodkov na dan 2 (RR 1,19, 95 % CI: 1,05-1,36), število prenesenih zarodkov (RR 1.57, 95% CI: 1,19-2,07) in število prenosov 5 dni starih zarodkov (RR 2,21, 95 % CI: 1,37-3,55).*

Zaključek: *Pri napovedi uspešnosti postopkov zunajtelesne oploditve pri ženskah, starih ≥40 let, je treba poleg starosti upoštevati tudi druge napovedne dejavnike: število predhodnih postopkov, število zarodkov dobre kakovosti na dan 2, število prenesenih zarodkov in prenos blastocist.*

Ključne besede:
in vitro fertilizacija,
pozno reproduktivno obdobje,
delež zanositev,
delež spontanih splavov,
delež porodov,
napovedni dejavniki

***Corresponding author:** Tel. + 386 41 708 878; E-mail: vida.ga.lo.1@gmail.com

1 INTRODUCTION

A woman's fertility potential declines with age and 50% of women over 40 will have some difficulty in their attempts to have children (1). Numerous factors contribute to this decline, the most prominent being a decrease in egg quality in association with the rising concentration of FSH and decreasing concentrations of AMH and inhibin B (2). Changes in sexual activity might also contribute to diminished fecundity and so can other disorders that develop with aging such as endometriosis, pelvic inflammatory disease, ovarian surgery, chemotherapy, smoking etc. (2). Pregnancy in late reproductive period is associated with a higher risk of miscarriage compared to younger women: it is caused by autosomal trisomy as a consequence of meiotic non-disjunction (3, 4). These biological changes are reflected in infertility treatment outcome since no current treatment can compensate for natural decline of fertility due to advanced age (5, 6).

Different treatment strategies have been proposed to these patients, but in vitro fertilization (IVF) has been found to be the most successful (7). However, effectiveness of IVF with autologous oocytes decreases with female age, mainly attributed to age-related decline of oocyte quality and quantity (6). Studies have shown that the live birth rate after IVF in women ≥40 years ranges from 4.7 to 15.7% and it drops to 1-2% in women older than 44 years (8-11). Due to a low success rate in advanced age many clinicians believe that IVF treatment should be limited to patients not older than 43-45 years (12-14). However, chronological and biological ovarian age are not always equivalent, and women of the same age do not all have the same chance for live birth after IVF (15). This is the main reason why the American Society for Reproductive Medicine (ASRM) has not recommended upper-age limits for women using their own eggs but has issued guidelines concerning treatment that has a poor prognosis or is futile. They define ''futility'' as interventions with less than a 1% likelihood of live birth, and ''very poor prognosis'' as odds of >1% but <5% (16). It is therefore very important to identify all predictive factors that discern between women who could really benefit from this procedure and women who are candidates for other treatment options, like oocyte donation.

The aim of our study was to determine predictive factors for live birth after IVF with autologous oocytes in women over 40 years of age.

2 METHODS

IVF/ICSI cycles with egg retrieval in women of ≥40 years of age performed between January 2006 and December 2015 were included in this retrospective study. The data were obtained from the database of all IVF/ICSI cycles conducted at the Department for Reproductive Medicine, University Medical Centre Maribor, Slovenia. In 99 patients (4.9%) no response to ovarian stimulation was observed, so they were excluded from the study.

Patients underwent ovarian stimulation using standard protocols: combination of GnRH analogues (GnRH agonist or GnRH antagonist) and recombinant FSH (Gonal-F, Serono International SA, Geneva, Switzerland) or HMG (Menopur, Ferring Pharmaceuticals Inc., Saint-Prex, Switzerland) that were previously described in detail (17). After oocyte fertilization using IVF or ICSI procedure, embryos were cultured in the BlastAssist extended culture media (Origio, Målov, Denmark). Embryo quality was assessed at day 2 and 3 after oocyte fertilization by an experienced embryologist. After consultation with the patients, time of embryo transfer was adjusted to day 3 or day 5 according to the doctor-patient agreement. Day 5 blastocyst transfer was suggested if more than three optimal embryos were available on day 3 according to our standard policies. Blastocysts were graded according to our established grading system 5 days after oocyte fertilization (18, 19). In brief, the blastocyst was considered optimal if it was fully expanded and the blastocoel completely filled the embryo. It contained a cohesive trophectoderm and a compact inner cell mass (ICM). No more than three embryos on day 3 and no more than two embryos on day 5 were transferred. Surplus blastocysts not selected for transfer were cryopreserved.

After embryo transfer, patients received luteal-phase support with 600 mg of vaginal progesterone daily (Utrogestan, Ferring Pharmaceuticals Inc., Saint-Prex, Switzerland). The serum hCG level was measured 16 days after oocyte pick-up and ultrasound was performed 2 weeks later, if the blood test confirmed pregnancy. Clinical pregnancy was defined as the presence of a gestational sac with a fetal heartbeat.

Patients' and cycles' characteristics were compared between the cycles with and without live birth. Statistical analysis was performed using Statistica 8.0 data software system analysis (Stat Soft Inc., Tulsa, OK, USA). The normal distribution of numeric variables was determined by the Shapiro-Wilk test. Student's t test or Mann-Whitney U test were used to assess these variables, depending on the data distribution. Mean and standard deviation for each continuous variable were calculated. Cross-tables and chi-square analysis were employed in the evaluation of the categorical data. The association between patients'/cycles' characteristics and live birth were also analyzed with univariate logistic regression. Variables proven statistically significant by univariate logistic analysis were tested with the multiple logistic regression model. Odds ratios and their 95% confidence intervals (CIs) were calculated. p value <0.05 was considered statistically significant.

The study was approved by our institutional review board and was a part of research programme P3–0327 funded by the Slovenian Research Agency.

3 RESULTS

A total of 1920 IVF/ICSI cycles with egg retrieval in women ≥40 were performed, leading to 1591 embryo transfers (82.8%). Clinical pregnancy rate per transfer, abortion rate and live birth rate were 18.1, 36.8 and 11.9%, respectively. Outcomes of IVF/ICSI cycles stratified by women's age are presented in Table 1. Women's age, number of previous cycles, number of oocytes retrieved, number of good quality embryos on day 2, number of transferred embryos, proportion of blastocyst transfer and number of frozen blastocysts were statistically different in IVF/ICSI cycles with live birth compared to cycles without live birth (Table 2).

Table 1. Outcome of IVF/ICSI cycles by age in women ≥40 years of age.

	40 years	41 years	42 years	43 years	44 years	≥45 years
No. of cycles	640	556	489	143	69	23
No. of embryo-transfers	539	465	401	113	53	19
No. of pregnancies (%)	129 (23.9)	85 (18.3)	49 (12.2)	18 (15.9)	6 (11.3)	1 (5.3)
No. of miscarriages (%)	36 (27.9)	31 (36.5)	16 (32.6)	(9) (50.0)	5 (83.3)	1 (100.0)
No. of live births (%)	93 (17.3)	54 (11.6)	33 (8.2)	9 (7.9)	1 (1.9)	0 (0.0)
No. of newborns	104	58	35	9	1	0

Table 2. Comparison of patients and cycles characteristics between successful and unsuccessful IVF/ICSI cycles in women ≥40.

	Live birth NO	Live birth YES	P-value
No. of cycles	1730	190	
Age (years)	41.26±1.18	40.78±0.90	<0.001
No. of previous cycles	2.80±3.12	2.06±2.02	0.001
Only male infertility (%)	33.29	31.58	NS
Only female infertility (%)	15.37	15.79	NS
Male and female infertility (%)	24.81	28.72	NS
Unexplained infertility (%)	26.53	27.89	NS
ICSI (%)	80.38	77.11	NS
Total FSH dose (IU x 75)	36.40±14.64	35.87±11.56	NS
Duration of stimulation (days)	9.63±3.17	10.03±2.31	NS
No. of oocytes	5.77±4.57	7.84±4.87	<0.001
No. of embryos	3.55±2.81	5.29±3.03	<0.001
No. of good quality embryos on day2	2.01±2.22	3.60±2.75	0.001
No. of embryos transferred	1.84±0.71	2.01±0.55	<0.001
Day 5 embryo transfer (%)	17.26	40.21	<0.001
No. of frozen blastocysts	0.30±0.98	1.03±1.68	<0.001
Duration of stimulation (days)	9.63±3.17	10.03±2.31	NS

These parameters were also found to be associated with live birth using univariate logistic regression. In the multivariate logistic regression model only women's age, number of previous cycles, number of good quality embryos on day 2, number of embryos transferred, and day 5 embryo transfer remained important independent prognostic factors for live birth (Table 3).

The same prognostic factors for live birth were important if a separate analysis for male and female causes of infertility was done.

Table 3. Multivariable logistic regression analyses assessing predictors of live birth after IVF/ICSI in women ≥40 years.

	42 years	43 years	44 years	≥45 years
Age (years)	-0.41	0.08	<0.001	0.66 (0.55-0.78)
No. of previous cycles	-0.12	0.04	0.001	0.88 (0.82-0.95)
No. of oocytes	0.05	0.04	0.22	0.95 (0.88-1.03)
No. of embryos	0.001	0.09	0.98	0.99 (0.82-1.20)
No. of good quality embryos on day 2	0.18	0.06	0.005	1.19 (1.05-1.36)
No. of embryos transferred	0.45	0.14	0.002	1.57 (1.19-2.07)
Day 5 embryo transfer (%)	0.79	0.24	0.001	2.21 (1.37-3.55)

4 DISCUSSION

The overall pregnancy rate in our study was 18.1%. Similar pregnancy rates were reported by other studies (11, 13, 20, 21). The highest pregnancy rate in our study was achieved at the age of 40, and it decreased beyond that age (Table 1). At the age of ≥45 it was only 5% accompanied by a 100 % abortion rate. However, the number of women 44 and 45 years of age included in our study was low, since in Slovenia, six IVF/ICSI cycles are covered by the insurance, but only until the age of 43. Similar dynamics of pregnancy rate, abortion rate and live birth rate were observed by Kim et al. who discovered significant decrease in clinical pregnancy rate and live birth rate with each year of increased age after the age of 40 (22).

In our study, patients with a successful outcome had a significantly higher number of oocytes compared to women with unsuccessful cycles (7.84±4.87 vs. 5.77±4.57), but still much lower than optimal, according to Sunkara's et al. analysis of over 400 000 IVF cycles. They discovered a strong association between the number of oocytes and live birth rate (LBR) that reached 16% in women ≥40, when at least 15 oocytes were obtained (23). Since ovarian reserve is declining with age (2) and stimulation with high doses of gonadotropins has only a limited influence on cycle outcome (24, 25), the number of oocytes to optimize LBR (~15 oocytes) is hardly ever achieved in the population of ≥40 years of age. Nevertheless, LBR in our study (11.9%) was in accordance with Sunkara's normogram based on age and number of oocytes and also with results reported by other researchers (11, 13, 23).

Still, using multivariate logistic regression we failed to show oocyte number to be an independent prognostic factor for live birth, which is not consistent with some other studies that showed oocyte number to be predictor for live birth (11, 22). Possible explanation is also that, in the multiple logistic regression model, the number of good quality embryos prevailed, since it reflected not only quantity, but also quality of oocytes. On the other hand, it was also demonstrated that the number of oocytes was a more important prognostic factor for cumulative live birth rate (CLBR) than for LBR. According to findings of some authors, it seems that the number of retrieved oocytes does not affect LBR in fresh cycle, but the higher the oocyte yield, the higher the probability to achieve a live birth after utilization of all cryopreserved embryos (26, 27). Since the number of frozen blastocysts in patients with no live birth in our study was very low (0.30±0.98) compared to patients with live birth (1.03±1.68), we refrained from calculating CLBR.

A multivariate logistic regression analysis performed by Kim et al. on 2362 cycles in women ≥40 years of age showed that maternal age, basal FSH levels, the number of high quality embryos and the number of transferred embryos were significant predictors of live birth (22). Their results are consistent with ours regarding the

importance of maternal age, number of good quality embryos, and number of embryos transferred as predictors of live birth. A recent report by Gunnala et al. confirmed the importance of age in patients ≥45 years of age: the overall pregnancy rate per transfer in their studied group aged 45.4±0.72 years was 18.7%, with a pregnancy loss of 82.1%. Patients who were 45 years old had significantly higher pregnancy rate than those aged 46 (14.1% vs. 8.6%), and they had live birth rate of 2.9% per started cycle and 4.4% per embryo transfer. In the entire cohort of 1078 cycles, only 21 cycles ended with birth. There was only one birth in women aged 46 and the rest in women aged 45. There were no live births in patients that had less than four oocytes retrieved. Other predictors (beside age) of positive pregnancy in women >45 years in their study were day 3 FSH and AMH levels, the number of of mature oocytes, the number of fertilized oocytes (2PN) and the number of embryos transferred (28).

The number of previous cycles, the number of transferred embryos and blastocyst transfer were also found to be important prognostic factor in our study. This is not surprising since many studies have reached the same conclusion but in an unselected group of women (29, 30). So it seems that the same predictors for live birth are important in women in late reproductive period and in younger women.

Prior to attempting an IVF treatment cycle, ovarian reserve (OR) testing is performed, since it gives us some information regarding what to expect from ovarian stimulation and can also predict live birth according to some studies (22). OR testing is routinely performed in our center in order to discuss with the patient the expected response to ovarian stimulation since chronological female age, although informative on pregnancy prospects in assisted reproduction, will often not correctly express a woman's reproductive potential, but the most reliable test of OR is response to stimulation (31). OR test results were not included in our study, since the patients with predicted poor ovarian response were not refrained from stimulation (32).

One limitation of the present study is the fact that it is a retrospective analysis and despite robust methodological approach, the presence of potential bias cannot be excluded. The number of women ≥44 years old is rather low. Not all factors that could affect IVF outcome were included.

5 CONCLUSIONS

Age-related natural fertility decline reflected in the results of infertility treatment with IVF in women ≥40 years of age using autologous oocytes. Decreasing live birth rate with age is a consequence of decreasing pregnancy and increasing miscarriage rate. When we counsel the patients about their prognosis of IVF treatment, there are other predictive factors that should also be taken into consideration besides age. These include the number of previous unsuccessful IVF cycles, the number of good quality embryos, the number of transferred embryos and blastocyst transfer.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethical committee of University Medical Centre Maribor (institutional review board).

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article (and its supplementary information files).

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

The study was a part of research programme P3-0327 funded by the Slovenian Research Agency.

AUTHORS' CONTRIBUTIONS

MR conceived and designed the study, performed the statistical analysis and drafted the manuscript. VGL participated in data interpretation, in drafting the manuscript and in editing the paper. Both authors read and approved the final manuscript.

REFERENCES

1. Speroff L, Glass RH, Kase NG. Clinical gynecologic endocrinology and infertility. 5th ed. Baltimore: Williams &Wilkins, 1994:809-39.
2. American College of Obstetricians and Gynecologists Committee on Gynecolocic Practice and Practice Committee. Female age-related fertility decline. Committee opinion 589. Feril Steril. 2014;101:633-4. doi: 10.1016/j.fertnstert.2013.12.032.
3. Balasch J, Gratacos E. Delayed childbearing: effects on fertility and the outcome of pregnancy. Curr Opin Obstet Gynecol. 2012;24:187-93. doi: 10.1097/GCO.0b013e3283517908.
4. Hassold T, Hall H, Hunt P. The origine of human aneuploidy: where we have been, were we are going. Hum Mol Genet. 2007;16:203-8. doi: 10.1093/humrep/ddm243.
5. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. Hum Reprod. 2004;19:1548-53. doi: 10. 1093/humrep/deh304.
6. Baird DT, Collins J, Egozcue J, Evers LH, Gianaroli L, Leridon H, et al. ESHRE Capri Workshop Group. Fertility and aging. Hum Repord Update. 2005;11:261-76. doi: 10.1093/humupd/dmi006.
7. Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL, Hornstein MD, et al. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). Fertil Steril. 2014;101:1574-81. doi: 10.1016/j.fertnstert.2014.03.012.
8. Armstrong S, Akande V. What is the best treatment option for infertile women aged 40 and over. J Assist Reprod Genet. 2013;30:667-71. doi: 10.1007/s10815-013-9980-6.
9. Klipstein S, Regan M, Ryley DA, Goldman MB, Alper MM, Reindollar RH. One last chance for pregnancy: a review of 2,705 in vitro fertilization cycles initiated in women age 40 years and above. Fertil Steril. 2005;84:435-45. doi: 10.1016/j.fertnstert. 2005.02.020.
10. Tsafrir A, Simon A, Revel A, Reubinoff B, Lewin A, Laufer N. Retrospective analysis of 1217 IVF cycles in women aged 40 years and older. Reprod BioMed Online. 2007;14:348-55.
11. Hipp H, Crawford S, Kawwass JF, Boulet SL, Grainger DA, Kissin DM, et al. National trends and outcomes of autologous in vitro fertilization cycles among women ages 40 years and older. J Assist Reprod Genet. 2017;34:885-9. doi: 10.1007/s10815-017-0926-2.
12. Hourvitz A, Machtinger R, Maman E, Baum M, Dor J, Levron J. Assisted reproduction in women over 40 years of age: how old is too old? Reprod Biomed Online. 2009;19:599-603.
13. Serour G, Mansour R, Serour A, Abulghar M, Amin Y, Kamal O, et al. Analysis of 2,386 consecutive cycles of in vitro fertilization or intracytoplasmic sperm injection using autologuos oocytes in women aged 40 years or above. Fertil Steril. 2010;94:1707-12. doi: 10.1016/j.fertnstert.2009.09.044.
14. Klitzman RL. How old is too old? Challenges faced by clinicians concerning age cutoffs for patients undergoing in vitro fertilization. Fertil Steril. 2016;106:216-24. doi: 10.1016/j.fertnstert.2016.03.030.
15. Alviggi C, Humaidan P, Howles CM, Tredway D, Hillieret SG. Biological versus chronological ovarian age: Implications for assisted reproductive technology. Reprod Biol Endocrinol. 2009;7:101. doi: 10.1186/1477-7827-7-101.
16. Ethics Committee of American Society for Reproductive Medicine. Fertility treatment when the prognosis is very poor or futile: a committee opinion. Fertil Steril. 2012;98:e6-9. doi: 10.1016/j.fertnstert.2012.03.045.
17. Knez J, Kovačič B, Medved M, Vlaisavljević V. What is the value of anti-Müllerian hormone in predicting the response to ovarian stimulation with GnRH agonist and antagonist protocols? Reprod Biol Endocrinol. 2015;13:58. doi: 10.1186/s12958-015-0049-5.
18. Kovačič B, Vlaisavljević V, Reljič M, Čižek-Sajko M. Developmental capacity of different morphological types of day 5 human morulae and blastocysts. Reprod BioMed Online. 2004;8:687-94.
19. Kovačič B, Vlaisavljević V. Importance of blastocyst morphology in selection for transfer. In: Wu B, ed. Advances in embryo transfer. Rijeka: Intech, 2012:161-77.
20. Park HJ, Lyu SW, Seok HH, Yoon TK, Lee SW. Anti-Müllerian hormone levels as a predictor of clinical pregnancy in in vitro fertilization/intracytoplasmic sperm injection-embryo transfer cycles in patients over 40 years of age. Clin Exp Reprod Med. 2015;42:143-8. doi: 10.5653/cerm.2015.42.4.143.
21. Lee Y, Lee HJ, Jayeon Kim, Lyu SW, Kim YS, Lee WS, et al. Predictive value of antral follicle count and serum anti-Müllerian hormone: which is better for live birth prediction in patients aged over 40 with their first IVF treatment? Eur J Obstet Gynecol Reprod Biol. 2018;221:151-5. doi: 10.1016/j.ejogrb.2017.12.047.
22. Kim HO, Sung N, Song IO. Predictors of live birth and pregnancy success after in vitro fertilization in infertile women aged 40 and over. Clin Exp Reprod Med. 2017;44:111-7. doi: 10.5653/cerm.2017.44.2.111.
23. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod. 2011;26:1768-74. doi: 10.1093/humrep/der106.
24. Lensen SF, Wilkinson J, Leijdekkers JA, La Marca A, Mol BWJ, Marjoribanks J, et al. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). Cochrane Database Syst Rev. 2018;2:CD012693. doi: 10.1002/14651858.CD012693.pub2.
25. Haas J, Zilberger E, Machtinger R, Kedem A, Hourvitz A, Orvieto R. Do poor respoder patients benefit from increasing the daily gonadotropin dose during controlled ovarian hyperstimulation for IVF? Gynecol Endocrinol. 2015;31:79-82. doi: 10.3109/09513590.2014.959919.
26. Toftager M , Bogstad J, Løssl K, Prætorius 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: 556-67. doi: 10.1093/humrep/dew358.
27. Drakopoulos P, Blockeel C, Stoop D, Camus M, de Vos M, Tournaye H, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI: how many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? Hum Reprod. 2016;31:370-6. doi: 10.1093/humrep/dev316.
28. Gunnala V, Irani M, Melinck A, Rosenwaks Z, Spandorfer S. One thousand seventy-eight autologous IVF cycles in women 45 years and older: the largest single-center cohort to date. J Assist Reprod Genet. 2018;35:435-40. doi: 10.1007/s10815-017-1088-y.
29. 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;31:572-81. doi: 10.1093/humrep/dev336.
30. Van Loendersloot LL, van Wely M, Limpens J, Bossuyt PMM, Repping S, van der Veen F. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. Hum Reprod Update. 2010;16:577-89. doi: 10.1093/humupd/dmq015.
31. Broekmans FJ. Testing for ovarian reserbve in assisted reproduction programs: the current point of view. Facts Views Vis Obgyn. 2009:1:79-87.
32. La Marca A, Ferraretti AP, Palermo R, Ubaldi FM. The use of ovarian reserve markers in IVF clinical practice: a national consensus. Gynecol Endocrinol. 2015;32:1-5. doi: 10.3109/09513590.2015.1102879.