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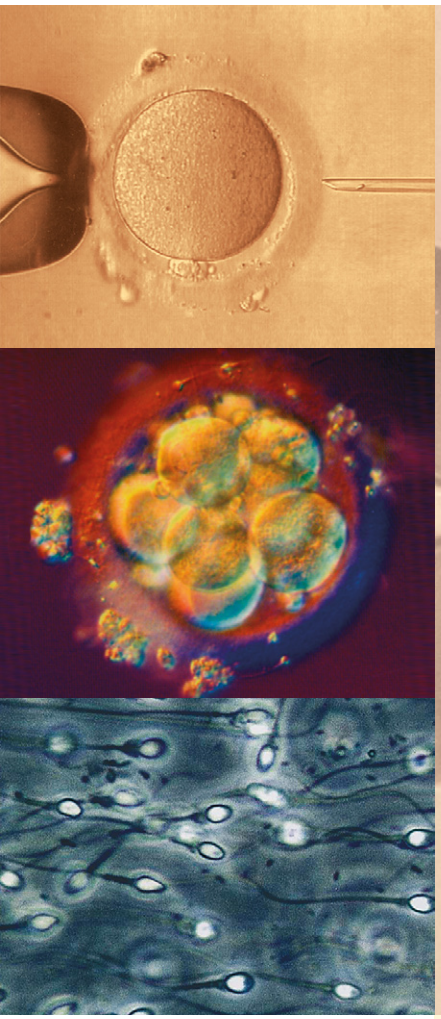

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Prediction of Oocyte Number for Take-Home Baby Rate in Fresh ART Cycles

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To guarantee the IVF success, the retrieval of several oocytes is mandatory to compensate those which reveal fertilization failure or growth arrest and in order to transfer a viable embryo. Thus, the aim of controlled ovarian hyperstimulation (COH) is the growth of multiple follicles and to obtain a high number of mature (metaphase II [MII]) oocytes. Various factors such as the etiology of infertility, the stimulation protocol, or female age can influence the quality as well as quantity of oocytes. However, the pivotal question is the optimal oocyte number for a successful IVF therapy. Therefore, the aim of this retrospective study was to investigate a putative correlation between the oocyte number obtained per fresh cycle for IVF success and the baby take-home rate. In the period 2006–2009, 1345 fresh cycles using the long GnRH-agonist protocol were evaluated. Patients were grouped according to their age and COH response. The number of oocytes obtained per ovum pick-up (OPU) and pregnancy outcome were found to be related to the age of patients. Pregnancy and birth rates were significantly lower in patients when oocyte number was below the expected median of the age group. **J Reproduktionsmed Endokrinol_Online 2015; 12 (1): 19–24.**

Key words: blastocyst development, maternal age, oocyte number at OPU, pregnancy rate, live birth rate/take-home baby rate, expected gamete performance

Introduction

More than 35 years ago, the first in-vitro fertilization (IVF) baby, Louise Brown, was born following a successful natural IVF cycle [1]. Nevertheless, as a major drawback of this method normally one mature egg is produced from a natural cycle and thus and success rates of mono-ovulation hampered by high cancellation rates due to failed oocyte retrieval und subsequent lack of transferable embryo(s). The introduction of controlled ovarian hyperstimulation (COH) to reproductive medicine was instrumental in surmounting this problem, leading to noticeably higher IVF success rates [2–4]. Various protocols for COH have been incorporated into assisted reproductive technologies (ART) to promote adequate oocyte counts for IVF. The most common stimulation protocols are based on gonadotropin-releasing hormone agonist (GnRHa) down-regulation, starting in the mid-luteal phase (long protocol: LP), and GnRH-antagonist (GnRHantag) stimulations [5]. According to reports, the number of oocytes harvested per oocyte pick-up (OPU) in a given patient is related in part to the protocol used [6], although other factors also are implicated in predicting IVF success. Aside from a diagnosis of infertility, the frequency of prior unsuccessful IVF attempts and serum hormone levels are considered critical for clinical success, in addition to fertilization rate (FR), quality of Day 5 embryos, and number of oocytes retrieved [7]. Furthermore, poor ovarian response to gonadotropin is a significant problem in IVF that correlates strongly with diminished ovarian reserve (DOR).

Regardless of the stimulation procedure invoked, maternal age is a key determinant that negatively impacts the number and quality of oocytes retrieved per OPU [8] and ostensibly serves as the best predictive index of DOR. It is common knowledge that DOR bears a high association, not only with a decrease of euploid oocytes but also with reduced pregnancy (PR) and birth rates. However, previous work on the relationship between the number of oocytes retrieved and ART success has demonstrated conflicting results. Although there has been some speculation on the optimal number of oocytes retrieved, no consensus figure has been reached to date. One reason is that most efforts have focused on rates of transferable embryos or PR and ongoing pregnancy rates (oPR), seldom taking live birth rate (LBR) into account [9]. Such studies have also been hampered by non-uniformity of stimulation protocols, the application of an embryo transfer on Day 3, and/or they are neglecting the age factor [9–12].This retrospective study was conducted to analyze number of oocytes retrieved as a factor of age, using a single stimulation protocol (GnRHa-LP). The developmental potential of each embryo and outcomes of IVF were monitored by way of implantation rate (IR), PR, delivery rate (DR), and LBR.

Material and Methods

Patients

Data from 1345 fresh IVF cycles accruing between January, 2006 and December, 2009 were reviewed retrospectively. Cycles, where ET was infeasible due to non-development of embryos (39 cycles), have been excluded. Infertility was attributable to male factors in 44% of couples, to female factors (often multifactorial, including more than one diagnosis) in 22%, and to both male and female factors in 25%. In 9% of couples, infertility was idiopathic. Primary sterility was diagnosed in 48% of patients, with the remaining 52% suffering secondary sterility. Due to the high percentage of male infertility, intracytoplasmatic sperm injection (ICSI) or intracytoplasmatic morphologically selected sperm injection (IMSI) was performed in the majority of the cases (96%). Mean age of patients at time of OPU was 35.8 years (range, 21–46 years). Patients were grouped by age (group I: 21–35 years; group II: 36–39 years; and group III: > 39 years). Median number of oocytes obtained per OPU was determined for each group. Patients with counts below the median were designated "poor responders," whereas those with counts be-

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Table 1. Age group I (21–35 years). Mean number of cumulus oocyte complexes (COCs) and metaphase II (MII) oocytes, the number of 2 pronuclei (2PN) number of (top-) embryos, number of embryos transferred as well as (ongoing) pregnancy rates, implantation rate, delivery and live birth rate were given.

Age group I 21–35 years	**Total number of patients: n = 572 Median: 10 oocytes/OPU**		
	Poor responders (1–9 oocytes)	**Normal responders (10–15 oocytes)**	**High responders (> 15 oocytes)**
Number of patients	227	239	106
Mean age (years)	31.6	31.3	31.3
Number of oocytes (mean)	1317 (5.8)	2797 (11.7)	2066 (19.5)
Number of MII (mean)	1122 (4.9)	2399 (10.0)	1749 (16.5)
Rate of MII (%)	85.2	85.8	84.9
Number of 2PN (mean)	886 (3.9)	1796 (7.5)	1366 (12.9)
FR (%)	79.0*	74.9	78.1*
Nb. blastocysts/embryos (mean)	553 (2.5)	1023 (4.3)	707 (6.7)
Rate embryos (%)	62.4*	57.0	51.8***
Nb. of top-blastocysts (mean)	150 (0.7)	213 (0.9)	149 (1.4)
Rate top-blastocysts (%)	16.9***	11.9	10.9
ET top-blastocysts (%)	104 (45.8)	118 (49.4)	55 (51.9)
Embryos/ET (mean)	407 (1.8)	423 (1.8)	169 (1.6)
PR (%)	93 (41.0)***	148 (61.9)	58 (54.7)
oPR (%)	80 (35.2)***	124 (51.9)	50 (47.2)
IR (%)	94 (23.1)***	152 (35.9)	62 (36.7)
Delivery rate (%)	74 (32.6)**	113 (47. 3)	45 (42.5)
Number of singletons	59	89	35
Number of twins	15	23	9
Number of triplets	–	1	1
LBR (%)	89 (21. 9)***	137 (32.4)	55 (32. 5)

ET = embryo transfer; FR = fertilization rate; IR = implantation rate; LBR = live birth rate; oPR = ongoing pregnancy rate; PR = pregnancy rate; n. s. = not significant; * = $p < 0.05$; **= $p < 0.01$; *** = $p < 0.001$.

tween the median and a cutpoint of 15 oocytes and those with counts > 15 were considered "normal" and "high" responders, respectively.

Stimulation Protocol

In all patients, GnRHa-LP (as previously described) was used for ovarian stimulation [13]. To down-regulate the pituitary gland, 0.1 mg of triptorelin (Decapeptyl®, Ferring Arzneimittel, Vienna, Austria) was injected subcutaneously on a daily basis, starting at mid-luteal phase of the previous cycle. Human menopausal gonadotropin (HMG) (Merional®, IBSA, Lugano, Switzerland; Menogon-HP®, Ferring Arzneimittel, Vienna, Austria) was also administered for follicular stimulation. From Day 6 or 7 of stimulation onwards, a transvaginal ultrasound scan was performed every 2–3 days to assess follicular size, up to a size of 18–20 mm. Final oocyte maturation was triggered by injecting 5000–10,000 IU β-human choriongonadotropin (HCG) (Pregnyl®, Organon, Vienna, Austria; Brevactid®; Ferring Arzneimittel, Kiel, Germany).

Oocyte Retrieval and Embryo Transfer

Transvaginal oocyte retrieval was conducted 35 hours after HCG-administration. HMG dosage was regulated by patient response from Day 6 onwards. Luteal phase support consisted of three 2 mg estradiol valerate tablets (Progynova®, Bayer, Leverkusen, Germany) daily and 100 mg progesterone (Prontogest®, IBSA, Lugano, Switzerland) given every 36 hours by intramuscular injection or alternatively as 3× 200 mg Utrogestan® tablets daily, intravaginally (Meda Pharma, Vienna, Austria). Additionally, 2500 IU β-HCG was administered on Days 3 and 8 after oocyte retrieval when there was no clear risk of ovarian hyperstimulation syndrome. In a previous cycle, each patient was subjected to cervical dilatation, using a no. 5 Hegar dilator, and the length of the uterine cavity was mechanically measured by means of a probe. Mucus was removed from the external uterine orifice prior to ET. Wallace catheters were used for all ETs.

Embryo Culture

Oocyte-cumulus complexes were cultured in HTF media (Life Global, Ontario, Canada) for 2–4 hours before fertilization by either standard insemination or ICSI/IMSI. Fertilized oocytes were maintained in a single medium (Life Global), with 7.5% human serum albumin (Life Global). Fertilization was then appraised 16–20 hours post-insemination. On Day 3, embryos were placed in fresh culture medium and cultured in 4-well dishes (Nunc A/S, Roskilde, Denmark) until transfer at Day 5. Prior to ET, each embryo was graded by degree of blastocoele expansion and by nature of both inner cell mass and trophectoderm, as described elsewhere [14]. Blastocysts expanded to 2-, 3-, 4-, and 5-cell stage, with A-grading for inner cell mass and trophectoderm or combined A- and B-grading were designated top-quality blastocysts.

Clinical Outcomes

PR was determined 17 days after ET by urinary β-HCG testing, defining oPR as

Table 2. Age group II (36–39 years). Mean number of cumulus oocyte complexes (COCs) and metaphase II (MII) oocytes, the number of 2 pronuclei (2PN) number of (top-) embryos, number of embryos transferred as well as (ongoing) pregnancy rates, implantation rate, delivery and live birth rate were given.

Age group II 36–39 years	**Total number of patients: n = 462 Median: 8 oocytes/OPU**		
	Poor responders (1–7 oocytes)	**Normal responders (8–15 oocytes)**	**High responders (> 15 oocytes)**
Number of patients	207	206	49
Mean age (years)	37.8**	37.4	37.7
Number of oocytes (mean)	987 (4.8)	2150 (10.4)	940 (19.2)
Number of MII (mean)	846 (4.1)	1856 (9.0)	793 (16.2)
Rate of MII (%)	85.7	86.3	84.4
Number of 2PN (mean)	670 (3.2)	1467 (7.1)	605 (12.4)
FR (%)	79.2	79.0	76.3
Nb. blastocysts/embryos (mean)	421 (2.0)	754 (3.7)	311 (6.4)
Rate embryos (%)	62.8***	51.4	51.4
Nb. of top-blastocysts (mean)	114 (0.6)	128 (0.6)	66 (1.4)
Rate top-blastocysts (%)	17.0***	8.7	10.9
ET top-blastocysts (%)	76 (36.7)	92 (44.7)	27 (55.1)
Embryos/ET (mean)	368 (1.8)	396 (1.8)	28 (57.1)
PR (%)	74 (36.7)**	103 (50.0)	28 (57.71)
oPR (%)	62 (30.0)**	88 (42.7)	22 (44.9)
IR (%)	76 (20.7)	104 (26.3)	29 (30.2)
Delivery rate (%)	56 (27.1)*	76 (36.9)	17 (34.7)
Number of singletons	44	59	13
Number of twins	12	16	4
Number of triplets	–	1	–
LBR (%)	68 (18.5)	93 (23.5)	21 (21.9)

ET = embryo transfer; FR = fertilization rate; IR = implantation rate; LBR = live birth rate; oPR = ongoing pregnancy rate; PR = pregnancy rate; n. s. = not significant; * = $p < 0.05$; **= $p < 0.01$; *** = $p < 0.001$.

the percentage of subjects with at least one viable fetus (positive fetal heart beat) confirmed by transvaginal ultrasound. The IR was defined as number of fetal heart beats observed per transferred embryo. The delivery rate (DR) is the number of patients giving birth after embryo transfer. LBR was defined as the number of children born per transferred embryos [15].

Statistical Analysis

Differences in the rates of implantation, pregnancy, miscarriage, and birth were evaluated using the Pearson's chi-squared test. A two-tailed t-test was used to test for differences in blastocyst quality and growth. Differences between the groups were considered statistically significant when the p-value was < 0.05. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 17.0 for Windows (SPSS Inc., USA).

Results

Number and Quality of Oocytes in Defined Age Groups

Age group I (21–35 year-olds) included 572 patients, with a median oocyte count of 10 (Table 1). Group II (36–39 years) included 462 patients, with a median oocyte count of 8 (Table 2). In group III (> 39 years), there were 311 patients, with a median oocyte count of 6 (Table 3). Interestingly, almost no differences in observed rates of MII oocytes were evident among all age and response groups.

Correlating Fertilization, Blastocyst, Pregnancy, and Delivery Rates with Age and COH Response

Compared with older patients, those of age group I (21–35 years) displayed some statistical differences in terms of FR and rates of (top-quality) embryos respectively; however, differences observed in IR, PR, DR, and LBR were highly significant. Embryo and top-quality blastocyst rates were higher in poor responders, but sharp, significant drops in PR, oPR, IR, DR, and LBR was recorded for poor responders of group I (Table 1).

Findings were similar for age groups II and III (Table 2, 3). Higher embryo and top-quality blastocyst rates were seen in poor responders (n = 207). On a percentage basis, top-quality ETs and numbers of embryos transferred to poor, normal, and high responders did not differ significantly within any age group (Table 1–3), but PR, oPR, IR, and DR were all significantly lower in poor responders by comparison (Table 2). Percentages of embryos and top-quality blastocysts were 2- and nearly 3-fold higher in poor responders (n = 134) than in high responders (71.6 vs 37.8% and 19.8 vs 6.8%, respectively; normal responders: 48.5% and 8.0%, respectively) (Table 3), whereas PR, IR, and DR were generally lower than in normal or high responders within same age groups. LBR declined substantially (as expected) in women > 39 years.

Table 3. Age group III (> 39 years). Mean number of cumulus oocyte complexes (COCs) and metaphase II (MII) oocytes, the number of 2 pronuclei (2PN) number of (top-) embryos, number of embryos transferred as well as (ongoing) pregnancy rates, implantation rate, delivery and live birth rate were given.

Age group III > 39 years	**Total number of patients: n = 311 Median: 6 oocytes/OPU**		
	Poor responders (1–5 oocytes)	**Normal responders (6–15 oocytes)**	**High responders (> 15 oocytes)**
Number of patients	134	156	21
Mean age (years)	41.6	41.2	41.1
Number of oocytes (mean)	464 (3.5)	1346 (8.6)	390 (18.6)
Number of MII (mean)	387 (2.9)	1119 (7.2)	333 (15.9)
Rate of MII (%)	83.4	83.1	85.4
Number of 2PN (mean)	313 (2.3)	890 (5.7)	249 (11.9)
FR (%)	80.9	79.5	74.8
Nb. blastocysts/embryos (mean)	224 (1.7)	432 (2.8)	94 (4.5)
Rate embryos (%)	71.6***	48.5	37.8**
Nb. of top-blastocysts (mean)	62 (0.5)	71 (0.5)	17 (0.8)
Rate top-blastocysts (%)	19.8***	8.0	6.8
ET top-blastocysts (%)	52 (38.8)	54 (34.6)	9 (42.9)
Embryos/ET (mean)	249 (1.9)	336 (2.2)	44 (2.1)
PR (%)	24 (17.9)*	45 (28.8)	9 (42.9)
oPR (%)	14 (5.6)*	33 (21.1)	5 (23.8)
IR (%)	15 (6.0)*	36 (10.7)	5 (11.4)
Delivery rate (%)	11 (8.2)*	25 (16.0)	2 (9.5)
Number of singletons	10	25	2
Number of twins	1	–	–
Number of triplets	–	–	–
LBR (%)	12 (4.8)	25 (7.4)	2 (4.5)

ET = embryo transfer; FR = fertilization rate; IR = implantation rate; LBR = live birth rate; oPR = ongoing pregnancy rate; PR = pregnancy rate; n. s. = not significant; * = $p < 0.05$; **= $p < 0.01$; *** = $p < 0.001$.

Only 12 babies were born after 134 ETs in poor responders, compared with 25 babies in 156 normal responders (4.8 vs 7.4% LBR).

Discussion

A heated debate continues over the number of oocytes that should be retrieved per IVF cycle for best chance of a live birth. The importance of this issue has grown with the more widespread use of fertility preservation. Patients opting for cryopreservation want to know how many oocytes are needed to enable conception at a later point in life. Similarly, there is still much controversy regarding the optimal stimulation protocol. Despite calls for mild or soft stimulations, standard hyperstimulation protocols remain essential for good results [16, 17].

Various factors such as patient age, ovarian response, and hormone levels are thought to influence oocyte and embryo quality, as well as the implantation process. The relationship between counts of retrieved oocytes, COH, hormonal levels, and age of recipients are undisputable. Many trials have been conducted to evaluate the optimal number of oocytes retrieved as a predictive index of IVF outcome(s).

Verberg et al [6] hypothesized in a meta-analysis that the optimal number of oocytes with the GnRHa-LP is 10 (IR 30.7%). Higher numbers of oocytes seemed to be needed in other reports. Van der Gaast also analyzed data from 7422 fresh IVF cycles where the GnRHa-LP was used. The highest PRs (31% and 28% per ET and per started cycle, respectively) were observed in a young patient collective at a level of 13 oocytes, whereas for women > 38 years of age, 17.6 ± 2.6 oocytes were found to be optimal [18].

Sunkara and colleagues conducted a large study, using the UK national ART registry, arriving at a peak of approximately 15 oocytes as the optimal number for a live birth. Although this study encompassed 400,135 IVF cycles over a period of 17 years, there were serious weaknesses. Differing stimulation protocols with varying culture conditions and transfer procedures undermined the reliability of conclusions drawn [10]. In another study, investigators reported an optimal number of 6–14 MII oocytes per OPU. The latter is in accordance with our findings in younger patients, albeit statistical power was lacking to discriminate by age group [12].

Compared with other investigations our approach was unique. We questioned whether the number of oocytes obtained per OPU (relative to stimulation protocol, patient age, hormonal influences, and ovarian reserve) correlated with LBR, as the primary outcome in IVF. We established a cut-off value based on the median number of oocytes retrieved at OPU. Of note, increased percentages of blastocysts and top-quality embryos were seen in poor responders within all age groups in comparison to normal responders (blastocysts: 21–35 years,

62.4% vs 57.0%; 36–39 years, 62.8% vs 51.4%; > 39 years, 71.6% vs 48.5%; top-quality embryos/patient: 21–35 years: 16.9% vs 11.9%; 36–39 years, 17.0% vs 8.7%; >39 years, 19.8% vs 8.0%). However, this increase was not mirrored by PR and DR data. Although recipients of top-quality embryos were comparable in number for all groups, significantly higher PR, oPR, and DR were found when at least median oocyte counts (21–35 years, 10 oocytes; 36–39 years, 8 oocytes; and > 39 years, 6 oocytes) were achieved, indicating that the potential of embryos to implant was higher in these subsets.

Similar observations were made by Figueira and colleagues and Nichi et al [19, 20]. They found similar fertilization- and top-embryo rates on Day 3 in poor as compared with normal responders, but in line with our findings, pregnancy rates were remarkable lower in the poor responder group. These researchers ultimately concluded that embryos derived from poor responders may have impaired biologic capacity [20]. Unfortunately, the above investigations involved Day 3 embryos, evaluating morphology before onset of embryonic genome activation (EGA). Indeed, it has been demonstrated that conventional morphologic scoring systems of oocyte and embryo quality on Day 3 do not correlate with patient age [21]; and advancing age bears a strong association with reduced implantation potential. Additionally and contrary to various other studies, we found considerably higher pregnancy and live birth rates. This observation, however, is probably due to the blastocyst culture and ET on Day 5 in our approach. The superiority of blastocyst culture and ET on Day 5 (better embryo selection due to the consideration of the late paternal effect and improved uterine and embryonic synchronicity) is reflected by increased implantation- and live birth-rates compared to cleavage stage (Day 2/3) ET. In past years, this phenomenon has been well-documented by numerous publications [13, 22–24].

Blastocyst score is the actually best predictor of implantation and pregnancy rates [25]. The rate of aneuploidy is much lower in embryos that reach blastocyst stage, and aneuploidy is less likely in top-quality blastocysts [26]. However, rates of aneuploidy may be higher in poor-responder subsets due to unfavorable genetic pre-condition(s). Although the data situation is in part still controversial, it was shown that monosomy and/or trisomy is more frequent in embryos of poor responders [27]. Additionally, another important aspect must be taken into consideration. To access adequate ovarian response higher dose of FSH are applied in the COH of poor responders which might also elevate the risk of embryonic chromosomal errors [28]. Hence, chromosomal abnormalities of the embryos may largely account for reduced implantation rates in poor responder patients despite having some good morphology embryos.

In summary, it is worth to mention that the question of the optimal oocyte number for the IVF outcome is, however, definitely not a simple one. Each trial aimed at this question has limitations of some nature. We also must concede that our analysis was restricted to fresh cycles and did not include cryo cycles in our approach as many patients had not yet presented for a subsequent cryo cycle. The calculation of the cumulative PR in the "normal and high responders" would probably strengthen our findings.

In addition, it has to be kept in mind that several other factors might also influence the IVF outcome e.g. the sperm parameters according to MSOME criteria, body weight, the medical history, and the lifestyle factors of patients [7, 29, 30]. As pointed out in a previous publication of ours [31], retrieved oocyte count is but one side of the coin. The current means of predicting individual chances to conceive rightly should be revised, basing projected IVF outcomes on blastocyst cultures and establishing "expected gamete performance" (EGP) benchmarks [31].

Conclusions

Although various publications have focused on the relationship between counts of oocyte retrieved and ART outcomes (e.g., LBR), there is no agreement to date on an optimal number of oocytes. This study demonstrates that oocyte number correlates strongly with PR and DR, based on median oocyte counts in distinct age groups. Ovarian response below the median is thus predictive of lower IVF success. Female age is doubtless a solid index of live birth in IVF therapy. This was supported by our study and an important reason to attach greater weight to this issue than previous studies. A large pool of information is still required to complete the picture, perhaps revising the accepted definition of "responder" in the course of future studies.

Conflict of Interest

No potential conflict of interest to this article was reported.

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