Fertilization rate as a novel indicator for cumulative live birth rate: a multicenter retrospective cohort study of 9,394 complete in vitro fertilization cycles

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Objective: To appraise the fertilization rate as a predictive factor for cumulative live birth rate (CLBR).
Design: Multicenter retrospective cohort study.
Setting: Ten in vitro fertilization clinics, whose data were collected and processed by the assisted reproductive technology (ART) Italian National Registry.
Patient(s): 7,968 couples undergoing 9,394 complete intracytoplasmic sperm injection cycles.
Intervention(s): None.
Main Outcome Measure(s): The primary outcome measure was the CLBR in association with the fertilization rate intervals (<65%–group 1; 65%–80%–group 2; and >80%–group 3). Further data stratification was performed on the basis of maternal age (<34, 35–38, and 39–42 years) and number of retrieved oocytes (5–7, 8–10, and > 10 oocytes).
Result(s): The CLBR was progressively higher in relation to the fertilization rate in groups 1, 2, and 3 (20.1%, 34.7%, and 41.3%, respectively). The number of recovered oocytes, embryo number per cycle, and cumulative pregnancy rate followed the same trend. The decrease in CLBR with increasing maternal age was significantly correlated with the fertilization rate and CLBR in all 3 maternal age groups. Multivariate logistic regression analysis showed fertilization rate as a factor independently associated with CLBR.
Conclusion(s): The present data indicated a positive association between the fertilization rate and the CLBR, suggesting the predictive clinical relevance of this parameter and its adoption as a key performance indicator. (Fertil Steril® 2021;116:766-73. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Fertilization, cumulative live birth rate, female age, oocytes, pregnancy

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The primary goal of assisted reproductive technology (ART) is to maximize the chances to achieve a healthy live birth from a treatment cycle while minimizing the odds of multiple pregnancies (1–3). Awareness and dedication to this aim should be a priority, especially for the interest the patients have in the outcome (4).

It is therefore crucial that ART specialists share with patients the objectives and the correct information relevant to treatment success rates and the health of the conceptus. For many years, the question of an ideal parameter able to express overall clinical efficacy has been intensely discussed (5). Concomitantly, increasingly successful cryopreservation technologies have supported a growing trend toward single embryo transfer and cryopreservation of supernumerary embryos (6–7).

Indeed, because they have an unaltered ability to implant and develop to term (8), cryopreserved embryos have become a main route to achieve a live birth and improve the cumulative outcome per treatment cycle (9, 10). In this regard, a formula expressing the success rate of a treatment cycle should not be limited only to the results of fresh embryo transfers; it should necessarily be extended to the use of cryopreserved embryos to provide an outcome measure as objective and comprehensive as possible. Consistent with this, the cumulative live birth rate (CLBR) was proposed as the outcome able to include the overall reproductive potential of a stimulation cycle, once fresh and cryopreserved embryos have been transferred (11–13). Not only is this outcome more appropriate to measure the clinical outcome with greater objectivity, but it additionally offers a better tool to comparatively assess the efficacy of different treatment options and their costs (12).

Notwithstanding, how to define and measure the clinical outcome cannot prescind from the intrinsic and case-specific factors, that strongly influence treatment success. Numerous studies aimed at characterizing outcome predictors. Maternal age was historically and correctly recognized as the single most important factor influencing the clinical outcome of ART. It is therefore largely adopted by clinicians and patients as the principal criterion on which to make the decision to undertake a treatment cycle. More recently, the ovarian reserve or ovarian response, the latter defined as the number of retrieved oocytes, additionally gained interest in this respect. However, the quest for novel, more comprehensive predictive factors is not over; new relevant evidence is starting to emerge. In a retrospective study, Cai et al (14) identified different independent factors able to predict the chances to achieve a clinical pregnancy after a completed in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycle. Among the parameters assessed by multivariate analysis, the fertilization rate was significantly associated with the clinical outcome. However, in that study, the magnitude of the influence was not precisely assessed.

The fertilization rate is a noteworthy parameter that is potentially more comprehensive than the ovarian response as a predictive factor, because it expresses a fundamental aspect of both oocyte and sperm developmental competence. In fact, unsurprisingly, it has been adopted as a key performance indicator of the IVF laboratory to assess laboratory, operator, and gamete competence (15).

In this perspective, compared with other established predictors, in the present multicenter retrospective study we assessed the ability of the fertilization rate to predict the treatment outcome expressed by the CLBR. To this end, the fertilization rate was classified in ranges according to the thresholds of competency and benchmark defined by the Vienna Consensus (15).

MATERIALS AND METHODS

In 2016, the Italian National Registry launched a new database platform to collect data from individual IVF treatments, overcoming the computational limitations of the previous data collection that occurred in an aggregate form. The database platform was then initially tested with 10 public and private IVF clinics. Data from couples undergoing nondonor ICSI cycles from January 2015 to December 2017 were extracted from this source and retrospectively reviewed. Patient consent to use the treatment data for the purpose of the present study was granted by the same regulatory framework guiding the collection of ART treatment records operated by the Italian National Registry on behalf of the Italian Ministry of Health, therefore Institutional Review Board approval was not necessary.

Patients' Eligibility Criteria

All women aged between 18 and 42 years undergoing an ovarian stimulation cycle were included. To meet the criteria for the logistic regression model used in the study, only completed treatment cycles were analyzed. We excluded from analysis: surgical sperm retrieval cases; oocyte retrievals for fertility preservation; cycles resulting in neither fresh nor frozen–thawed embryo transfers in a complete treatment cycle; cycles in which pregnancies were not achieved, but with the remaining embryos cryopreserved; cycles of preimplantation genetic testing; cycles with fertilization failure; and standard IVF (non-ICSI) cycles. Standard IVF cases were excluded because oocyte maturity, and therefore fertilization rate, cannot be accurately assessed at the time of insemination. In the final analysis, all patients included in the study completed an ICSI cycle, having achieved a live birth or having used all cryopreserved embryos.

Dataset

The cycles were stratified into 3 groups, depending on the fertilization rate intervals on the basis of the recommendations of the Vienna Consensus (group 1: <65%; group 2: 65%–80%; Group 3: >80%). These intervals of the ratio between the normally fertilized oocytes and the microinjected oocytes were defined by the threshold values for competency (65%) and the aspirational benchmark (>80%).

A total of 9,394 complete cycles with at least 1 normally fertilized oocyte was finally selected for the cumulative analysis. A complete cycle was oocyte retrieval, followed by fresh transfers or with cryopreserved embryos, until all of the embryos produced were used or the birth of a live child.

Harnessing the large size of the original dataset, further cycle stratifications were performed on the basis of the women's age (<34, 35–38, and 39–42 years) and the number of oocytes retrieved (5–7, 8–10, and >10 oocytes). The stratification for these age groups was chosen because it was conventionally used in the processing of clinical data.

The primary outcome measure was the CLBR, and the delivery of a singleton, twin, or other multiples was registered as 1 delivery (16).

Statistical Analysis

Multivariable stratified analyses were performed, testing for differences between groups. We compared the populations through analysis of variance with the one-way ANOVA procedure for a quantitative dependent variable.

Univariable and multivariable logistic regressions were performed to evaluate associations with cumulative live birth. The model included patient and cycle characteristics. We tested all 2-way interactions between pairs of predictors included in our multivariable analyses and used a Bonferroni-correction (for multiple testing) *P*-value threshold of .05 to define statistical evidence of an interaction. The predictive value of the resulting model was assessed by calculating the area under the curve of the receiver operator characteristics (AUROC). To evaluate the level of agreement between the estimated and the observed probabilities (calibration), the Hosmer–Lemeshow test was used. All statistical analyses were performed using IBM SPSS Statistics 26.

RESULTS

In the overall set of 9,394 complete ICSI cycles included in the study, the fertilization rates in the intervals <65%, 65%–80%, and >80% were observed in 3,691, 2,099, and 3,703 cycles, respectively.

The cycle characteristics and clinical outcome of study groups are reported in Table 1. No statistically significant difference in maternal age was observed between the fertilization rate groups ($P=.640$). Predictably, the numbers of fertilized oocytes and the available embryos were statistically significantly different among the groups ($P<.001$, in both cases). The number of embryos increased progressively in fertilization rate groups 1, 2, and 3. The same trend was observed for the cumulative pregnancy rate and the CLBR (20.1%, 34.7%, and 41.3%, respectively; $P<.001$).

Analysis of the relationship between the fertilization rate and the other key performance indicators (KPIs), such as the cleavage rate and implantation rate, showed a consistent trend of improved performance in groups 3 and 2 compared with 1 group.

In particular, the cleavage rate showed a positive correlation with increasing fertilization rate (95.8%, 98.0%, and 98.3% in groups 1, 2, and 3, respectively; $P<.01$). In addition, a positive association was observed between the fertilization rate and the implantation rate, irrespective of whether this outcome was expressed as the overall rate (18.4%, 22.9%, and 26.2% for groups 1, 2, and 3, respectively; $P<.01$) or after transfer at the cleavage (16.1%, 18.7%, and 21.5%, respectively; $P<.01$) or blastocyst stage (30.5%, 33.6%, and

TABLE 1

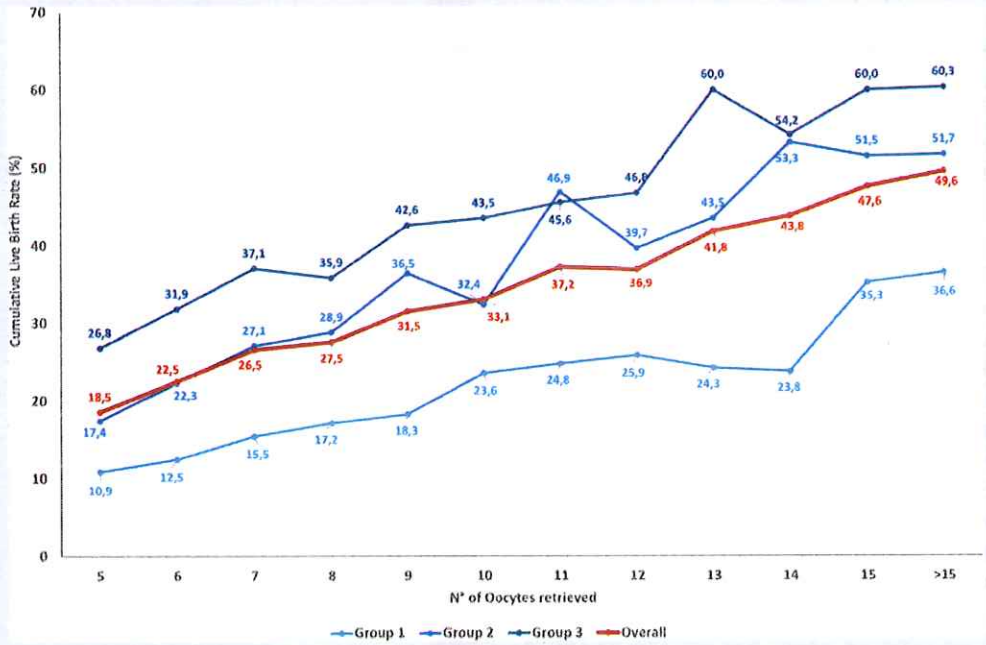
Cycle characteristics and clinical outcome of study groups.

	Level of fertilization rate (FR) groups			
	Group 1	Group 2	Group 3	Total
No. of oocyte retrievals (%)	3,691 (38.9)	2,099 (22.1)	3,703 (39.0)	9,493 (100)
No. of MII oocytes (%)	26,656 (74.5)	16,302 (75.6)	26,940 (75.1)	69,898 (75.0)
Age—mean ± SD [95% CI]	36.07 ± 4.3 [35.93–36.21]	36.17 ± 4.1 [36.00–36.35]	36.08 ± 4.0 [35.95–36.21]	36.1 ± 4.2 [36.01–36.18]
No. of retrieved oocytes (mean ± SD) [95% CI]	35,786 (9.70 ± 4.6) [9.55–9.84]	21,552 (10.27 ± 4.9) [10.06–10.48]	35,893 (9.69 ± 4.8) [9.54–9.85]	93,231 (9.82 ± 4.8) [9.73–9.92]
No. of inseminated oocytes (mean ± SD) [95% CI]	24,961 (6.76 ± 3.1) [6.66–6.86]	15,053 (7.17 ± 3.1) [7.04–7.31]	24,204 (6.54 ± 2.7) [6.45–6.62]	64,218 (6.76 ± 3.0) [6.70–6.83]
N. of fertilized (2pn) oocytes (mean ± SD) [95% CI]	11,000 (2.98 ±1.9) [2.92–3.04]	10,776 (5.13 ± 2.3) [5.04–5.23]	21,919 (5.92 ± 2.5) [5.84–6.00]	43,695 (4.60 ± 2.6) [4.55–4.66]
No. of available embryos (mean ± SD) [95% CI]	6,951 (1.88 ± 1.3) [1.84–1.92]	5,709 (2.72 ± 1.5) [2.66–2.78]	11,166 (3.02 ± 1.6) [2.96–3.07]	23,826 (2.51 ± 1.6) [2.48–2.54]
No. of pregnancies (%)	969 (26.3)	883 (42.1)	1,796 (48.5)	3,648 (38.4)
No. of CLBR per OPU (%)	743 (20.1)	729 (34.7)	1,529 (41.3)	3,001 (31.6)

Note: CI = confidence interval; CLBR = cumulative live birth rate; FR = fertilization rate; MII = metaphase II; OPU = oocyte pickup; SD = standard deviation.

Scaravelli. Fertilization rate and clinical outcome. Fertil Steril 2021.

FIGURE 1



Cumulative live birth rate according to number of oocytes retrieved and level of fertilization rate.

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36.5%, respectively; $P<.05$) (Supplemental Table 1, available online).

A subsequent subanalysis revealed an increase in the CLBR as a function of the number of recovered oocytes per cycle or the fertilization rate (Fig. 1). The cycles in group 1 had results significantly lower than the average results, the cycles in group 2 had results comparable to the average, and the cycles with high fertilization (group 3) had results significantly higher than the average.

The same trend was found after stratification by age as shown in Figure 2. In patients aged <34 years, the CLBR increased significantly with increasing levels of fertilization from 29% to 48.8% to 55.6% ($P<.001$). In the 35–38 years old patient group, the increase in the CLBR was from 22% to 36.9% to 42.3%, respectively, in the 3 fertilization rate groups ($P<.001$). In older patients (39–42 years old), the CLBR rose from 10% to 18.8% up to 25.2% in the group with the highest fertilization rate ($P<.001$).

In addition to the women's age, the fertilization rate groups were further compared, in consideration of the impact of the number of retrieved oocytes on CLBR. Supplemental Figure 1A to C illustrates the CLBR in relation to the intervals of the women's age and the number of retrieved oocytes. In the lower range of retrieved oocytes (5–7), the CLBR was positively associated with the fertilization rate in the entire population, even after subanalysis according to the women's age (Supplemental Fig. 1A). In the middle range of the number of retrieved oocytes (8–10), the CLBR increased significantly with increasing fertilization rate in the general population and in the younger, but not the middle or older, women's age groups (Supplemental Fig. 1B). In the higher range of number of retrieved oocytes (>10), the CLBR increased significantly with increasing fertilization rate in the general population and in the older women's age group. In cycle with the middle and older maternal age, differences in CLBR were observed between the lower and the middle fertilization rate groups, whereas a further increase was not found with fertilization rates >80% (Supplemental Fig. 1C).

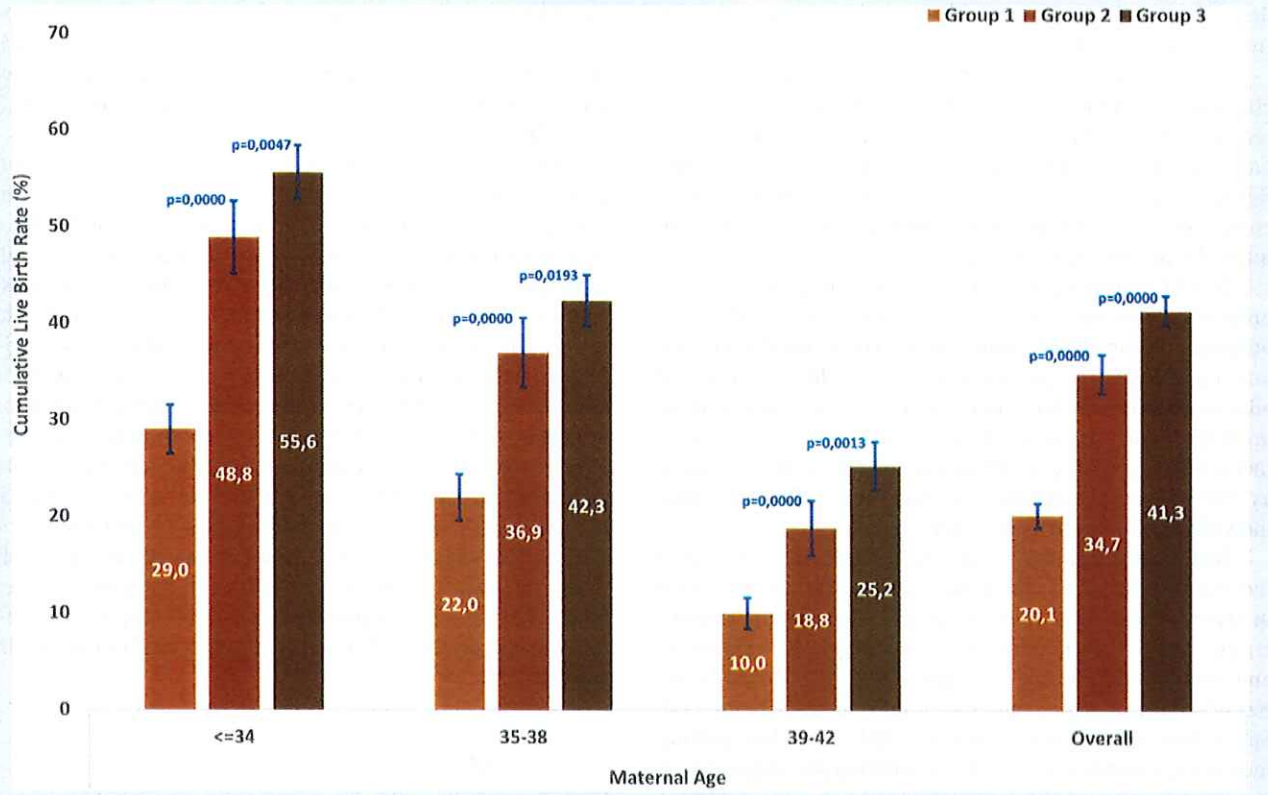
Supplemental Figure 2 shows the impact of the fertilization rate, after normalization for the number of recovered and inseminated oocytes, on the number of fertilized oocytes and on the number of embryos suitable for transfer or cryopreservation.

Finally, to further control for possible patient-specific confounding factors, the maternal age, number of retrieved oocytes, percent of inseminated oocytes, and fertilization rate were evaluated in a multivariate logistic regression analysis. The inseminated oocytes were analyzed as a percentage rather than absolute values. This allowed analysis of retrieved and inseminated oocytes as mutually independent variables. From this assessment, the fertilization rate emerged as a factor independently associated with the CLBR, to a degree equivalent to or greater than that of the number of retrieved oocytes (Table 2).

DISCUSSION

The present data indicated a positive association between the fertilization rate and the CLBR, suggesting the predictive clinical relevance of this parameter and its adoption as a KPI.

FIGURE 2



Cumulative live birth rate according to age, number of oocytes retrieved and level of fertilization rate.

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Collection, management, and interpretation of the outcome data of ART treatments are essential to develop awareness of safety, efficacy, and efficiency (17–19). Aimed at fulfilling such goals, IVF registries play an essential role in the interest of the public, patients, policy makers, and the scientific community.

The CLBR has progressively gained importance as a suitable outcome measure in IVF, because it recapitulates the

TABLE 2

Multivariate logistic regression analysis.

Groups	Categories	Univariable odds ratio of cumulative live birth (95% CI)	Multivariable odds ratio of cumulative live birth (95% CI)	*P* value
Maternal age (years)	39–42	1	1	<.001
	35–38	2,394 (2,129–2,692)	2,212 (1,959–2,499)	
	≤34	3,268 (3,232–4,071)	3,358 (2,976–3,789)	
No. of retrieved oocytes	5–7	1	1	<.001
	8–10	1,523 (1,358–1,706)	1,418 (1,257–1,599)	
	≥11	2,688 (2,423–2,983)	2,716 (2,422–3,046)	
% inseminated oocytes	<60%	1	1	<.001
	60%–74.9%	1,03 (0,91–1,166)	1,255 (1,097–1,435)	
	75%–87%	1,046 (0,925–1,182)	1,436 (1,255–1,644)	
	>87%	1,163 (1,029–1,314)	1,736 (1,513–1,993)	
% fertilization	<65%	1	1	<.001
	65% – 80%	2,111 (1,871–2,382)	2,144 (1,889–2,433)	
	≥80%	2,791 (2,516–3,095)	3,076 (2,757–3,432)	

Note: CI = confidence interval.

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overall chances of success of a treatment cycle (9–13, 20). However, computation of this outcome is not straightforward, because it requires information on the destiny of both fresh and cryopreserved embryos derived from a single oocyte recovery.

Unfortunately, registry collection of the data required to elaborate the CLBR is technically challenging and for such a reason often incomplete. Ten representative IVF clinics freely participated in a pilot project promoted by the Italian ART Registry that aimed to assess the feasibility of data cycle collection in a nonaggregated format. This inspired and made the present study possible.

In ART treatment, several parameters are associated with pregnancy outcome, such as age, duration of infertility, baseline hormone levels, antral follicle count, oocyte number, and oocyte/embryo quality (14, 21–24). Identification of additional and possibly more comprehensive independent predictors, such as the fertilization rate, is a goal aimed at increasing our ability to predict the CLBR, now recognized as the ultimate outcome measure, thus allowing more individualized treatment decisions.

Historically and on the basis of the evidence, the role of the female gamete has overshadowed the role of the sperm in embryogenesis and, more generally, reproduction. However, the sperm actively participates in the genetic, epigenetic, and cellular makeup of the embryo (25, 26). Crucially, an essential part of sperm function unfolds at fertilization (13). Sperm function and its expression in ART is therefore gaining increasing interest (13, 27, 28), as additionally suggested by the identification of the fertilization rate as a key indicator of the IVF laboratory performance (15).

Consistent with this, a retrospective cohort study published by Rosen et al. (29) in 2010 on 3,603 couples undergoing IVF treatment demonstrated that the fertilization rate was associated with the implantation rate. The present study expanded on this, assessing the possible impact of the fertilization rate on the CLBR by attempting to integrate both oocyte- and sperm-derived functions in a single parameter. The large number of cycles collected in the present study indeed allowed quantification of the impact of the fertilization rate on the CLBR, while controlling for other important outcome predictors, such as maternal age and number of retrieved oocytes.

The present data indicated a positive association of the fertilization rate with the CLBR, thereby suggesting that fertilization, in addition to representing an assay for gamete quality and laboratory performance, has an independent clinical significance. This should not be surprising, because the regulatory mechanisms required for fertilization are believed to influence the development and health of the conceptus (30).

In most IVF programs, on average, fertilization rates of 70%–75% are not uncommon. However, among individual cycles, a large variability in fertilization rates is observed because of the effects of parental and mutually interactive factors (29). In addition, although ICSI alleviates the impact of sperm quality on outcome, the present data indicates a difference in fertilization rates between centers, with a predictable downstream impact effect on the CLBR. This suggests the importance of monitoring the fertilization rate as a laboratory KPI to maximize operator performance and overall clinical outcome. Overall, this context attributes particular significance to the fertilization rate as a predictive factor for the CLBR. In fact, compared with the number of retrieved oocytes (a parameter widely adopted as an outcome predictor), the fertilization rate represents a more inclusive factor, expressing both gamete quality (both maternal and paternal) and laboratory performance.

Irrespective of the number of retrieved oocytes and maternal age, we observed that the rates of fertilization were positively associated with the CLBR, presumably as a downstream effect of the number of fertilized oocytes and, consequently, the number of embryos available for treatment. Not only did this trend clearly emerge from the overall data analysis, but in addition, it was observed in subgroups classified according to maternal age. Further analysis to control for the number of retrieved oocytes, a well-established predictor of CLBR (24, 31), revealed that in cycles with poor oocyte recovery, the positive association between the fertilization rate and the CLBR was significant for all fertilization rate ranges. In cycles with high oocyte recovery (>10) and young or intermediate-aged women, significant increases in CLBR were not observed in association with fertilization rates >65%. This may be explained by a possible compensatory effect because of the high number of good quality oocytes in such patients.

CONCLUSION

In the final analysis, the data of this study support the concept of an independent impact of the fertilization rate on the CLBR, offering a new, more inclusive tool to predict the overall outcome of an IVF cycle. Further analyses on the importance of the fertilization rate are needed to confirm this hypothesis.

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Tasa de fecundación como un nuevo indicador de la tasa acumulada de recién nacido: un estudio multicéntrico de cohorte retrospectivo de 9.394 ciclos de fecundación in vitro completos.

Objetivo: Evaluar la tasa de fecundación como un factor predictivo de la tasa acumulada de recién nacido (CLBR).

Diseño: Estudio multicéntrico de cohorte retrospectivo.

Entorno: Diez clínicas de fecundación in vitro cuyos datos fueron recopilados y procesados por el Registro Nacional Italiano de técnicas de reproducción asistida (ART).

Paciente(s): 7.968 parejas que realizaron 9.394 ciclos completos de inyección intracitoplasmática de espermatozoides.

Intervención(es): Ninguna

Principal(es) medida(s) de resultado(s): La medida principal de resultado fue la CLBR asociada con intervalos de fecundación (<65%– grupo 1; 65%–80%–grupo 2; and >80%–grupo 3). Además, se realizó estratificación de los datos basándose en la edad materna (<34, 35–38 y 39–42 años) y en el número de ovocitos obtenido (5–7, 8–10 y > 10 ovocitos).

Resultado(s): la CLBR fue progresivamente mayor en relación con la tasa de fecundación en los grupos 1, 2 y 3 (20.1%, 34.7% y 41.3%, respectivamente). El número de ovocitos obtenidos, de embriones por ciclo y la tasa acumulada de gestación siguieron la misma tendencia. La disminución en la CLBR con el aumento de la edad materna estuvo significativamente correlacionada con la tasa de fecundación y la CLBR en todos los 3 grupos de edad materna. El estudio de regresión logística multivariable mostró que la tasa de fecundación es un factor independientemente asociado a la CLBR.

Conclusión(es): Los datos actuales indican una asociación positiva entre la tasa de fecundación y la CLBR, sugiriendo la relevancia clínica predictiva de este parámetro y su adopción como indicador clave de rendimiento.