

AGE OR OVARIAN RESERVE? A COMPARATIVE STUDY OF IVF OUTCOMES IN YOUNG WOMEN WITH DOR AND OLDER WOMEN WITH NOR

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Abstract

The aim of this study was to evaluate whether chronological age or ovarian reserve exerts a greater influence on in vitro fertilization (IVF) outcomes. A retrospective cohort analysis was conducted, including 108 women undergoing IVF at In vitro OG Medical Centre Dimitrov between 2018 and 2024. Participants were classified as OLDER NOR (age > 35 years, AMH $\geq$ 1.5 ng/ml) and YOUNG DOR (age $\leq$ 35 years, AMH $\leq$ 1.1 ng/ml). Although women in the OLDER NOR cohort exhibited higher AMH levels, younger women with diminished ovarian reserve achieved better clinical outcomes – higher fertilization, clinical pregnancy, and live birth rates. These findings suggest that chronological age has a stronger impact on embryo competence and implantation potential than ovarian reserve markers alone, highlighting the predominant role of age in determining reproductive success in IVF cycles.

Key words: diminished ovarian reserve (DOR), normal ovarian reserve (NOR), Anti-Müllerian hormone (AMH), fertilization rate, in vitro fertilization (IVF)

Introduction. Infertility impacts a considerable percentage of couples globally, with female age and ovarian reserve being critical factors influencing the success of assisted reproductive technologies (ART).

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Diminished ovarian reserve (DOR) is a clinical condition characterized by a reduction in the quantity and/or quality of oocytes within the ovary, leading to impaired reproductive potential. Clinically, it is associated with reduced responsiveness to ovarian stimulation, a lower yield of mature oocytes, poorer embryo quality, and a lower chance of clinical pregnancy, even in younger women [1]. Furthermore, patients with DOR are predisposed to recurrent pregnancy loss and fetal chromosomal abnormalities [2].

Ovarian reserve is commonly assessed through biochemical and ultrasonographic markers. DOR is associated with low levels of anti-Müllerian hormone (AMH) (< 1.1 ng/ml), elevated follicle-stimulating hormone (FSH) (> 10 mIU/mL), and reduced antral follicle count (AFC) (< 7) [3]. The etiology of the disorder in young women has not been fully studied yet, but some of the causes of its occurrence are genetic aberrations, autoimmune diseases, viral infections, chemotherapy, radiotherapy, pelvic surgery, environment, or idiopathic factors [4].

Advanced maternal age (> 35 years) is an additional well-established determinant of IVF success, primarily due to a decline in oocyte quality and increased rates of aneuploidy. According to some studies in women above the age of 43, the chance of producing a chromosomally normal blastocyst is likely to be less than 5% [5]. It is also known that aged oocytes tend to have a harder zona pellucida, so blastocysts expand but have difficulties hatching [6].

The interplay between age and ovarian reserve is complex: young women with DOR may present with oocyte numbers comparable to older women, while older women with normal ovarian reserve (NOR) may retain a relatively high oocyte yield.

Despite extensive research on the independent effects of age and ovarian reserve on IVF outcomes, direct comparisons between these patient profiles remain limited. Understanding whether younger women with DOR achieve comparable fertilization rates, embryo development, and pregnancy outcomes to older women with NOR could provide valuable insights for patient counselling, treatment planning, and prognostic assessment in ART.

This study aims to compare embryological and clinical outcomes in two distinct patient populations undergoing in vitro fertilization: young women with diminished ovarian reserve and older women with normal ovarian reserve.

Materials and methods. Study design. This retrospective cohort study included 108 women who underwent in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) at “Invitro OG Medical Centre Dimitrov”, between 2018 and 2024. Patients were allocated to one of two groups according to age and ovarian reserve:

Group 1 ($n = 52$): Young with diminished ovarian reserve (Young-DOR) – age ≤ 35 years and anti-Müllerian hormone (AMH) ≤ 1.1 ng/mL.

Group 2 ($n = 56$): Older with normal ovarian reserve (Older-NOR) – age > 35 years and AMH ≥ 1.5 ng/mL.

Inclusion criteria were women undergoing their first or subsequent fresh IVF/ICSI cycle during the study period with available baseline ovarian reserve tests (AMH, antral follicle count, and day-2/3 FSH when available) and complete embryology and clinical outcome data. Exclusion criteria were: use of donor oocytes, cycles cancelled before oocyte retrieval, preimplantation genetic testing cycles, uterine anomalies precluding embryo transfer, known chromosomal abnormalities in either partner, and incomplete records.

The parameters that were evaluated included oocyte yield, maturity, fertilization rates, embryo quality, implantation, clinical pregnancy outcomes and live birth rate.

Obtaining of the gametes, fertilization and embryo culture. Standard protocols for ovarian stimulation have been used. The oocytes were retrieved by transvaginal aspiration of ovarian follicles under ultrasound guidance. Fertilization was achieved using either conventional IVF or ICSI and the obtained embryos were cultured to day 3 (8–10 blastomeres), day 4 (morula) or day 5 (blastocysts stage) in sequential media (Vitrolife or Origio). The embryos were evaluated on a daily basis for their quality [7].

Embryo transfer. The catheter for embryo transfer was introduced into the uterus under ultrasound control. After the procedure, it was inspected under a microscope to make sure that all the embryos have been placed.

Pregnancy outcomes. The serum hCG level was measured 14 days after the embryo transfer. A biochemical pregnancy was identified when hCG levels were ≥ 25 IU/L. Pregnancy was confirmed by detection of cardiac activity of the embryos under ultrasound inspection.

Statistical analysis. The Shapiro–Wilk test was used to determine whether the samples exhibited a normal distribution. The statistical significance was assessed using *t*-test, Fisher's exact test and Mann–Whitney U. A probability of $p < 0.05$ was considered significant.

Results. The analysis comprised 108 women divided into two groups: OLDER NOR (age > 35 ; AMH ≥ 1.5 ng/ml) ($n = 56$) and YOUNG DOR (age ≤ 35 ; AMH ≤ 1.1 ng/ml) ($n = 52$).

Fertilization methods (ICSI and IVF) were evenly distributed across the studied cohorts, with no statistically significant difference ($p = 0.386$). Similarly, the body mass index (BMI) was comparable between the cohorts ($p = 0.75$). Therefore, these parameters did not influence the different clinical outcomes observed between the two groups.

Our results demonstrated that, despite their more favourable ovarian reserve and oocyte yield (Fig. 1), patients in the OLDER NOR group had lower clinical outcomes (Fig. 2). They were characterized by significantly more retrieved oocytes ($p < 0.001$), antral follicle count ($p < 0.001$), more mature MII oocytes ($p < 0.001$), and more fertilized 2PN embryos ($p < 0.001$) than YOUNG DOR. However, the fertilisation rate was significantly higher in the YOUNG DOR cohort

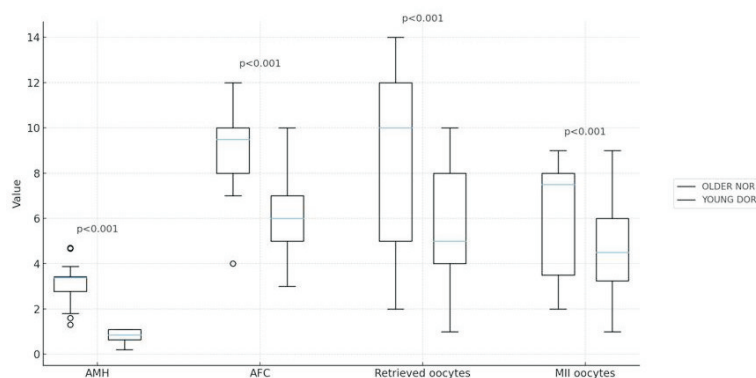


Fig. 1. Ovarian reserve markers and oocyte yield

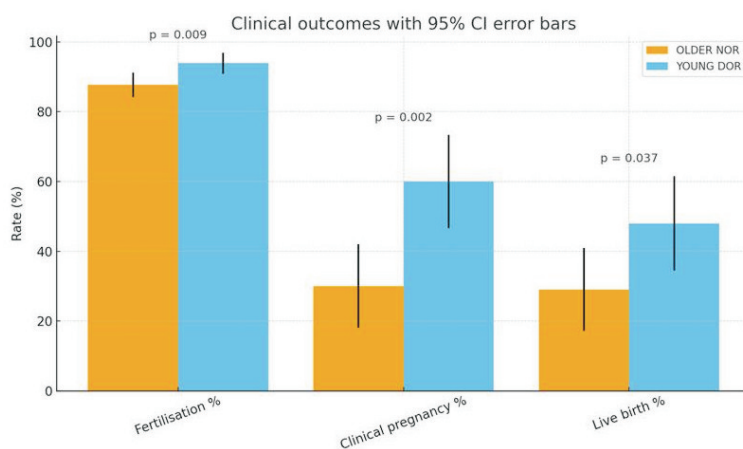


Fig. 2. Fertilisation rate and clinical outcomes

($p = 0.009$). This group also demonstrated better clinical pregnancy ($p = 0.002$) and live birth rates ($p = 0.037$). The number of good-quality embryos ($p = 0.22$) and the implantation rate per transferred embryos ($p = 0.06$) did not differ significantly between cohorts (Table 1).

In summary, although the OLDER NOR group demonstrated a better quantitative ovarian response, the YOUNG DOR group achieved significantly higher fertilisation, clinical pregnancy, and live birth rates. The second cohort also showed a trend towards a higher implantation rate per transferred embryos, although the difference did not reach statistical significance. These findings indicate that chronological age exerts a stronger impact on embryo competence and implantation potential than ovarian reserve markers alone.

Discussion. This study evaluated the relative influence of chronological age and ovarian reserve on in vitro fertilization (IVF) outcomes by comparing women over 35 years with normal ovarian reserve and younger women with diminished

T a b l e 1

Comparison of clinical and laboratory parameters between OLDER NOR and YOUNG DOR patient groups. Values are presented as mean $\pm$ standard deviation (SD) or percentage (%), as appropriate. Statistical significance was assessed using the independent-samples *t*-test for continuous variables and the χ^2 test (or Fisher's exact test when appropriate) for categorical variables. (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; n.s. – not significant)

Parameter	OLDER NOR ($n = 56$)	YOUNG DOR ($n = 52$)	<i>p</i> -value
Age (years)	37.98 $\pm$ 2.04	31.71 $\pm$ 2.30	< 0.001***
AMH (ng/ml)	2.92 $\pm$ 0.85	0.88 $\pm$ 0.27	< 0.001***
AFC	9.54 $\pm$ 1.73	5.96 $\pm$ 1.33	< 0.001***
BMI (kg/m ²)	24.55 $\pm$ 4.30	24.33 $\pm$ 3.09	0.75 n.s.
Retrieved oocytes	8.91 $\pm$ 3.39	4.96 $\pm$ 2.44	< 0.001***
MII oocytes	6.43 $\pm$ 2.35	4.21 $\pm$ 2.18	< 0.001***
2PN zygotes	5.57 $\pm$ 2.28	3.83 $\pm$ 1.83	< 0.001***
Fertilisation (%)	87.70 $\pm$ 13.33	93.93 $\pm$ 11.07	0.009**
Good quality embryos	3.04 $\pm$ 1.31	2.71 $\pm$ 1.42	0.22 n.s.
Implantation/ Transfers (%)	28.57 $\pm$ 44.58	44.50 $\pm$ 41.29	0.06 n.s.
Clinical pregnancy (%)	30%	60%	0.002**
Live birth (%)	29%	48%	0.037*

ovarian reserve. Although the OLDER NOR cohort exhibited a quantitatively stronger ovarian response, the YOUNG DOR group achieved better clinical outcomes, including higher fertilization, clinical pregnancy, and live birth rates. In the literature, the impact of diminished ovarian reserve remains controversial. According to some research, DOR reduced clinical pregnancy and live birth rates in younger women undergoing fresh embryo transfer cycles [8]. However, other studies indicated that conception outcomes were comparable for women with diminished ovarian reserve and identically aged women with normal ovarian reserve when a transfer was performed and the procedure was not cancelled [9]. These findings suggest that biological age exerts a more profound effect on reproductive potential than the quantitative markers of ovarian reserve [10, 11].

Age-associated reproductive decline is primarily attributed to oocyte quality rather than quantity. Accumulating evidence indicates that mitochondrial dysfunction, spindle abnormalities, and epigenetic dysregulation are key contributors to meiotic errors and chromosomal aneuploidy [12].

CIMADOMO et al. [13] provided an extensive analysis of the biological mechanisms underlying reproductive ageing, demonstrating that oocytes from older women exhibit impaired meiotic spindle function, compromised chromosome segregation, increased aneuploidy rates, and altered epigenetic regulation. These defects accumulate long before menopause and persist regardless of ovarian reserve markers. Their work strongly supports the argument that even women with

normal AMH or AFC values in their late thirties are biologically disadvantaged due to age-related molecular alterations, reducing developmental competence and implantation potential [13].

Complementary evidence from LABARTA et al. [14] further clarifies these mechanisms by demonstrating that mitochondrial dysfunction plays a central role in the age-dependent decline in oocyte competence. Their findings showed that oocytes from older women present reduced mitochondrial membrane potential, diminished ATP production, altered mtDNA replication, and impaired metabolic efficiency. These mitochondrial abnormalities critically affect meiotic progression, fertilisation, and preimplantation development. Consequently, older women may generate a higher number of oocytes, yet the functional quality of these gametes is compromised, resulting in reduced blastulation, implantation, and cumulative pregnancy rates despite preserved ovarian reserve [14].

Consequently, even women with normal AMH levels in their late thirties may produce a higher number of oocytes but with compromised developmental competence, which leads to lower cumulative pregnancy potential [15].

Our data also reflect that the number of retrieved oocytes and zygotes did not necessarily translate into superior implantation or live birth rates. Similar conclusions have been drawn in recent meta-analyses, which demonstrate that ovarian reserve tests (AMH and AFC) are excellent predictors of ovarian responsiveness but not of embryo euploidy, implantation, or live birth [16, 17]. Conversely, younger women with DOR tend to have a smaller follicular cohort but produce oocytes of higher competence, resulting in better reproductive outcomes per embryo transferred [18].

The slightly higher, though statistically non-significant, implantation rate in the YOUNG DOR group may be influenced by endometrial receptivity and embryo–endometrial synchrony, which are known to decline with age [19]. These findings emphasise that endometrial and embryonic factors act synergistically in achieving successful implantation, and the impact of age extends beyond gamete quality alone.

Overall, these findings underscore that ovarian reserve parameters are useful for stimulation planning but have limited prognostic value for reproductive success. Chronological age therefore appears to be the principal factor determining both oocyte quality and implantation capacity. Future studies integrating genetic and metabolic profiling of oocytes and embryos may provide further insight into the biological mechanisms linking age, ovarian function, and IVF outcomes [20].

Conclusions. In conclusion, while ovarian reserve defines the quantitative reproductive capacity, biological age dictates qualitative potential. Recognising this distinction is essential for accurate counselling, realistic patient expectations, and the development of age-adapted clinical strategies in assisted reproduction.

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