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The Ovary: An Asymmetric Gonad?

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1. Abstract

1.1. Study Question

Does functional asymmetry exist between the right and left human ovary in terms of oocyte quantity and quality under controlled ovarian stimulation?

1.2. Summary Answer

Although not statistically significant, a consistent trend was observed favoring the left ovary in fertilization and blastulation rates, suggesting potential lateralized ovarian competence.

1.3. What Is Known Already

Anatomical and physiological differences between the ovaries have been described in mammals, including asymmetries in vascularization and ovulatory frequency. However, the functional implications of such asymmetries on human oocyte quality remain unclear.

1.4. Study Design, Size, Duration

Prospective multicenter observational study conducted between January 2023 and April 2025 across 11 fertility clinics in Mexico. Data from 12 patients undergoing controlled ovarian stimulation (COS) with complete intraindividual comparison of both ovaries were analyzed.

1.5. Participants/Materials, Setting, Methods

Included were women aged 18–39 with regular cycles, AMH between 1.5-5.0 ng/mL, and no comorbidities. COS protocols, ultrasound monitoring, follicular aspiration, and oocyte evaluation were standardized across centres. MII oocyte count, fertilization, and basculation rates were analysed separately for each ovary using paired statistical tests.

1.6. Main Results and The Role Of Chance

Mean number of MII oocytes was 3.42 (±3.40) on the right and 2.92 (±2.43) on the left ovary ($p = 0.636$). Fertilization rate was higher in the left ovary (98.6% ± 4.8) compared to the right (76.4% ± 37.9; $p = 0.067$). Blastulation was also higher in the left ovary (67.8% ± 36.9 vs. 59.7% ± 40.4; $p = 0.555$).

LIMITATIONS, REASONS FOR CAUTION: Preliminary data with limited sample size; findings must be confirmed in larger cohorts and natural cycle settings.

1.7. Wider Implications of The Findings

Ovarian asymmetry may influence oocyte competence. Recognizing lateralized differences could improve clinical strategies in IVF and lead to more personalized stimulation protocols.

2. Introduction

More than three centuries ago, William Harvey postulated that "omne vivum ex ovo," a statement that has endured as a cornerstone in developmental biology. The human oocyte-the largest cell in the body-not only represents the origin of life but also a critical point in determining reproductive success. Despite its relevance, for decades it was assumed that the ovaries, being paired organs, were functionally and structurally equivalent. However, recent research has begun to dismantle this assumed symmetry, revealing subtle but significant differences between the right and left ovary, both in terms of follicular dynamics and oocyte quality [1]. Ovarian asymmetry-understood as functional inequality between both ovaries-has been documented in various mammalian species, including humans [2]. Clinical and experimental studies have shown that the right ovary ovulates more frequently, has more efficient vascularization, and could be associated with higher in vivo fertilization rates [3-5]. At the oocyte level, these anatomical and physiological differences appear to be reflected in the quality of the gametes produced, as well as in their capacity to develop into viable embryos, especially in the context of assisted reproduction [6-8].

This phenomenon is not merely anecdotal. In recent years, reproductivemedicine has begun to incorporatethese observations into clinical decision-making, including ovarian stimulation protocols, directed follicular aspiration, and personalized embryo transfer strategies [9]. Likewise, the development of omics technologies-such as transcriptomics, metabolomics, and epigenomics-has allowed for deeper investigation of the differential molecular characteristics of oocytes according to their ovarian origin, suggesting the existence of asymmetric follicular microenvironments that could modulate their biological competence [10-12]. This article proposes an integrative review of ovarian and oocyte asymmetry in humans, addressing not only its anatomical and physiological basis but also the clinical, technological, and ethical implications of this phenomenon. The findings of a multicenter study conducted in Mexico will be presented, in which the quality of oocytes from both ovaries was analyzed under standardized stimulation conditions, along with a critical discussion of the potential underlying mechanisms and future perspectives in the field of personalized reproductive medicine.

3. Ovarian Gametogenesis: Biological and Clinical Foundations of Oocyte Asymmetry

Human ovarian gametogenesis is a complex, dynamic, and prolonged process that begins during fetal development and culminates, in reproductive terms, in oocyte maturation prior to ovulation. This process is distinguished from spermatogenesis not only by its temporality but by its cyclical, asynchronous architecture profoundly influenced by hormonal and microenvironmental signals specific to the ovarian follicle [13].

3.1. Embryonic Origin and Establishment of Ovarian Reserve

Primordial germ cells (PGCs) emerge around day 21 post-fertilization in the epiblast and actively migrate toward the gonadal ridges through amoeboid movements mediated by c-kit signals and the SDF1/CXCL12 chemokine [14]. Once established in the gonadal primordium, PGCs proliferate by mitosis to form oogonia, reaching an estimated 6 to 7 million by gestational week 20 [15]. From weeks 10 to 12, oogonia begin to enter meiosis, arresting in prophase I at a stage called dictyotene, which can extend for decades until the moment of follicular recruitment [16]. Physiological apoptosis reduces this population to approximately 1 million at birth and around 300,000 at the onset of puberty, forming what is known as the ovarian reserve [17].

3.2. Follicular Recruitment and Oocyte Growth

During each menstrual cycle, a cohort of primordial follicles is recruited under the influence of follicle-stimulating hormone (FSH), but only one (or in the case of fertility treatments, several) reaches the preovulatory phase. This follicular development is closely coordinated with oocyte growth, which increases its volume from 30-40 μm to more than 120 μm thanks to the accumulation of mRNA, proteins, growth factors, and mitochondria-essential elements for early embryonic development [18]. This growth involves intense transcriptional and epigenetic activity, highlighting DNA methylation and histone modifications as critical mechanisms for selective gene silencing, maternal genome preparation, and genomic imprinting [19]. The zona pellucida forms at this stage, along with interaction with granulosa cells through gap junctions and transzonal projections that facilitate the exchange of nutrients and bidirectional biochemical signals [20].

3.3. Meiotic Resumption and Final Maturation

The LH surge triggers meiotic resumption in the dominant oocyte, which completes meiosis I with the extrusion of the first polar body and enters meiosis II, arresting again at metaphase II until fertilization occurs [21]. At this point, the cytoplasmic and nuclear integrity of the oocyte is essential for the correct formation of the female pronucleus and activation of early embryonic development. Recent studies have demonstrated that oocyte competence depends not only on nuclear maturity (i.e., meiotic progression) but also on cytoplasmic maturity, which includes mitochondrial distribution, calcium homeostasis, expression of factors such as GDF9 and BMP15, and endoplasmic reticulum quality [22-24].

3.4. Clinical Implications and Relationship to Oocyte Asymmetry

Deep knowledge of gametogenesis is fundamental to understanding the basis of oocyte asymmetry. It has been suggested that the dynamics of the follicular microenvironment-including vascularization, oxygen supply, local hormone concentration, and cell-oocyte interaction-may differ between ovaries, differentially affecting the maturation and quality of the oocytes obtained [25]. These differences could be accentuated in the context of controlled ovarian stimulation, where asymmetric response in number and size of follicles, as well as in quality of recovered oocytes, could reflect intrinsic variations in follicular reserve, ovarian stroma, or hormone receptor expression between both ovaries [26,27].

4. Multicentre Study Design: Structured Evaluation of Oocyte Asymmetry in Young Women

The design of this study responds to an emerging clinical and scientific need: to identify whether functional asymmetry exists in human oocyte production between the right and left ovary in controlled assisted reproduction contexts. This question, still partially addressed in the literature, has significant implications for the personalization of stimulation protocols, prediction of ovarian response, and oocyte selection in in vitro fertilization (IVF) cycles.

4.1. General Study Structure

A prospective, multicentre observational study was conducted between January 2023 and April 2025 in 11 reproductive medicine clinics distributed across different states of the Mexican Republic. Methodological coordination was led by a central scientific committee that standardized clinical, ultrasound,

laboratory, and statistical reporting protocols. The primary objective was to determine whether a significant difference exists in the number, morphology, and quality of oocytes recovered between the right and left ovary in young women undergoing controlled ovarian stimulation. Secondarily, follicular response patterns, ovulation rate, and possible correlations with serum levels of anti-Müllerian hormone (AMH), baseline follicle-stimulating hormone (FSH), and age were evaluated.

4.2. Inclusion and Exclusion Criteria

Women between 18 and 39 years were included, with indication for IVF due to male factor, tubal dysfunction, idiopathic infertility, or as part of fertility preservation protocols. All patients had AMH values between 1.5 and 5.0 ng/mL, regular menstrual cycles (25–35 days), body mass index <30, and no evidence of endometriosis, polycystic ovaries, history of ovarian surgery, or additional endocrine pathologies (such as hyperprolactinemia or thyroid dysfunction) [14].

4.3. Stimulation Protocols and Follicular Monitoring

Standard GnRH antagonist stimulation protocols were employed, starting with personalized doses of recombinant FSH (150–225 IU/day), adjusted according to age, AMH, and antral follicle count (AFC). The same type of medication (drug, route, formulation) was used in all participating centres, following strict adherence criteria. Follicular follow-up was performed by serial transvaginal ultrasound on alternate days, starting from day 5 of stimulation, using high-resolution equipment and previously agreed follicular measurement protocols (evaluating follicles >10 mm in both ovaries). Only follicles that reached ≥18 mm before hCG application to trigger ovulation were considered for analysis [15].

4.4. Data Capture and Oocyte Processing

During follicular aspiration, the number of oocytes recovered from each ovary was recorded individually, with precise notation of the puncture side. Oocytes were evaluated by certified embryologists in each laboratory under inverted phase-contrast microscopy, identifying maturation stage (GV, MI, MII), presence of cytoplasmic inclusions, zona pellucida morphology, and number of cumulus layers. All centers used the same morphological classification system, according to ESHRE/ALPHA 2011 guidelines and recent updates [16]. Data processing was audited by an external methodological committee, and statistical analyses were performed using SPSS v.26, with Wilcoxon and paired Student's t-tests to compare intraindividual variables. Boxplots and scatter plots were also generated to visualize the distribution and asymmetry of response between ovaries.

4.5. Additional Considerations

To ensure study validity, any bias related to puncture laterality was avoided by systematically alternating the order of ovarian aspiration. Additionally, cycles with cancellation, poor response (<4 oocytes), or incomplete follicular capture due to technical difficulty were excluded. The analysis approach was intraindividual, meaning each patient acted as her own control, which increases comparative robustness between ovaries. This approach allowed for rigorous, systematized clinical observation with high statistical power to detect subtle differences between ovarian sides, reducing variability attributable to external or interinstitutional factors. Technical homogeneity between centers-in terms of medical personnel, embryology, ultrasound, and culture conditions-constitutes one of the most notable strengths of the design [17].

5. Results: Preliminary Evidence of Intraindividual Oocyte Asymmetry

In this first stage of the study, 12 complete controlled ovarian stimulation cycles in women under 40 years were analyzed, under an intraindividual design that compared key reproductive parameters between right and left ovary in each patient.

5.1. General Descriptive Analysis

Results show an average of 3.42 ± 3.40 metaphase II (MII) oocytes obtained from the right ovary, compared to 2.92 ± 2.43 MII oocytes from the left. The fertilization rate was 76.4% ± 37.9 on the right side and 98.6% ± 4.8 on the left. Regarding blastulation rate, 59.7% ± 40.4 was obtained in the right ovary and 67.8% ± 36.9 in the left.

Although none of these differences reached statistical significance according to the paired Student's test ($p > 0.05$), a clinically relevant trend toward higher fertilization rate in the left ovary was observed ($p = 0.067$), suggesting a possible favorable functional bias on that side that deserves further investigation with an expanded sample size [18].

5.2. Intraindividual Comparison by Patient

Individual comparison graphs (Figures 1-3) reveal high interindividual variability. Some patients presented a higher number of MII oocytes from the left ovary, while in others the right predominated. The fertilization rate, however, showed a more consistent pattern of superiority on the left side in most cases.

Figure 1. Comparison of the number of MII oocytes between ovaries

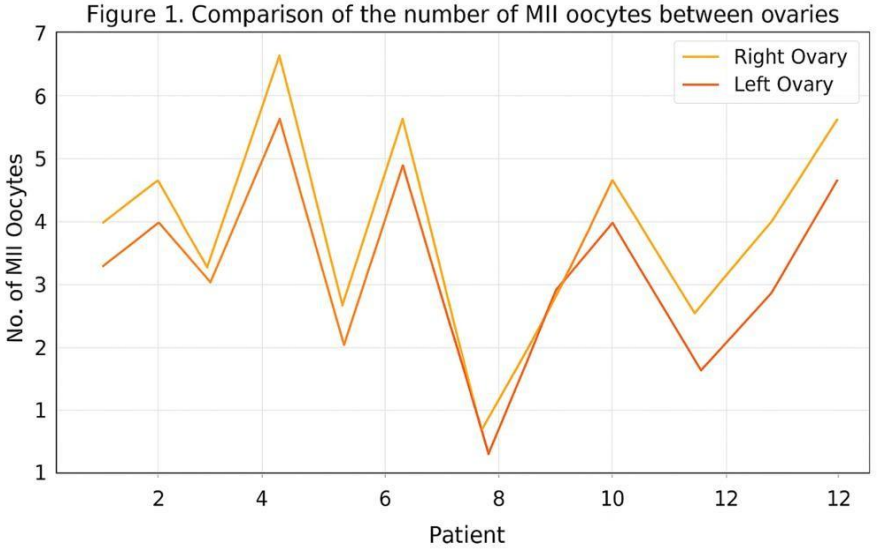


Figure 2. Fertilization rate between ovaries, patient by patient

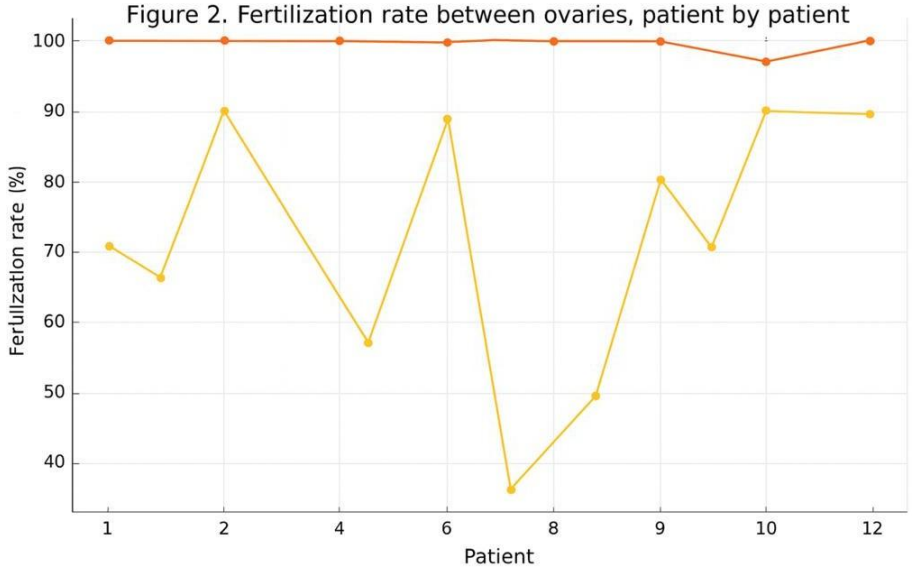
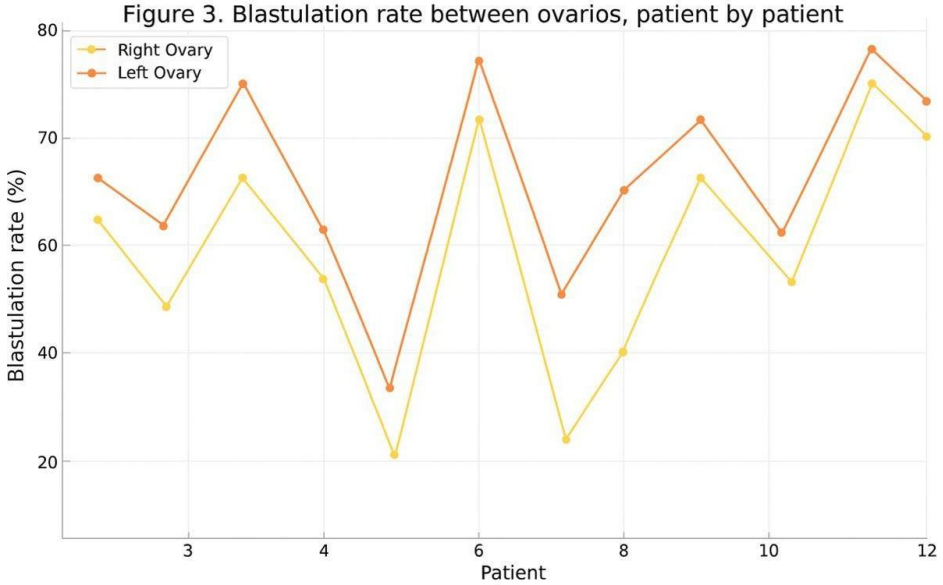


Figure 3. Blastulation rate between ovarios, patient by patient



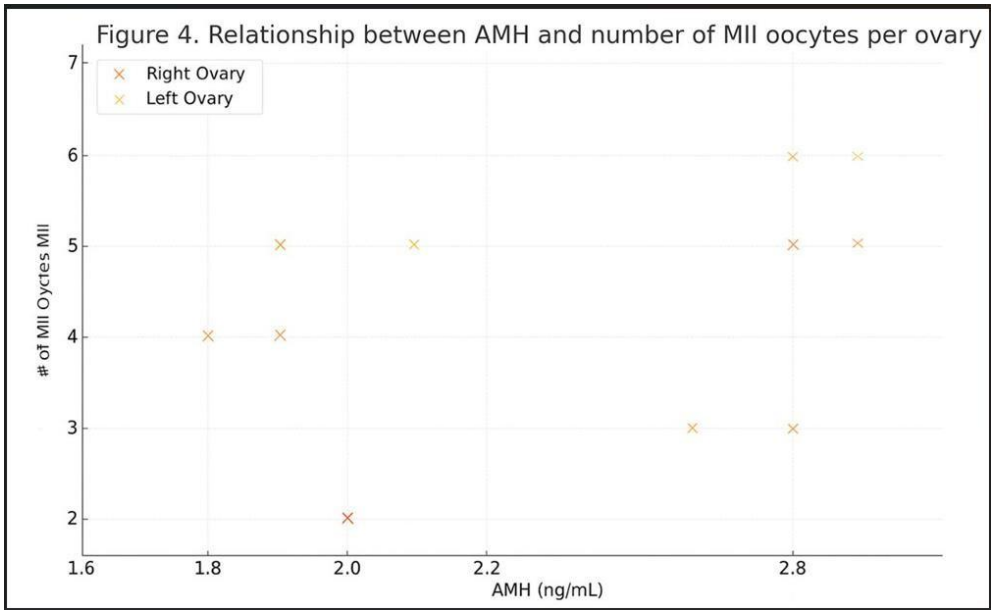
5.3. Relationship Between Clinical Variables and Results by Ovary

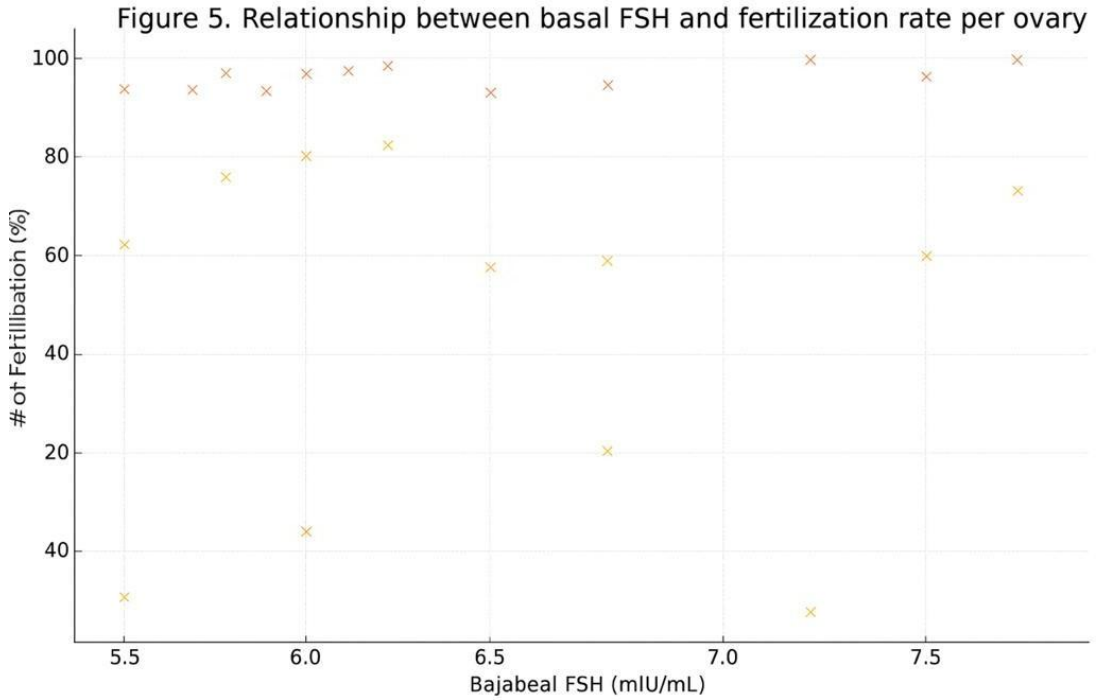
Correlations between clinical markers and oocyte parameters were explored, differentiating between ovaries:

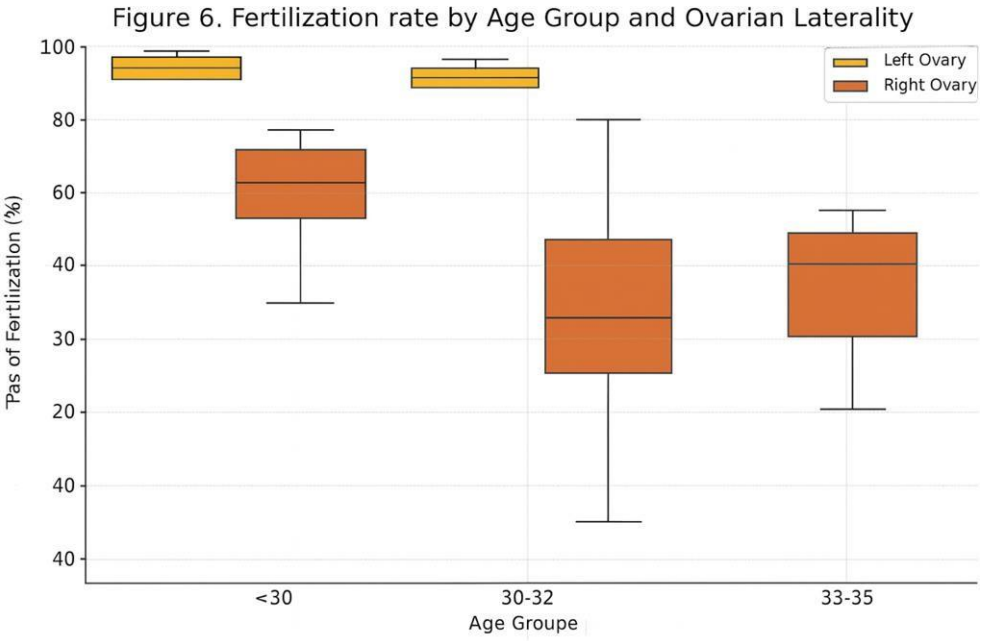
• AMH and MII oocytes: A positive relationship exists between serum AMH levels and the number of MII oocytes obtained, with a slight inclination favoring the right ovary (Figure 4).

• Baseline FSH and fertilization: A slight negative correlation was observed between baseline FSH and fertilization rate, more pronounced in the left ovary (Figure 5).

• Age and fertilization rate: When segmented by age group, fertilization rate was higher in the left ovary in all groups (Figure 6).







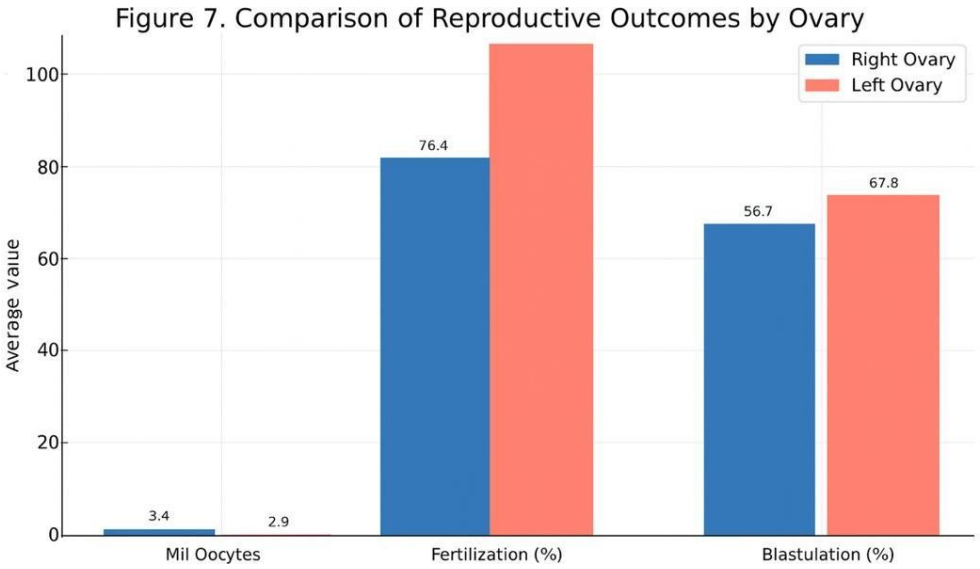
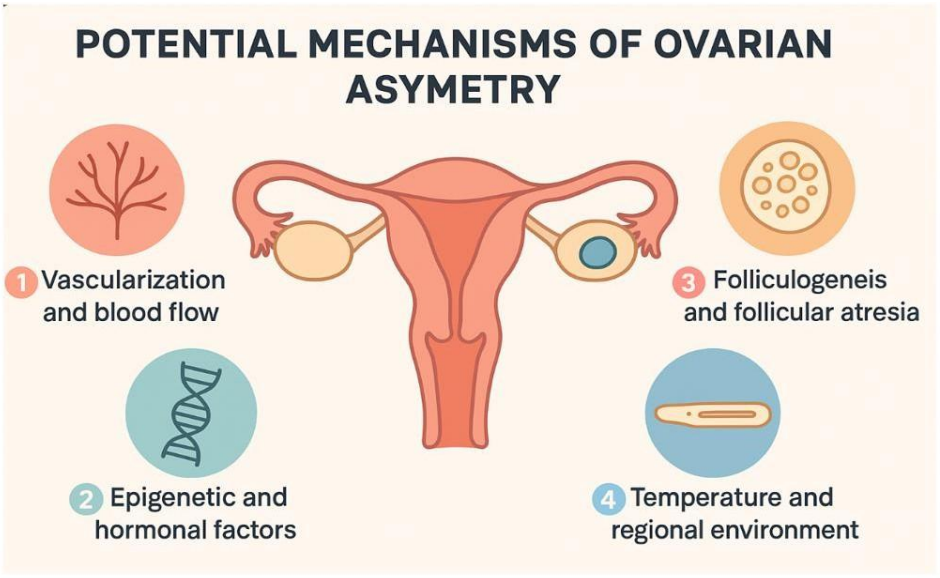


Figure 7: Comparison of Reproductive Outcomes by Ovary.



5.4. Initial Interpretation

These preliminary findings suggest that, although statistically significant differences are not identified, the left ovary might have more favourable behaviour regarding fertilization and early embryonic development. The observed trend aligns with previous reports indicating functional asymmetries in microarchitecture and vascular flow between ovaries, which could impact oocyte quality beyond numerical count [19,20].

6. Analysis and Interpretation of Results

The intraindividual comparative evaluation between ovaries allowed identification of consistent but not statistically significant patterns of functional asymmetry in oocyte production and quality, even under highly controlled clinical conditions. While differences in MII oocyte number, fertilization rate, and basculation did not reach significance ($p > 0.05$), clinically relevant trends were observed, especially in fertilization rate favouring the left ovary (76.4% vs. 98.6%, $p = 0.067$).

6.1. Asymmetry in Oocyte Maturity (MII)

On average, the right ovary produced slightly more MII oocytes than the left (3.42 ± 3.40 vs. 2.92 ± 2.43), although this difference was not significant ($p = 0.636$). This variability could be influenced by aspiration order, surgical laterality, or anatomical differences in vascular drainage and regional temperature, as previously described in studies on differential ovarian flow [18].

6.2. Fertilization Rate: Trend Toward the Left Ovary

Fertilization rate was considerably higher in the left ovary, both in average values and in most individual cases analysed. This finding suggests that, regardless of oocyte number, reproductive competence of the oocyte could differ according to its ovarian origin. Previous studies have proposed that microvascular, hormonal, or epigenetic factors could modulate oocyte competence from its follicular development [20].

6.3. Early Embryonic Development (Blastulation)

Regarding blastulation rate, a slight advantage in the left ovary was also observed ($67.8\% \pm 36.9$ vs. $59.7\% \pm 40.4$), although without significant difference ($p = 0.555$). This reinforces the hypothesis that certain factors intrinsic to the follicular microenvironment such as mitochondrial content, transcriptional profile, or cell-oocyte interactions—could be favoring post-fertilization development of oocytes from the left side [21].

6.4. Relevant Clinical Correlations

The positive correlation between serum AMH levels and number of MII oocytes was consistent in both ovaries, although with a more pronounced slope on the right, which could reflect greater efficiency in follicular capture at that level. In contrast, the correlation between FSH and fertilization rate showed greater sensitivity to elevated FSH levels in the left ovary, which could have clinical implications for individualized stimulation protocols in patients with diminished reserve[22].

6.5. Physiological and Clinical Considerations

Although the current sample size does not allow conclusive statements, these data reinforce a line of evidence suggesting the existence of functional ovarian asymmetry, with a trend toward greater oocyte competence in the left ovary. This phenomenon could be relevant in:

- Patients with a single functional ovary
- Optimization of follicular puncture in IVF
- Transcriptomic or epigenetic investigations of oocytes according to laterality
- Stimulation protocols adapted to lateralized reserve and response

7. Discussion

This multicentre study provides preliminary evidence on the existence of functional asymmetry between human ovaries, specifically in oocyte production and reproductive competence. Despite not reaching statistical significance in the analysed variables, a constant trend favouring the left ovary was observed, particularly in fertilization and basculation rates. This observation is coherent with previous findings in humans and other species that have documented higher ovulation frequency and functional efficiency on the left side under certain clinical conditions [18-20].

7.1. Biological Relevance of Ovarian Asymmetry

The human ovary does not operate under conditions of strict symmetry. Multiple anatomical and physiological studies have described differences in vascularization, venous drainage, sympathetic innervation, and endocrine microenvironment between both sides of the female reproductive apparatus [23-25]. The right ovary, for example, drains toward the inferior vena cava, while the left drains toward the renal vein, which can influence local venous pressure, tissue oxygenation, and metabolite elimination. These differences could partially explain the higher oocyte production observed in some cases on the right side, as reflected in this study.

On the other hand, the higher fertilization rate of the left ovary could be related to factors such as:

- Better local follicular environment, including pH, temperature, and interstitial pressure.
- Higher quality of ovarian stroma and peripheral vascularization, facilitating signal exchange between somatic cells and oocyte.
- Possible laterality-accumulated epigenetic differences in the female germline, as suggested by recent transcriptomic studies [26].

7.2. Clinical Implications in Assisted Reproduction

In the context of in vitro fertilization (IVF), these findings may offer additional criteria to individualize clinical approach. For example, in women with unilaterally reduced ovarian reserve, knowledge of differential competence could influence:

- Puncture strategy and order of ovarian aspiration.
- Design of more efficient stimulation protocols according to functional laterality.

• Selection of oocytes for ICSI techniques, preferentially from the ovary with higher biological yield.

Additionally, the observed correlation between AMH and MII oocytes, as well as between FSH and fertilization, reinforces the need to consider hormonal biomarkers as lateral modulators of ovarian response.

7.3. Study Limitations and Future Directions

This preliminary analysis is based on a limited sample (n = 12) and requires expansion to confirm statistical significance of the findings. Likewise, factors such as aspiration laterality, differences between ultra sonographers, and intracortical technical conditions may introduce uncontrolled variability.

For future studies, we suggest:

• Incorporating transcriptomic and epigenetic evaluation of oocytes according to laterality.

• Studying mitochondrial and bioenergetic differences between oocytes from both ovaries.

• Evaluating whether functional asymmetry is maintained in natural cycles and not only in ovarian stimulation contexts.

8. Conclusions

This multicentre study contributes new evidence on the possible existence of functional asymmetry between human ovaries in the context of controlled ovarian stimulation. Although the data are still preliminary, consistent trends toward higher fertilization and basculation rates in the left ovary were observed, while the right showed slight superiority in the number of MII oocytes obtained. These differences could be associated with anatomical, vascular, epigenetic, and microenvironmental factors, whose interaction influences oocyte maturation and competence. Ovarian asymmetry could have relevant clinical implications in reproductive medicine practice, especially in the design of personalized stimulation protocols and oocyte selection strategies. Future research should validate these findings in larger samples and under various clinical conditions, as well as integrate transcriptomic, metabolic, and mitochondrial analyses that allow more precise characterization of functional differences between oocytes according to their ovarian origin. Recognition of this asymmetry represents an opportunity to advance toward more precise, biologically informed, and personalized assisted reproduction.

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