Journal of Reproductive Medicine and Embryology



# **Time to Reconsider: Cost-Effectiveness in ART**

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### Abstract

The cost-benefit of any procedure is evaluated by comparing the monetary value of the benefits it provides with the costs incurred to achieve its goals. A positive cost-benefit occurs when the net monetary value of the benefits exceeds the costs. In the case of fertility treatments, such as ART, they should only be provided when the benefits (e.g., a live birth) outweigh the costs. The Centers for Disease Control and Prevention (CDC) (2019) reports that infertility impacts one in eight couples globally. Key factors contributing to this include a growing trend toward delayed childbearing. Given the high costs and complexity of ART, there is an urgent need to implement simpler and more affordable diagnostic methods, mild ovarian stimulation, and streamlined culture procedures. At the same time, optimizing infertility care to improve its availability, affordability, safety, and effectiveness is crucial. In the current review, we will discuss the cost variations and effectiveness among different ART procedures.

Keywords: Cost effectiveness; ART; ICSI; IVF; SCS.

### **ART Worldwide**

The Centers for Disease Control and Prevention (CDC) (2019) reports that infertility impacts one in eight couples globally (1). Key factors contributing to this include a growing trend toward delayed childbearing, resulting in higher rates of age-related infertility, alongside a rise in infertility linked to medical conditions such as obesity and declining

sperm counts (2-4). This increased demand for ART services is projected to drive the global fertility treatment market's value to approximately US\$27 billion by 2026 (5).

JRME® Volume. 1, Issue no. 3, September 2024

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# ART in low- middle-income countries (LMIC)

In low- and middle-income countries (LMICs), an estimated 52.6 to 200 million couples experience involuntary childlessness, with infertility rates ranging from 3.5% to 16.7% (6). Although ART procedures are often the preferred treatment option, they remain prohibitively expensive and are typically not covered by government funding. As a result, access to fertility care is largely restricted to those who can afford costly diagnoses and treatments through the private sector (7).

### ART in Egypt

In recent years, Egypt has encountered economic difficulties, with rising inflation and currency devaluation greatly affecting ART services (8). Additional challenges include new regulations on import and export trades, limited access to credit, and slow, cumbersome customs procedures, which have resulted in shortages of consumables and culture systems related to ART procedures, as well as medications for ovarian stimulation (9). Given the high costs and complexity of ART, there is an urgent need to implement simpler and more affordable diagnostic methods, mild ovarian stimulation, and streamlined culture procedures. At the same time, optimizing infertility care to improve its availability, affordability, safety, and effectiveness is crucial (10).

### Cost-benefit of ART service

The cost-benefit of any procedure is evaluated by comparing the monetary value of the benefits it provides with the costs incurred to achieve its goals. A positive cost-benefit occurs when the net monetary value of the benefits exceeds the costs. In the case of fertility treatments, such as ART, they should only be provided when the benefits (e.g., a live birth) outweigh the costs (11).

When assessing the cost-effectiveness of using a specific ART method (conventional IVF or

ICSI) for oocyte insemination, it must be analyzed from two perspectives (11):

The financial/ accessibility burden (Efficiency).
The technical outcome (Efficacy).

## 1. The financial/ accessibility burden (Efficiency).

There is a notable cost variations between conventional IVF and ICSI (Table 1). Furthermore, the ICSI procedure is generally more time-consuming and resource-intensive compared to conventional IVF. As a result, c-IVF emerges as a more straightforward and costeffective option with better accessibility. Considering the current economic conditions, IVF should be the treatment of choice. However, the critical question is whether it serves as an effective alternative that can deliver similar benefits as ICSI, This will be explored further in this review.

### Table 1:Factors concerning cost variationsbetween conventional IVF and ICSI

Conventional IVF	ICSI
Simple procedure	Multi-step procedure
Basic equipped lab	Specialised equipped lab
limited number of embryologists	Multi-task highly skilled embryologists
Limited consumables	Various types of consumables
Simplified culture system	Different types of media

### 2. The technical outcome (Efficacy).

Numerous studies have compared the outcomes of ICSI and c-IVF across various populations. Since its inception over 40 years ago, in vitro fertilization (IVF) has become a foundational method for fertility treatment. In 1992, Palermo and colleagues successfully introduced intracytoplasmic sperm injection (ICSI) to assist couples for whom c-IVF and sub-zonal insemination (SUZI) had failed (12). Following this pioneering case report, ICSI has become the preferred option for couples facing severe male factor subfertility (12). Over the years, ICSI has also been utilized to treat couples with mild male infertility and even cases of unexplained infertility (13).

### **Restoring the Path:**

A recent Cochrane systematic review analyzed three randomized controlled trials (RCTs) that compared ICSI with c-IVF, involving a total of 1,539 couples undergoing fertility treatment, all of whom had males with normal sperm count and motility. The findings indicate that if the probability of achieving a live birth (LB) with conventional IVF is estimated at 32%, the likelihood of LB with ICSI ranges from 30% to 41%. Additionally, two studies assessed viable intrauterine pregnancies for both ICSI and c-IVF, suggesting that if the chance of a viable intrauterine pregnancy following conventional IVF is 33%, the probability with ICSI would fall between 28% and 38%. The authors concluded that the existing studies comparing ICSI and c-IVF show no significant advantage of one method over the other in terms of achieving live births, clinical pregnancies, viable intrauterine pregnancies, or even causing adverse events (14).

Another open-label randomized controlled trial published in 2024 examined the efficacy and safety of ICSI compared to c-IVF in couples experiencing infertility due to non-severe male factors. The primary analysis included 1,154 couples in the ICSI group and 1,175 couples in the c-IVF group. The results showed that a live birth after the first embryo transfer occurred in 390 couples (33.8%) in the ICSI group and 430 couples (36.6%) in the c-IVF group (p=0.16). Considering that ICSI is an invasive procedure associated with additional costs and potential risks to offspring health, its routine use in this population is not recommended (15).

Gingold et al. (2024) published a report from SART that analyzed data from 318,930 cycles, comparing clinical outcomes between nonindicated ICSI (261,414 cycles, or 82.0%) and cIVF (57,516 cycles, or 18.0%). To our knowledge, this study is the first to utilize the SART national registry to explore the clinical implications of using ICSI, stratified by type of embryo transfer (fresh, frozen-thawed with PGT, and frozen-thawed without PGT) and its indications. The findings indicate that non-indicated ICSI is associated with fewer available blastocysts for transfer and lower pregnancy and live birth rates compared to c-IVF. interestingly, the live birth and clinical pregnancy rates in frozen-thawed cycles with PGT and without PGT were comparable to those observed in c-IVF (16).

Another retrospective cohort study by Song et al. (2021) compared ICSI to c-IVF in patients with unexplained infertility. The findings showed that patients in the c-IVF group had more 2PN and higher fertilization rates compared to those in the ICSI group, despite both groups having a similar retrieved. number of oocytes Possible explanations for this discrepancy may include increased chromosomal concerns about anomalies, molecular disturbances, changes in DNA methylation, imprinting disorders, lower implantation potential, and potential oocyte damage due to the invasiveness of the ICSI technique. The authors concluded that ICSI does not improve live birth rates but is associated with higher cancellation rates (17).

Women aged 38 and older represent an increasing proportion of patients seeking ART. These older women are more likely to have fewer oocytes, which justifies the use of ICSI to enhance the chances of fertilization. Additionally, older women are more inclined to undergo PGT, as this enables the selection of euploid embryos for transfer, thereby increasing the likelihood of pregnancy and reducing the risk of multiple gestations (18).

This concept has been challenged by a metaanalysis conducted by Sunderam et al. in 2020, which compared fertilization rates between ICSI and c-IVF among women aged 38 and older with a non-male factor infertility diagnosis. This analysis included seven studies with a total of 8,796 retrieved oocytes (ICSI: 4,369; IVF: 4,427). The results indicated no significant difference in fertilization rates between ICSI and c-IVF (RR 0.99, 95% CI). Heterogeneity was noted among the studies ( $I^2 = 58.2$ ; P < 0.05), but this was eliminated when the analysis was restricted to poor responders (RR 1.01, 95% CI 0.97–1.05; P = 0.6) (19).

Furthermore, a prospective randomized study involving patients aged 40 and older or those with four or fewer oocytes due to non-severe male factor infertility found significantly higher fertilization rates and a trend toward higher clinical pregnancy rates in the con c-IVF group compared to the ICSI group. In cases of advanced maternal age combined with low oocyte numbers, ICSI was associated with a markedly lower chance of fertilization and clinical pregnancy. These findings suggest that ICSI does not provide any advantages over conventional IVF regarding fertilization, embryo quality, implantation, or pregnancy rates for couples with advanced maternal age or low oocyte counts (20).

These recently published data have prompted international organizations to address the lowercost variations of Assisted Reproductive Technologies (ART) and the urgent need to introduce often-overlooked, simple yet effective procedures for infertile couples, especially those in low- and middle-income countries (LMIC). In this context, we will explore one of the most straightforward and affordable systems for IVF culture: the "Simplified Culture System" (SCS).

## IVF with simplified culture system "Walking Egg lab system"

Simplified IVF was conducted as outlined by Van Blerkom et al. 2014, The generation of CO2 was achieved by mixing 11.5 mg of citric acid with 50 mg of sodium bicarbonate in 3.0 ml of water. This mixture produces immediate effervescence and the release of CO2, which helps to equilibrate the pH of the medium to approximately 7.30 (21). The required sperm concentration is based on the number of COCs to be inseminated, typically ranging from 1,000 to 5,000 motile-washed spermatozoa, and this method has been reported to be highly effective for cases of moderate to severe male factor infertility (22).

# Several strong reasons highlight the safety of the Simplified Culture System (SCS):

1. The enclosed system, which remains undisturbed from insemination to embryo transfer, effectively maintains temperature and pH levels, providing extra physical protection for gametes and developing embryos (23).

2. It significantly lowers the expenses related to medical gases, complex incubation equipment, consumables, and the infrastructure typically needed in high-end IVF laboratories (21).

3. Its efficacy is evidenced by the report of the birth of the first seven healthy babies, followed by the birth of an additional four healthy babies after cryo-thawing cycles (24).

Therefore, we can endorse the adoption of the Simplified Culture System (SCS) in ART, as it provides:

- A safe alternative with highly promising perinatal outcomes.

- A significant advancement in human rights, equity, and social justice.

- The establishment of an SCS laboratory has proven to be an appealing investment option

### Conclusions

- Conventional IVF (C-IVF) is comparable to ICSI for non-male factor infertility, unexplained infertility, and advanced maternal age.
- C-IVF is more effective and offers greater cost benefits.
- The implementation of new, simple, and lowcost techniques could alleviate financial burdens associated with fertility treatments.

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