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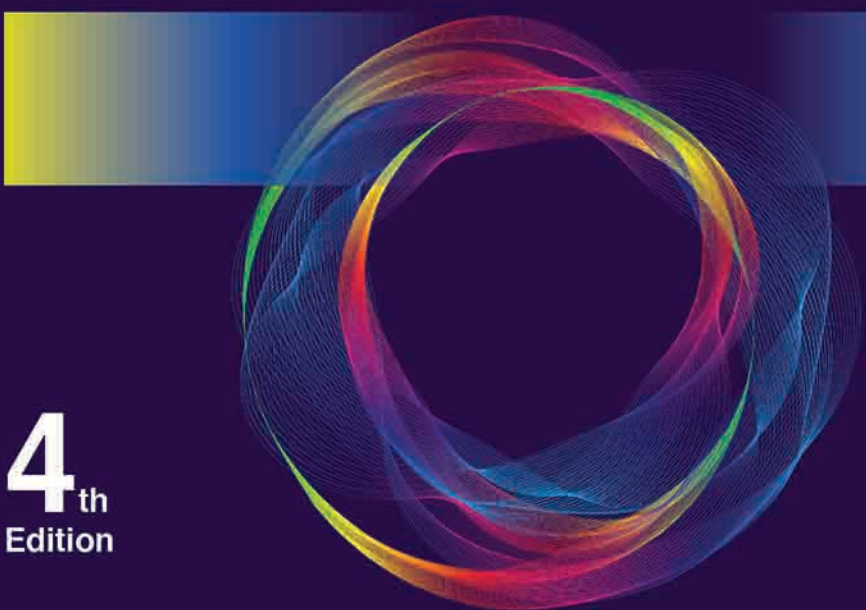
Intrauterine Insemination



4th Edition

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5
CHAPTER

Intrauterine Insemination as a Treatment Option in Resource-limited Medical Settings

Gautam N Allahbadia, Swati Gautam Allahbadia, Akanksha Allahbadia Gupta

ABSTRACT

Intrauterine insemination (IUI) is the oldest and most frequently performed procedure to alleviate infertility. In fact, in resource-limited economies, IUI is the only procedure that can be performed for the majority of couples seeking some form of assisted reproduction simply because in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) is unaffordable to them. Being far less invasive, cheaper, and accompanied by a reduced chance of complications like ovarian hyperstimulation syndrome in comparison to IVF/ICSI, IUI is considered the first-line treatment option. It offers less psychological burden for couples and hence has a lower dropout rate and good compliance with treatment. IUI may be performed with or without ovarian stimulation (OS). Controlled OS, even oral fertility tablets, with IUI offers significant benefits in terms of pregnancy outcomes compared with natural cycle or timed intercourse while reducing associated controlled ovarian hyperstimulation (COH) complications such as multiple pregnancies and ovarian hyperstimulation syndrome. Globally, the prognostic indicators of success with IUI include age of patient, duration of infertility, stimulation protocol, infertility etiology, timing of insemination, and processed total motile sperm count being over 10 million. After >50 years since it was first used, IUI has evolved through various innovations but still struggles to find its place in infertility management in developed economies because of the low success rates as compared to IVF. After the introduction of revised guidelines from the National Institute for Health and Care Excellence (NICE) in 2013, there has been a surge in the use of IVF as a primary treatment modality even in developing economies. But in resource-poor settings, IUI has firmly found its place with ready-to-use sperm preparation kits.

INTRODUCTION

Infertility affects over 50 million couples worldwide with a prevalence estimated at 7–20% in developing economies and as high as 35–40% in Africa.[1] Infertility treatments are not considered a priority in many

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developing economies. The most often used arguments against promoting fertility treatments are overpopulation, other health priorities [e.g., family planning, vaccinations, malaria, and human immunodeficiency virus (HIV)], limited government budgets, and limited experience of providers with inadequate facilities for performing sophisticated procedures. There is a complete absence of affordable and accessible fertility services in some very poor countries, possibly due to underdeveloped infrastructure in addition to cultural, religious, and legal barriers.[2] This deficiency has led to considerable interest by NGOs, policymakers, and fertility specialists in developing more affordable treatment strategies such as ready-to-use sperm preparation kits for intrauterine insemination (IUI) even in remote locations without an in vitro fertilization (IVF) center infrastructure. However, there is a paucity of evidence and systematic reviews on the safety and efficacy profile of these kits, as well as the ability to replicate the results in different laboratories and under various field conditions and on how to integrate these relatively low-cost fertility interventions into existing health systems and infrastructures.

DISCUSSION

Infertility is a long-standing reproductive health issue in sub-Saharan Africa. A 2022 study from Gambia in West Africa examined the availability of infertility services in public and private facilities as part of a wider endeavor to improve fertility care policy and practice in the country.[3] A cross-sectional survey using Qualtrics was administered to 38 health facilities. A total of 25 facilities (66%) offered infertility services, of which 13 (52%) were public and 12 (47%) private. Although the availability of screening tests was similar between health institutions, most diagnostic and treatment services were available only in the private sector. Treatment services included: (1) Ovarian stimulation (OS) ($n = 16$, 42%), (2) reversal of tubal ligation and/or blockage (tuboplasty) ($n = 4$, 11%), and (3) IUI ($n = 3$, 8%). Assisted reproductive technologies (ARTs) such as IVF and intracytoplasmic sperm injection (ICSI) were not available in public or private sectors. Reported barriers to the integration of infertility services in existing reproductive health services included a lack of specialized training, an absence of national guidance on infertility management, and a shortage of appropriate equipment, supplies, and medication. The availability of infertility services in Gambia follows a trajectory that is like most African countries in which services are mostly obtainable through the private sector. Yet, access to private care is expensive and geographically restricted, which exacerbates inequalities in accessing fertility care for all.

A study from Indonesia reported barriers to access which included low confidence in infertility treatment, high rates of switching between providers due to treatment failure, the low number and difficult location of clinics, the

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lack of a well-established referral system, the cost of treatment, and patients with the fear of receiving the diagnosis of infertility, the fear of vaginal examinations, or embarrassment.[4] In Thailand, basic fertility treatment is considered out of reach for most average-income people. In addition, three-quarters of infertility clinics are in urban centers, limiting physical accessibility for rural populations.[5] An Indian study described the drawback of the growing number of centers (now estimated to be over 5,000 clinics in India) where there are poor regulatory guidelines in the country.[6] The options for infertility treatment in India vary from pharmacotherapy, often clomiphene citrate as the initial approach for most women, to more expensive ART options. Often, patients still turn to alternative systems of medicine and faith healing, hoping for a quick and successful outcome, with IUI being the most common fertility intervention. Despite the financial constraints, the majority of the couples consented to the first IVF cycle, but they had to stop treatment when repeated cycles of IVF were indicated. The authors did not report on live birth rates.[6] Infertility and its challenges and barriers to care can be deduced from evidence on IUI in a survey from Pakistan: 90% of the respondents declined IUI because of religious and cultural taboos, and if they received treatment, they were not willing to disclose this to their family.[7] An intensive course with training in hystero-contrast-sonography and one-step IUI was a possible tool as a first step to introduce basic infertility care into resource-poor settings, like Eritrea, before advancing to ART.[8] The aim of a recent study from Nepal was to find out the pregnancy rate among women undergoing IUI in a single center.[9] From 225 women undergoing IUI, pregnancy was achieved in 23 (10.22%). The mean age of the pregnant women was 29.17 ± 3.34 years and the mean duration of infertility was 3.93 ± 2.90 years. More than half of the pregnant women [13 (56.52%)] had undergone insemination with the husband's semen, whereas the remaining 10 women (43.48%) had undergone insemination with donor semen.

A cost-effectiveness analysis was conducted alongside a randomized controlled trial (RCT) where 738 couples were randomized to gonadotropins (369) or clomiphene citrate.[10] The direct medical costs of both strategies were compared. The direct medical costs included costs of medication, cycle monitoring, insemination, and, if applicable, pregnancy monitoring. Gonadotropins are more expensive compared with clomiphene citrate in couples with unexplained infertility undergoing IUI, without being significantly more effective.[10]

Active interventional methods, such as IUI or IVF, are often sought for unexplained infertility. Despite the National Institute for Health and Care Excellence (NICE) recommending IVF for unexplained infertility, this recommendation has generated an ongoing debate, with few fertility clinics discontinuing the use of IUI as the first-line management of choice.[11]

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In contrast to NICE, recent guidelines released by the European Society for Human Reproduction and Embryology (ESHRE) in August 2023 support the use of IUI as first-line treatment. High-quality evidence behind such interventions is lacking, with current literature providing conflicting results. Man et al. published a literature review exploring whether IUI or IVF should be used as first-line treatment for couples with unexplained infertility, in the context of current guidelines.[12] This review highlights a large discrepancy in the literature when examining the pregnancy outcomes of IUI and IVF treatments. Evidence shows that intrauterine insemination increases live birth and clinical pregnancy (CP) rates by three-fold compared to expectant management. The literature comparing IUI to IVF is less certain. The review finds the literature implies IVF should be used as first-line management, but the paucity of high-quality RCTs, coupled with the heterogeneity of the identified studies and a lack of research among women aged >40 years, warrants the need for further large RCTs. The decision to offer intrauterine insemination with ovarian stimulation (IUI-OS) or IVF should be based on patient prognostic factors. The authors suggest that IUI-OS could be offered as the first-line treatment for unexplained infertility for women aged <38 years, with a good prognosis, and IVF could be offered first to those aged >38 years.[12]

Intrauterine insemination involves the deposition of processed semen in the upper uterine cavity close to the time of ovulation. The rationale behind IUI is to increase the gamete density at the site of fertilization.[13] The first report of IUI was published by Cohen[14] in 1962, and since then, this technique has evolved through various innovations. Semen preparation techniques for medically-assisted reproduction (MAR), including IUI, were developed to select the motile, morphologically normal spermatozoa. The yield of actively motile, morphologically normal spermatozoa might influence treatment choices and therefore outcomes.[15]

Boomsma et al.[16] compared the effectiveness of three different semen preparation techniques [gradient, swim-up, and wash and centrifugation (WAC)] on clinical outcomes (live birth and CP rates) in subfertile couples undergoing IUI in a clinical review. Their results suggested that if the chance of pregnancy after the use of a gradient technique is assumed to be 24%, the chance of pregnancy after using the swim-up technique is between 14 and 30%. Considering the quality of evidence, the authors were uncertain whether there is a difference in CP rates after a conventional swim-up (CSW) technique versus WAC. The results suggested that if the chance of pregnancy after the use of a wash technique (WAC) is assumed to be 38%, the chance of pregnancy after using the CSW technique is between 9 and 41%. If the chance of pregnancy after the use of a wash technique (WAC) is assumed to be 13%, the chance of pregnancy after using the density gradient-swim-up (DGC-SW)

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technique is between 8 and 46%. They concluded that there is insufficient evidence to recommend any specific semen preparation technique: CSW versus DGC-SW versus WAC.[16]

A study by Çil et al. from Turkey retrospectively examined the relationship between two different sperm preparation methods used in IUI over 8 years in terms of pregnancy and live birth rates.[17] They evaluated the data of semen samples between December 2012 and March 2020. A total of 384 samples prepared with CSW and 361 samples prepared with DGC-SW obtained from men applying for IUI were analyzed. The basal progressive sperm count was significantly higher in pregnant couples in both CSW and DGC-SW groups ($p = 0.032$ and $p = 0.035$, respectively). In each group, the postwashed total progressive motile sperm count obtained by CSW and DGC-SW methods was significantly higher in pregnant patients ($p < 0.05$). There was no significant difference between CSW and DGC-SW methods in pregnancy achievement ($p = 0.399$, $\chi^2 = 0.712$). Live birth and miscarriage rates were not different between the groups ($p = 0.243$, $\chi^2 = 2.827$). They concluded that there is no significant difference between CSW and DGC-SW for pregnancy and live birth rates. In other words, the choice of sperm preparation method does not affect the pregnancy rate in couples undergoing IUI.[17]

Bacterial flora can be isolated from many semen samples of subfertile males. Bacteriospermia can compromise the outcome of IUI by contaminating the postprocessed sperm sample. The objective of a Sri Lankan study was to determine the efficacy of penicillin and streptomycin in eliminating the bacteria from semen samples in the sperm-processing procedure and to assess the effects of antibiotics on sperm motility, survivability, and pregnancy rates.[18] This prospectively controlled study was carried out in couples undergoing IUI with their informed consent. The authors summarized that a penicillin–streptomycin combination could eliminate nonspecific bacteria from semen samples during sperm processing in this population. The types of antibiotics and dosage used did not seem to have any harmful effects on human sperm.[18]

In order to evaluate the possible benefit of sperm preparation using a commercially available, ready-to-use Percoll gradient kit (PerWash, FertiPro, Belgium) for IUI, a two-center study was performed by Depypere et al. who compared this method with conventional sperm preparation by means of centrifugation–resuspension.[19] In the Percoll group, 25 out of 52 (48%) couples achieved pregnancy requiring 136 cycles of insemination, with a per-cycle success rate of 18.4%. This result was significantly better ($p < 0.01$) than the per-cycle pregnancy rate of 8.9%, which is 23 pregnancies out of 65 cases treated during 259 cycles of insemination with conventionally prepared semen. The authors concluded that sperm preparation for IUI using the Percoll gradient kit gives a better success rate and can be applied in cases with more severe sperm deficiency.[19]

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Sperm preparation is critical to achieving a successful IUI and requires the processing of a semen sample to remove white blood cells, wash away seminal plasma, and reduce sample volume.[15] Jafek et al. published their results with an automated instrument capable of performing sperm preparation starting with a diluted semen sample.[20] They compared their device against density gradient centrifugation by processing 0.5 mL portions of patient samples through each treatment. In 5 minutes of operating time, the instrument recovered an average of 86% of all sperm and 82% of progressively motile sperm from the original sample while removing white blood cells, replacing the seminal plasma, and reducing the volume of the sample to the clinically required level. In 25 minutes of operating time, density gradient centrifugation recovered an average of 33% of all sperm and 41% of progressively motile sperm. The automated instrument could improve access to IUI as a treatment option by allowing satellite doctor's offices to offer IUI as an option for patients without the clinical support required by existing methods.[20]

RECENT ADVANCES

Evans et al. setup a study to find out the CP rate per ovarian stimulation with intrauterine insemination (OS-IUI) treatment cycle in patients with repetitive cycles up to a maximum of eight cycles.[21] A total of 37,565 consecutive OS-IUI cycles from 18,509 patients were included in this study. After statistical adjustment, the mean predicted probability of CP for cycles 1 to 8 was 15.7% per cycle. The mean predicted probability of CP from cycles 2 to 4 was only 1.7% lower compared with cycle 1 as the reference. The mean predicted probability of CP from cycles 5 to 8 was not significantly different compared with the reference cycle. The modeling of consecutive cycles suggested that the adjusted cumulative predicted probability of getting pregnant from IUI continues to increase with each of the eight successive cycles. This important study outlines that CP rates are satisfactory in up to eight consecutive IUI treatment cycles.[21] These data are useful for counseling, especially in those patients for whom IVF is not financially or ethically feasible.

High-quality recent data in well-structured trials suggest that biases against IUI procedures and in favor of IVF are invalid. It is unethical to continue to misinform patients and stakeholders.[11] Recent well-structured RCTs show IUI treatment cycles to be efficient, with minimal risk and above all improved cost-effectiveness when compared to IVF for live births.[11]

CONCLUSION

Due to the availability of the Internet and current reproductive medicine dissemination even to remote, economically deprived areas, the NGOs,

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doctors, and district governing bodies have realized that IUI has been revalidated[11,12,21] and is still considered the gold standard even in the absence of tertiary reproductive care and facilities. Today, vendors and distributors in resource-poor countries have made available, cheap, and ready-to-use sperm preparation kits with antibiotic- and HEPES-supplemented media (which maintain stability for even up to 1 year). Training with videos over the Internet allows nurses and doctors to learn the correct techniques of insemination. Clomiphene citrate is still the gold standard for most of the stimulation IUI cycles in resource-poor settings. Persistence in performing repeated IUIs has been scientifically revalidated,[21] and IUI is helping millions of couples in disadvantaged settings to complete their families.

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Intrauterine Insemination

Intrauterine insemination (IUI) has evidently stood the test of time as a simple, safe, relatively noninvasive, cost-effective, and reliable first-line treatment option for couples with unexplained, mild male factor, cervical factor and anovulatory infertility, endometriosis, and sexual and ejaculatory dysfunction. This concise, practical, and updated edition by Gautam N Allahbadia encompasses everything the reader needs to know about IUI from sperm physiology, the basic setup required, semen preparation techniques, indications, the IUI technique complications, outcomes, predictors of success, and gamete cryopreservation to a comparative evaluation of controlled ovarian hyperstimulation (COH) protocols used with IUI and with other techniques and its regulation in the legal scenario. The fertile discussions, detailed in aptly titled chapters by renowned scientific personalities, aired herein, aim to highlight the significance of using IUI prior to proceeding with more advanced, expensive, or invasive techniques that are beset with complications. It educates the clinician on the prudent and judicial use of this technique to create a clinically, financially, and psychologically amicable and result-oriented solution that caters to a broader spectrum of society. By facilitating the access of a hyperactivated and progressively sperm-rich fraction to the oocyte, IUI enables satisfactory pregnancy rate, especially when combined with ovarian simplicity and affordability of IUI making it an indispensable technique for the masses, especially in resource, technology, and economy-limited settings.



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