THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (November–December 2017) 67(6):385–392
DOI 10.1007/s13224-017-1060-x

GUEST EDITORIAL

Intrauterine Insemination: Fundamentals Revisited

Gautam N. Allahbadia[1]

Received: 7 October 2017 / Accepted: 9 October 2017 / Published online: 25 October 2017

About the Author

Gautam Nand Allahbadia is the Emeritus Editor of the Journal of Obstetrics and Gynecology of India as well as the IVF Lite (Journal of Minimal Stimulation IVF). He is the Medical Director of Medcare Fertility Centre, Jumeira, Dubai, UAE, as well as Rotunda—The Center for Human Reproduction, the world-renowned Infertility clinic at Bandra, Mumbai, India. He is a noted world authority on Ultrasound-guided Embryo Transfers and one of the pioneers in Third Party Reproduction in Southeast Asia. Dr. Allahbadia was responsible for India's first trans-ethnic surrogate pregnancy involving a Chinese couple's baby delivered by an unrelated Indian surrogate mother. He cherishes over 150 peer-reviewed publications, 140 book chapters, and 22 textbooks, the latest being a comprehensive text, entitled "Minimal Stimulation IVF," and is on the Editorial Board of several International Journals. Dr. Allahbadia has recently been elected as the Vice President of the World Association of Reproductive Medicine (WARM), headquartered in Rome, and "Mumbai's Top Doc" for 2012 by a peer nomination process. You can read more about his work at www.gautamallahbadia.com.

Abstract Intrauterine insemination (IUI) is an assisted conception technique that involves the deposition of a processed semen sample in the upper uterine cavity, overcoming natural barriers to sperm ascent in the female reproductive tract. It is a cost-effective, noninvasive first-line therapy for selected patients with functionally normal tubes, and infertility due to a cervical factor, anovulation, moderate male factor, unexplained factors, immunological factor, and ejaculatory disorders with clinical pregnancy rates per cycle ranging from 10 to 20%. It, however, has limited use in patients with endometriosis, severe male factor infertility, tubal factor infertility, and advanced maternal age $\geq$ 35 years. IUI may be performed with or without ovarian stimulation. Controlled ovarian stimulation, particularly with low-dose gonadotropins, with IUI offers significant benefit in terms of pregnancy outcomes compared with natural cycle or timed intercourse, while reducing associated COH complications such as multiple pregnancies and ovarian hyperstimulation syndrome. Important prognostic indicators of success with IUI include

Gautam N. Allahbadia is the Emeritus Editor of the Journal of Obstetrics and Gynecology of India as well as the IVF Lite (Journal of Minimal Stimulation IVF) and Medical Director at Rotunda—The Center for Human Reproduction, Mumbai, India and Medcare Fertility Center, Jumeira, Dubai, UAE.

✉ Gautam N. Allahbadia
ivfwaladoc@gmail.com

[1] Rotunda-The Center for Human Reproduction, Bandra, Mumbai, India

age of patient, duration of infertility, stimulation protocol, infertility etiology, number of cycles, timing of insemination, number of preovulatory follicles on the day of hCG, processed total motile sperm > 10 million, and insemination count $> 1 \times 106$ with $> 4\%$ normal spermatozoa. Alternative insemination techniques, such as Fallopian tube sperm perfusion, intracervical insemination, and intratubal insemination, provide no additional benefit compared to IUI. A complete couple workup that includes patient history, physical examination, and clinical and laboratory investigations is mandatory to justify the choice in favor of IUI and guide alternative patient management, while individualizing the treatment protocol according to the patient characteristics with a strict cancelation policy to limit multi-follicular development may help optimize IUI pregnancy outcomes.

Introduction

Despite revolutionary advances in the field of assisted reproduction, such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and subzonal insemination (SUZI), intrauterine insemination (IUI) remains an inexpensive, noninvasive, and effective first-line therapy for selected patients with cervical factor, moderate male factor, unexplained infertility, immunological infertility, and infertility due to ejaculatory disorders and is now also proposed as a therapy for endometriosis, ovarian dysfunction, and even for tubal factor. Though the technique of IUI has essentially remained the same, several advances in the type of stimulation protocols, gonadotropins, sperm preparation techniques, and ultrasound monitoring have led to promising success rates with IUI.

Strict patient selection criteria and individualized stimulation protocols tailored according to the age and etiology of the patient with a strict cycle cancelation policy will help to reduce the associated complications, such as multiple pregnancies and OHSS, while maximizing the overall pregnancy outcome. Three to six IUI cycles may be offered before considering alternate therapy. However, patients with advanced maternal age, severe male factor infertility, tubal pathology, or severe endometriosis will benefit from a direct referral to IVF/ICSI.

Semen parameters that must be considered in an IUI program include the semen processing time, processed total motile sperm count, rapid progressive motility after processing, sperm morphology before and after processing, inseminating motile sperm count (IMSC), IUI insemination time, and 24-h sperm survival. Delaying semen processing from 30 min up to 1 h and/or delaying IUI from 90 min up to 2 h after collection compromises the pregnancy outcome in gonadotropin-IUI cycles [1]. A universal threshold level above which IUI can be performed with acceptable pregnancy rates has not been determined yet [2]. However, IUI success may be impaired in couples with processed total motile sperm (PTMS) < 10 million [3], sperm survival $< 70\%$ [4], $< 5\%$ normal spermatozoa, inseminating motile count (IMC) $< 1 \times 106$ [2], and prewash IUI-semen pregnancy score (IUI-SPS) < 150 [5], necessitating alternative therapy. The PTMS count has been independently associated with fertility after IUI ($P = 0.0014$) [3]. PTMS $\geq 10 \times 106$, their 24-h sperm survival threshold of $\geq 70\%$ [4], normal morphology before sperm separation $\geq 15.5\%$ [odds ratio (OR) $= 2.2$, ($P = 0.02$)], rapid, progressive motility $\geq 25.5\%$ after sperm separation ($P = 0.029$), and curvilinear velocity (VCL) after sperm separation ≥ 102.65 μm/s ($P = 0.002$) independently predict pregnancy outcome in patients with male factor infertility [6]. These variables would be helpful in counseling patients for future management [6].

Discussion

In couples with a cervical factor, diagnosed by a well-timed, nonprogressive, post-coital test with normal semen parameters [7], higher pregnancy rates (PRs) have been reported following IUI compared to expectant management (51 vs. 33%, respectively) [8] with acceptable pregnancy rates even without COH (9.7%) and without an increased risk for multiple pregnancy compared to COH (12.7%) [7]. Cumulative pregnancy rates of 19.7, 36.8, and 36.8% have been reported for a maximum of three IUI cycles in patients with a cervical factor without superovulation [9]. Pregnancy rates of 12.8, 29.3, and 38.3% for a maximum of three cycles have been reported in couples with a male factor without superovulation [9], 7% per cycle following COH–IUI with clomiphene citrate (CC) and 12% per cycle with follicle-stimulating hormone (FSH) with multiple birth rates averaging 13% [10]. Despite the belief that IVF may be a more cost-effective primary treatment option compared to IUI in lieu of the low success rates with IUI and the subsequent requirement for IVF in the event of failure [11], the results of randomized controlled trials (RCTs) using live birth rates rather than pregnancy rates, and taking into account efficacy, complications, especially multiple pregnancy rates, patient compliance, and cost-efficiency, suggest that the initial treatment for idiopathic infertility should be IUI as opposed to IVF [12].

Controlled ovarian hyperstimulation with IUI is recommended in early-stage and surgically corrected endometriosis when the pelvic anatomy is normal, while combined surgery with gonadotropin-releasing hormone (GnRH) analog treatment has been proposed to be a first-line therapy followed by IVF as second-line therapy in

advanced cases [13]. Comparable clinical PRs per cycle have been reported in women with minimal, mild endometriosis, and unexplained infertility (21 vs. 18.9 vs. 20.5%) following COH–IUI with comparative cumulative live birth rates within four cycles of COH and IUI (70.2, 68.2, 66.5%, respectively); CPR/cycle with or without COH–IUI was lower in women with surgically untreated minimal to mild endometriosis than in women with unexplained infertility [14]. However, in patients with minimal or mild endometriosis with pathological utero-tubal transport documented by hysterosalpingoscintigraphy (HSSG), IUI yields poor pregnancy rates despite normal semen parameters and patent Fallopian tubes, necessitating recourse to IVF/ICSI [15]. Though IVF reduces time to pregnancy in early-stage disease compared to controls, it does not increase the chance of pregnancy after 3 years [16]. In patients with stage IV endometriosis and in women > 38 years of age, significantly higher PR, fecundity, and cumulative fecundity have been reported following IVF-ET compared to COH–IUI. Hence, IVF-ET should be the first-line approach in the management of infertility in such patients, and if COH–IUI is attempted, it should not exceed 3–4 cycles [17].

IUI may be contraindicated in women with sperm-immobilizing antibodies owing to antibodies secreted in the female reproductive tract that might impair sperm passage, inhibit fertilization, and prevent normal post-fertilization processes [18]. The total antral follicle number is reported to decrease with age. In women > 35 years with antral follicle counts (AFCs) < 5, the application of COH/IUI may not be indicated [19].

Pittrof et al. [20] reported a significantly higher number of preovulatory follicles (43.6, 59.9, 12.6%, $P < 0.0001$) and significantly higher pregnancy rates ($P = 0.038$) in CC/tamoxifen + gonadotropin—stimulated cycles compared to natural cycles [20]. However, Chen and Liu [21] concluded that though stimulated IUI is superior to natural cycle IUI cycles in patients < 35 years, natural cycle is preferable for patients ≥ 35 years. There were no significant differences in the abortion and delivery rates between the OI and the natural cycle insemination ($P > 0.05$) [21]. IUI in the spontaneous cycle carries fewer health risks than does IUI after mild hormonal stimulation and, therefore, should be the first-choice treatment [22]. Ovarian stimulation by clomiphene citrate (CC) and IUI remains the first-choice treatment for ovulatory dysfunction, unexplained infertility, endometriosis, or male subfertility [23] with pregnancy rates averaging 7% per cycle [10]. Though no consensus exists about the drug of first choice to be used as hyperstimulation and there are no significant differences in clinical pregnancy (38 vs. 34.3%) and live birth rates (28.2 vs. 26.9%) between CC and rFSH, a randomized multicenter parallel trial concluded that being less expensive, CC seems the more cost-effective drug and, therefore, can be offered as drug of first choice [24].

A meta-analysis of 43 trials involving 3957 women concluded that gonadotropins might be the most effective drugs when IUI is combined with ovarian hyperstimulation, yielding higher pregnancy rates compared to antiestrogens, comparable PRs with different types of gonadotropins, no improvement with GnRH agonist or antagonist but increased multiple pregnancy rates and OHSS rates with increased doses of gonadotropins, and significantly higher multiple pregnancy rates with the agonist. When gonadotropins are used for ovarian stimulation, low-dose protocols are advised since pregnancy rates do not differ from those obtained with high-dose regimens, whereas the chances to encounter negative effects from ovarian stimulation such as multiple pregnancies and OHSS are limited with low-dose gonadotropins. Further research is needed for each comparison made [25]. No significant differences have been reported among low-dose gonadotropin protocols that differed in gonadotropin dosage (4/6/8/ampoules of 75 IU FSH) or the mode of administration in terms of cycle parameters, suggesting that an individualized and more intensive approach to ovarian stimulation is necessary for many women with unexplained infertility [26]. With regard to the mode of administration, daily recombinant FSH (follitropin beta) stimulation has been associated with higher CPRs (42 vs. 19%, respectively), higher total recombinant FSH dose (825 vs. 625 IU), and endometrial thickness (10.1 vs. 9.3 mm) compared to alternate-day FSH stimulation in women with anovulatory or unexplained infertility for over 12 months who had not responded to or not conceived with CC treatment though the duration of stimulation and the median number of follicles over 14 mm, AFC, and day-3 serum FSH were comparable between the groups. However, prospective randomized trials would be needed to determine whether this is indeed the case [27]. Mahani and Afnan [28] reported the highest CPRs/cycle and CPR/patient following IUI in patients stimulated with hMG compared with CC, CC + hMG, or natural cycle.

Studies have reported a beneficial effect of the use of the aromatase inhibitor letrozole (2.5–5 mg/day from day 3–7 of the IUI cycle) alone/co-administered with gonadotropins compared to CC, CC + gonadotropins, or gonadotropins alone in terms of comparable if not higher CPR/cycle and take home baby rates. Significantly higher serum levels of LH, endometrial thickness, and progesterone at the time of hCG administration have been observed despite a significantly lower serum E2 level [29–31] with significantly lower costs, risks, and patient inconvenience in patients with unexplained infertility [29, 30, 32, 33] endometriosis, and combined indications [34], and lower FSH dose

requirement and IUI cancelation rates in patients with ovulatory infertility [35] and older infertile women [31].

Liang et al. investigated the influence of the time interval from the end of semen processing to artificial intrauterine insemination with husband's sperm (AIH–IUI) on the rate of clinical pregnancy [36]. This study involved 191 AIH–IUI cycles with the same ovulation induction protocol. After Percoll density gradient centrifugation, they divided the sperm into four groups based on the incubation time: 0–19, 20–39, 40–59, and 60–80 min, and again into another four groups according to the total progressively motile sperm count (TPMC): (0–9), (10–20), (21–30), and $> 30 \times 10^6$. They analyzed the correlation of the clinical pregnancy rate with the time interval from the end of sperm processing to AIH–IUI and with other influencing factors, such as maternal age, infertility duration, and semen quality. The rate of clinical pregnancy was significantly higher in the 20–39-min group (18.3%) than in the 0–19-, 40–59-, and 60–80-min groups (12.7, 11.4 and 9.1%) (all $P < 0.05$). The (10–20) $\times 10^6$ group achieved a remarkably higher pregnancy rate (16.7%) than the (0–9), (21–30), and $> 30 \times 10^6$ groups (0, 11.4, and 8.3%) (all $P < 0.05$). Logistic multivariate analysis showed that the rate of clinical pregnancy was decreased with the increased age of the women (OR 0.89, 95% CI 0.83–0.94) but significantly elevated in the 20–39-min group (OR 2.11, 95% CI 1.34–3.13) and of (10–20) $\times 10^6$ group (OR 2.06, 95% CI 1.32–3.46). The time interval from the end of sperm processing to AIH–IUI is a significant factor influencing the rate of clinical pregnancy of AIH–IUI [36].

Çok et al. reported on the comparison of the effect of preserving prepared sperm samples at room temperature or at 37 °C before intrauterine insemination (IUI) on clinical pregnancy rate [37]. Clinical pregnancy rates were similar in IUI cycles in which prepared sperm samples were preserved at 37 °C and at room temperature (9.3 vs. 8.9%). Clinical pregnancy rates in IUI cycles with two follicles were higher than IUI cycles with one follicle (10.8 vs. 7.6%) ($P = 0.002$). Further statistical analysis after splitting data according to the number of the follicles revealed that there was no statistical difference between clinical pregnancy rates after IUI cycles in which prepared sperm samples were preserved at 37 °C or at room temperature in both one-follicle (7.6 vs. 7.6%) and two-follicle cycles (11.5 vs. 10.1%). Preserving prepared sperm samples at room temperature had no negative effect on clinical pregnancy rates when compared with preserving prepared sperm samples at 37 °C during IUI cycles [37].

A modified application technique of intrauterine insemination (IUI) is slow release insemination (SRI), first described by Muharib et al. [38], who postulated higher pregnancy rates with a slow release of spermatozoa for 3 h. To investigate this approach, two randomized controlled, crossover pilot studies were performed from 2004 to 2006 in Israel and Germany to compare SRI with the standard bolus IUI. Marschalek et al. aimed to present the results and perform a meta-analysis on available data for SRI [39]. Univariate comparisons of pregnancy rates were performed using one-tailed z tests for method superiority. For meta-analysis, a fixed-effect Mantel–Haenszel weighted average of relative risk was performed. Fifty treatment cycles (IUI: $n = 25$, SRI: $n = 25$) were performed in Germany, achieving four pregnancies (IUI 4%, SRI 12%, $P > 0.05$). Thirty-nine treatment cycles (IUI: $n = 19$, SRI: $n = 20$) were performed in Israel achieving six pregnancies (IUI 10.5%, SRI 20%; $P > 0.05$). Meta-analysis of all eligible studies for SRI ($n = 3$) revealed a combined relative risk for pregnancy after SRI of 2.64 (95% CI 1.04–6.74), $P = 0.02$). In conclusion, these results lend support to the hypothesis that the pregnancy rate might be improved by SRI compared to the standard bolus technique [39].

Multiple pregnancies are a recognized adverse effect of assisted reproductive technologies; nevertheless, there is no consensus on the incremental risk associated with the ovarian stimulation (OS) used alone and intrauterine insemination (IUI). The relationship between OS and IUI and the risk of major congenital malformations (MCM) is unclear. Chaabane et al. set up a study [40] to summarize the literature and evaluate the risk of multiple pregnancy and MCM associated with OS used alone and IUI used with or without OS compared to natural conception (spontaneously conceived infants without any type of fertility treatments). They carried out a systematic review to identify published papers between 1966 and 2014 in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. They included observational studies and randomized clinical trials related to the risk of multiple pregnancies and MCM conceived following OS alone or IUI compared to natural conception (spontaneously conceived infants without any fertility treatments). There were 63 studies included in this review. The systematic review suggests that the use of any OS alone was associated with an increased risk of multiple pregnancies compared to natural conception (pooled RR 8.80, 95% CI 5.09–15.20; $P = 0.000$; 9 studies). Similar increases in the risk of multiple pregnancies were observed following clomiphene citrate used without assisted reproductive technologies. Compared to natural conception, the use of IUI with or without OS was associated with an increased risk of multiple pregnancy (pooled RR 9.73, 95% CI 7.52–12.60; $P = 0.000$; 6 studies). Compared to natural conception, the use of any OS alone was associated with an increased risk of any MCM (RR pooled 1.18, 95% CI 1.03–1.36; 11 studies), major musculoskeletal malformations (pooled RR 1.48, 95% CI 1.21–1.81; 7 studies), and malformations of

the nervous system (pooled RR 1.73, 95% CI 1.15–2.61; 6 studies). Compared to natural conception, the use of IUI was associated with an increased risk of any MCM (pooled RR 1.23, 95% CI 1.10–1.37; 10 studies), major urogenital (pooled RR 1.52, 95% CI 1.04–2.22; 7 studies), and musculoskeletal malformations (pooled RR 1.54, 95% CI 1.20–1.98; 7 studies). The increased risk of multiple pregnancy and certain types of MCM associated with the use of less invasive fertility treatments, such as OS and IUI, found in this review, highlights the importance of the practice framing [40].

Heterogeneity in OS protocols, the combination with other fertility agents, the limited number of studies, and the methodological quality differences reduce our ability to draw conclusions on specific treatment. More observational studies, assessing the risk of multiple pregnancy or MCM, as a primary outcome, using standardized methodologies, in larger and better clinically defined populations are needed.

Recent Advances

The transcriptome of spermatozoa used in homologous IUI reveals profound differences between expression profiles of sperm samples that impregnate successfully and those that do not. These differences might improve the predictive power of sperm evaluation to estimate IUI success by complementing the basic sperm analysis [41]. Three-dimensional (3D) and 3D power Doppler (PD) when used with 2D ultrasound and color Doppler for pre-hCG follicular assessment improve pregnancy rates in IUI cycles by enabling an assessment of the follicular volume, perifollicular resistance index, and perifollicular vascularity index, all of which may influence the conception rates [42].

Abdel Razik's study evaluated the effects of nitric oxide donor's treatment on the pregnancy rate and uterine blood flow in patients with unexplained infertility undergoing clomiphene citrate stimulation and intrauterine insemination [43]. A total of 120 patients were randomly allocated to a control group who received 100 mg clomiphene citrate daily from day 5 to 9 of cycle plus placebo vaginal tablets, and a study group received clomiphene citrate plus isosorbide mononitrate 10-mg vaginal tablets. Vaginal ultrasound was done before treatment and every other day starting from day 12 of cycle to count mature follicles, and ovulation was triggered by IM injection of 10,000 IU hCG when one follicle measured 18 $\geq$ mm followed by intrauterine insemination after 36 h. The endometrial thickness, uterine arteries resistance and pulsation indices, and endometrial vascular flow and vascular flow indices were measured before treatment and at day of hCG injection. The study group had significant higher pregnancy rate/cycle, higher endometrial, and lower uterine artery blood flow indices ($P < 0.05$) [43].

Kutlu et al. assessed the relationship between the estrogen–progesterone alterations before and after ovulation trigger and treatment success in intrauterine insemination (IUI) cycles (54). Two hundred and fifty-one women with infertility underwent ovulation induction followed by IUI. For all subjects, estradiol and progesterone concentrations were evaluated on the trigger and IUI day. The results were analyzed to assess the relationship between hormone levels and positive pregnancy test. There were 34 women with a positive pregnancy test following controlled ovarian stimulation and IUI cycle. Estradiol and progesterone levels on the trigger day and the day of IUI were compared within groups with and without positive pregnancy tests. The comparison revealed significantly increased levels of progesterone after trigger in both groups; however, although there were estradiol level drops in both groups, the drop in the group with negative pregnancy tests was statistically significant. Significant drops in estradiol concentrations after ovulation trigger are associated with IUI cycle treatment failure [44].

The parameters measured in the standard semen analysis may be insufficient for exact differentiation between fertile and infertile men. Therefore, Boyraz et al. assumed that the high rate of apoptotic sperm in ejaculate may play a role on the etiology of unexplained infertility [45]. Couples with unexplained infertility treated by ovulation induction and intrauterine insemination were consecutively enrolled ($n = 94$). To determine the proapoptotic sperm rate, the ejaculate from patients was stained with annexin V. Thirteen of the 94 couples (13.8%) conceived after intrauterine insemination. The annexin V-positive sperm rate was found to be 20.0% in the whole group. In women failing to conceive, the annexin V-positive sperm rate was 20.8% compared to 15.7% in patients who achieved pregnancy [45]. Although there is a trend toward higher preapoptotic sperm rate in couples failing to get pregnant with insemination, the difference did not reach statistical significance [45].

The advanced methods for semen preparation include molecular sperm selection strategies such as hyaluronic acid-mediated sperm selection, annexin V magnetic-activated cell separation (MACS) that utilizes colloidal superparamagnetic microbeads (approximately 50 nm in diameter) conjugated with annexin V to separate apoptotic and nonapoptotic spermatozoa, and annexin V molecular glass wool filtration [46].

The Future is Now

Swierkowski-Blanchard conducted an observational pilot study to determine the impact of the frequency and intensity of uterine contractions (UCs) at the time of IUI on subsequent fertility [47]. One hundred volunteer women scheduled for IUI between April 2011 and July 2013, in whom UCs were assessed during the ultrasound before IUI was included. A two-dimensional sagittal uterus elastography was recorded for 5 min. The elasticity index, defined as the mean ratio of elastographic measurements between the subendometrial area (of interest) and the endometrial area (control), was computed. UC frequency, endometrial thickness and volume, and subendometrial vascularization were also measured. These parameters, along with characteristics of the IUI cycle, were entered into a logistic regression model for predicting ongoing pregnancy. The elasticity index was significantly higher (2.4 ± 1.3 vs. 1.5 ± 0.7, i.e., with stiffer myometrium), and the endometrium was significantly less echogenic in future pregnant women. Factors closely reaching significance were age, previous fertility, day 3 hormonal assessments, number of inseminated spermatozoa, endometrial thickness, and UC count. In multivariate analysis, low UC frequency (< 2.8/min; odds ratio [OR] $= 0.039$), high elasticity index (> 1.7; OR 63.26), high endometrial thickness on the ovulation triggering day (> 8 mm; OR 28.21), and low patient age (< 32 years; OR 0.001) were predictive of pregnancy after IUI. A low frequency and high intensity of UCs at the day of IUI appear associated with a higher pregnancy rate. Elastography provides a promising innovative tool for IUI monitoring [47].

Uterine contractibility is considered a powerful prognostic factor in predicting the embryo transfer outcome. Moreover, uterine contractions are known to be stimulated by prostaglandins, which are produced by cyclooxygenase from arachidonic acid. As such, suppressing the inflammatory response and contractions using anti-inflammatory and relaxant agents is expected to result in increased success rate of embryo transfer and artificial insemination. Zarei et al. investigated the effect of piroxicam administration on the success rate in intrauterine insemination (IU) cycles in patients presenting with unexplained infertility [48]. This randomized, placebo-controlled clinical trial included 260 women with unexplained infertility undergoing IUI cycles. Patients were randomly assigned to receive either piroxicam ten mg/day on days 4–6 after IUI or placebo (control group). The main outcome measures were number of IUI cycles, pregnancy, abortion, and multiple pregnancy rates. The pregnancy rate was found to be 25 (19.2%) and 16 (12.3%) in piroxicam and control groups, respectively ($P = 0.039$). Five patients (3.8%) in piroxicam group experienced twin pregnancy, whereas only three patients (2.3%) in control group had twin pregnancy ($P = 0.361$). The pregnancy rate per cycle was also significantly higher in those who received piroxicam as compared to controls (11.16 vs. 6.66; $P = 0.021$). Administration of piroxicam after IUI is associated with decreased number of cycles, as well as increased pregnancy rate and pregnancy rate per cycle in IUI cycles. However, piroxicam did not have any effect on abortion, multiple pregnancy, and ongoing pregnancy rates [48].

Conclusions

IUI is a simple, cost-effective, noninvasive first-line therapy for cervical factor, anovulatory infertility, moderate male factor, unexplained infertility, and immunological infertility with clinical pregnancy rates ranging from 10 to 20%. Controlled ovarian hyperstimulation with close monitoring of folliculogenesis and ovulation to avoid adverse complications, such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies, may be used to obtain the adequate number of follicles. IUI is the preferred conception-enhancing technique for women < 35 years, functional tubes, short period of infertility, and moderate male infertility, particularly in technology-limited settings, and four to six IUI cycles may be performed before considering alternate therapy such as IVF [49, 50]. It is the method of choice versus timed intercourse or natural cycle IUI [51].

References

1. Yavas Y, Selub MR. Intrauterine insemination (IUI) pregnancy outcome is enhanced by shorter intervals from semen collection to sperm wash, from sperm wash to IUI time, and from semen collection to IUI time. Fertil Steril. 2004;82(6):1638–47.
2. Ombelet W, Deblaere K, Bosmans E, et al. Semen quality and intrauterine insemination. Reprod Biomed Online. 2003;7(4):485–92.
3. Miller DC, Hollenbeck BK, Smith GD, et al. Processed total motile sperm count correlates with pregnancy outcome after intrauterine insemination. Urology. 2002;60(3):497–501.
4. Branigan EF, Estes MA, Muller CH. Advanced semen analysis: a simple screening test to predict intrauterine insemination success. Fertil Steril. 1999;71(3):547–51.
5. Bedaiwy MA, Sharma RK, Alhussaini TK, et al. The use of novel semen quality scores to predict pregnancy in couples with male-factor infertility undergoing intrauterine insemination. J Androl. 2003;24(3):353–60.
6. Shibahara H, Obara H, Hirano Y, et al. Prediction of pregnancy by intrauterine insemination using CASA estimates and strict criteria in patients with male factor infertility. Int J Androl. 2004;27(2):63–8.

7. Steures P, van der Steeg JW, Verhoeve HR, et al. Does ovarian hyperstimulation in intrauterine insemination for cervical factor subfertility improve pregnancy rates? Hum Reprod. 2004;19(10):2263–6.
8. Steures P, van der Steeg JW, Hompes PG, et al. Effectiveness of intrauterine insemination in subfertile couples with an isolated cervical factor: a randomized clinical trial. Fertil Steril. 2007;88(6):1692–6.
9. Check JH, Bollendorf A, Zaccardo M, et al. Intrauterine insemination for cervical and male factor without superovulation. Arch Androl. 1995;35(2):135–41.
10. ESHRE Capri Workshop Group, Aboulghar M, Baird DT, Collins J, et al. Intrauterine insemination. Hum Reprod Update. 2009;15(3):265–77.
11. Pashayan N, Lyratzopoulos G, Mathur R. Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility. BMC Health Serv Res. 2006;6:80.
12. Homburg R. The case for initial treatment with intrauterine insemination as opposed to in vitro fertilization for idiopathic infertility. Hum Fertil (Camb). 2003;6(3):122–4.
13. Ozkan S, Arici A. Advances in treatment options of endometriosis. Gynecol Obstet Invest. 2009;67(2):81–91.
14. Werbrouck E, Spiessens C, Meuleman C, et al. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril. 2006;86(3):566–71.
15. Kissler S, Hamscho N, Zangos S, et al. Diminished pregnancy rates in endometriosis due to impaired uterotubal transport assessed by hysterosalpingoscintigraphy. BJOG. 2005;112(10):1391–6.
16. Hansen KA, Eyster KM. A review of current management of endometriosis in 2006: an evidence-based approach. S D Med. 2006;59(4):153–9.
17. Dmowski WP, Pry M, Ding J, et al. Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation-intrauterine insemination or in vitro fertilization-embryo transfer. Fertil Steril. 2002;78(4):750–6.
18. Shibahara H, Koriyama J, Shiraishi Y, et al. Diagnosis and treatment of immunologically infertile women with sperm-immobilizing antibodies in their sera. J Reprod Immunol. 2009;83(1–2):139–44.
19. Chang MY, Chiang CH, Chiu TH, et al. The antral follicle count predicts the outcome of pregnancy in a controlled ovarian hyperstimulation/intrauterine insemination program. J Assist Reprod Genet. 1998;15(1):12–7.
20. Pittrof RU, Shaker A, Dean N, et al. Success of intrauterine insemination using cryopreserved donor sperm is related to the age of the woman and the number of preovulatory follicles. J Assist Reprod Genet. 1996;13(4):310–4.
21. Chen L, Liu Q. Natural cycle versus ovulation induction cycle in intrauterine insemination (Article in Chinese). Zhonghua Nan Ke Xue. 2009;15(12):1112–5.
22. Goverde AJ, McDonnell J, Vermeiden JP, et al. Intrauterine insemination or in vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet. 2000;355(9197):13–8.
23. Custers IM, Steures P, Hompes P, et al. Intrauterine insemination: How many cycles should we perform? Hum Reprod. 2008;23(4):885–8.
24. Dankert T, Kremer JA, Cohlen BJ, et al. A randomized clinical trial of clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimulation in intrauterine insemination cycles for unexplained and male subfertility. Hum Reprod. 2007;22(3):792–7.
25. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev. 2007;2007(2):CD005356.
26. Hughes EG, Collins JA, Gunby J. A randomized controlled trial of three low-dose gonadotrophin protocols for unexplained infertility. Hum Reprod. 1998;13(6):1527–31.
27. Kabli N, Sylvestre C, Tulandi T, et al. Comparison of daily and alternate day recombinant follicle-stimulating hormone stimulation protocols for intrauterine insemination. Fertil Steril. 2009;91(4):1141–4.
28. Mahani IM, Afnan M. The pregnancy rates with intrauterine insemination (IUI) in superovulated cycles employing different protocols (clomiphene citrate (CC), human menopausal gonadotropin (HMG) and HMG + CC) and in natural ovulatory cycle. J Pak Med Assoc. 2004;54(10):503–5.
29. Wang CW, Horng SG, Chen CK, et al. Ovulation induction with tamoxifen and alternate-day gonadotrophin in patients with thin endometrium. Reprod Biomed Online. 2008;17(1):20–6.
30. Barroso G, Menocal G, Felix H, et al. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. Fertil Steril. 2006;86(5):1428–31.
31. Bedaiwy MA, Shokry M, Mousa N, et al. Letrozole co-treatment in infertile women 40 years old and older receiving controlled ovarian stimulation and intrauterine insemination. Fertil Steril. 2009;91(6):2501–7.
32. Tehrani Nejad ESh, Abediasl Z, Rashidi BH, et al. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate gonadotropins in controlled ovarian hyperstimulation: a prospective, simply randomized, clinical trial. J Assist Reprod Genet. 2008;25(5):187–90.
33. Baysoy A, Serdaroglu H, Jamal H, et al. Letrozole versus human menopausal gonadotrophin in women undergoing intrauterine insemination. Reprod Biomed Online. 2006;13(2):208–12.
34. Bedaiwy MA, Forman R, Mousa NA, et al. Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation. Hum Reprod. 2006;21(11):2838–44.
35. Mitwally MF, Casper RF. Aromatase inhibition reduces the dose of gonadotropin required for controlled ovarian hyperstimulation. J Soc Gynecol Investig. 2004;11(6):406–15.
36. Liang JY, Li ZT, Yang XH, et al. Time interval from the end of sperm processing to artificial intrauterine in semination with husband's sperm correlates to the rate of clinical pregnancy. Zhonghua Nan Ke Xue. 2015;21(6):532–5.
37. Çok T, Çağlar Aytaç P, Şimşek E, et al. The effect of preserving prepared sperm samples at room temperature or at 37 °C before intrauterine insemination (IUI) on clinical pregnancy rate. Turk J Obstet Gynecol. 2015;12(1):6–10. doi:10.4274/tjod.31644.
38. Muharib NS, Abdel Gadir A, Shaw RW. Slow release intrauterine insemination versus the bolus technique in the treatment of women with cervical mucus hostility. Hum Reprod. 1992;7(2):227–9.
39. Marschalek J, Franz M, Gonen Y, et al. The effect of slow release insemination on pregnancy rates: report of two randomized controlled pilot studies and meta-analysis. Arch Gynecol Obstet. 2017;295(4):1025–32. doi:10.1007/s00404-017-4290-3 **Epub 2017 Feb 14**.
40. Chaabane S, Sheehy O, Monnier P, et al. Ovarian stimulation, intrauterine insemination, multiple pregnancy and major congenital malformations: a systematic review and meta-analysis—the ART_Rev study. Curr Drug Saf. 2016;11(3):222–61.

41. García-Herrero S, Meseguer M, Martínez-Conejero JA, et al. The transcriptome of spermatozoa used in homologous intrauterine insemination varies considerably between samples that achieve pregnancy and those that do not. Fertil Steril. 2009;94:1360–73.
42. Panchal S, Nagori CB. Pre-hCG 3D and 3D power Doppler assessment of the follicle for improving pregnancy rates in intrauterine insemination cycles. J Hum Reprod Sci. 2009;2(2):62–7.
43. Abdel Razik M, El-Berry S, El-Nezamy A, et al. Nitric oxide donors increase the pregnancy rate in patients with unexplained infertility undergoing clomiphene citrate stimulation and intrauterine insemination: a randomized controlled pilot study. Gynecol Endocrinol. 2017;33(3):199–202. doi: 10.1080/09513590.2016.1240775.
44. Kutlu T, Özkaya E, Şanverdi I, et al. The relationship between estradiol-progesterone alterations after ovulation trigger and treatment success in intrauterine insemination cycles. Turk J Obstet Gynecol. 2016;13(2):56–61. doi:10.4274/tjod.45656.
45. Boyraz G, Selcuk I, Sokmensuer LK, et al. Evaluation of the relation between preapoptotic sperm rate in ejaculate and intrauterine insemination success rate in patients with unexplained infertility. J Obstet Gynaecol. 2016;36(8):980–3.
46. Paasch U, Grunewald S, Glander HJ. Sperm selection in assisted reproductive techniques. Soc Reprod Fertil Suppl. 2007;65:515–25.
47. Swierkowski-Blanchard N, Boitrelle F, Alter L, et al. Uterine contractility and elastography as prognostic factors for pregnancy after intrauterine insemination. Fertil Steril. 2017;107(4):961–8. doi:10.1016/j.fertnstert.2017.02.002.
48. Zarei A, Mahboubi M, Parsanezhad ME, et al. Effects of piroxicam administration on pregnancy outcome in intrauterine insemination (IUI) cycles: a randomized clinical trial. Clin Exp Obstet Gynecol. 2016;43(2):225–9.
49. Abdelkader AM, Yeh J. The potential use of intrauterine insemination as a basic option for infertility: a review for technology-limited medical settings. Obstet Gynecol Int. 2009;2009:584837.
50. Katzorke T, Kolodziej FB. Significance of insemination in the era of IVF and ICSI (Article in German). Urol A. 2010;49:842–6.
51. De Sutter P. Rational diagnosis and treatment in infertility. Best Pract Res Clin Obstet Gynaecol. 2006;20(5):647–64.