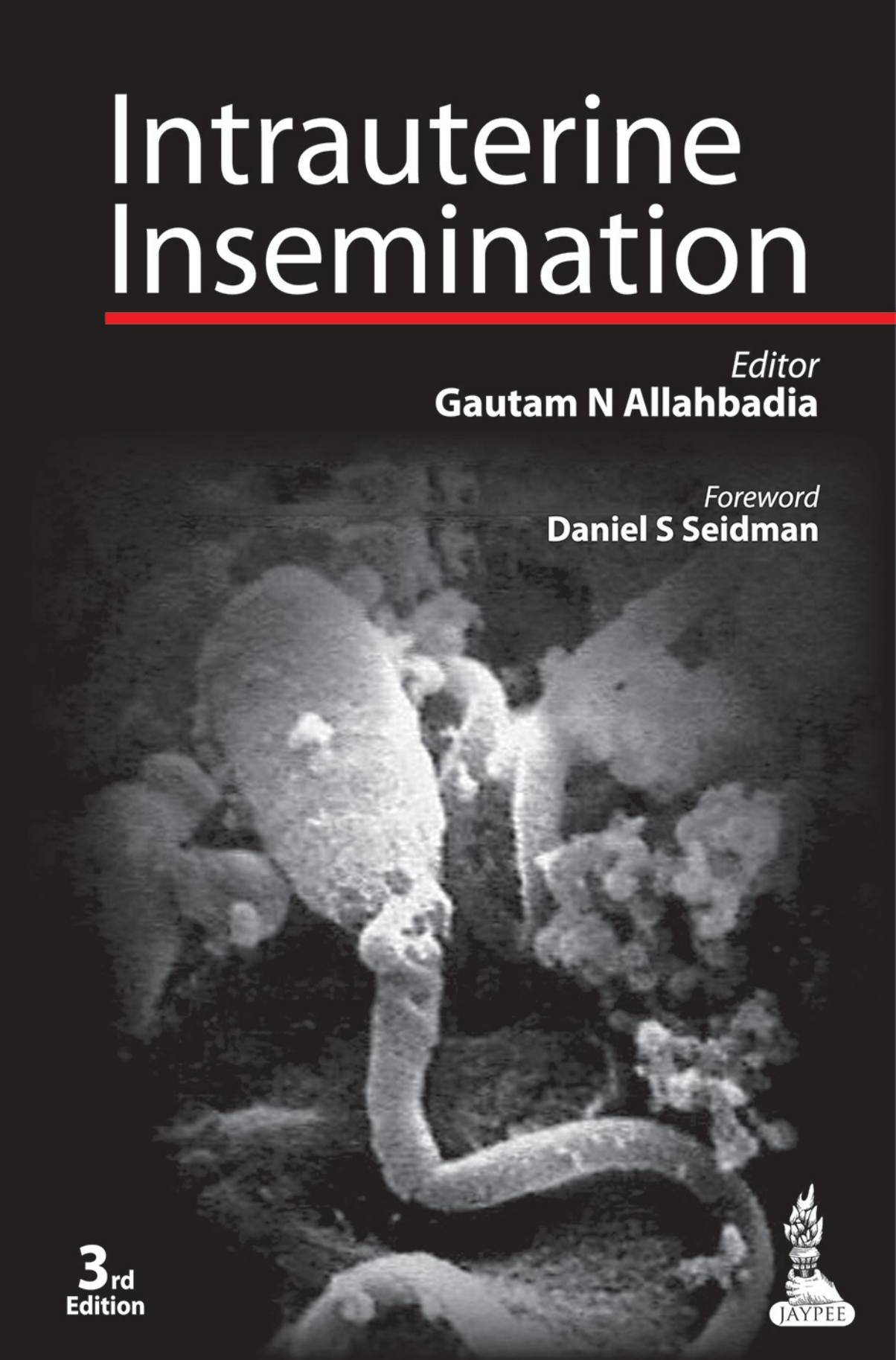
Intrauterine Insemination

Editor
Gautam N Allahbadia

Foreword
Daniel S Seidman



3rd Edition

JAYPEE

Contents

Vishvanath C Karande

CHAPTER 3

Patient Selection and Management to Optimize Success in an Intrauterine Insemination Program

Intrauterine insemination (IUI) is a commonly used technique in the management of infertility. In this procedure, the semen sample is processed to separate the sperm from the seminal plasma. The sperm is then deposited in the uterine cavity around the time of ovulation with a catheter. We thus bypass the acidic vagina and the potentially hostile cervical mucus in an attempt to increase the chance of fertilization. Natural cycle monitoring with timed IUI is recommended only in patients with coital issues or when donor sperm is being used. Indications for IUI include unexplained infertility, minimal or mild endometriosis, mild male factor, ejaculatory factor, immunological and cervical factor. Patients with severe tubal disease should be treated surgically or with in vitro fertilization (IVF). In younger patients (age < 35 years), it is reasonable to start with oral medications (Clomiphene citrate, Tamoxifen, Letrozole) for 3 to 4 cycles. The next step arguably should be IVF. In older patients (age > 35 years and definitely, in patients aged > 40 years), the pregnancy rates with oral medications are low and it is reasonable to start with gonadotropins for 3 to 4 cycles before proceeding with IVF. The success rates with IUI will depend on the medication used, patient age, semen parameters and ovarian reserve. The couple with the best chance of pregnancy is a woman under 30 years with cervical or anovulatory infertility and a man with a total motile sperm count > 5 million spermatozoa.

JAYPEE BROTHERS

Introduction

Intrauterine insemination (IUI) was initially reported by Cohen in 1962.[1] It has since, become a widely utilized technique for the treatment of infertility. Indications for its use have been extremely varied and it has often been used empirically. In this chapter, we will discuss patient selection and management to optimize success in an IUI program. This includes indications for IUI, factors that effect success rates and its limitations. Issues, such as ovulation induction, cycle

TABLE 3.1: Indications for intrauterine insemination

1. Unexplained infertility
2. Mild male factor
   - Oligo/astheno/teratozoospermia
3. Endometriosis
   - Minimal or mild endometriosis
4. Immunological factors
   - Female (cervical/humoral)
   - Male (seminal/humoral)
5. Ejaculatory failure
   - Anatomical
   - Neurological
   - Psychogenic
6. Cervical factor
   - Insufficient production
   - Altered quality

monitoring, use of donor sperm, and other techniques, such as Fallopian sperm perfusion, are beyond the scope of this chapter.

Clinical Discussion

Indications for IUI

The indications for IUI are summarized in Table 3.1. Let us discuss each one in some detail.

Unexplained infertility

Infertility is said to be unexplained when a couple fails to conceive and no definite cause for infertility can be diagnosed after a complete work up (semen analysis, tubal patency assessment, and laboratory assessment of ovulation). The average incidence of unexplained infertility is approximately 20% among infertile couples. The incidence varies from 5% to 28% depending on the strictness of the criteria used for the definition.[2] The effectiveness of IUI for this indication has been debated. The main debatable points have been whether success should be attributed either to the IUI, to the close monitoring of the cycle or to the use of ovulation inducing agents. The benefit of IUI versus intercourse for unexplained infertility in natural cycles is modest at best.[2] To achieve statistically significant improvement, a protocol that included three IUI cycles needed to be followed. IUI achieved one additional pregnancy in 14 IUI couples (95% CI: 8,23) compared with control couples.

Bhattacharya et al.[3] in a pragmatic randomized controlled trial, compared the impact of Clomiphene citrate (CC) or unstimulated IUI with expectant management

JAYPEE BROTHERS

in 580 couples with "unexplained" infertility. They also included patients with mild male factor and minimal endometriosis. Patients were randomized to expectant management (n = 193), oral CC (n = 194), or unstimulated IUI (n = 193) for six months. Live birth rates were 32/193 (17%), 26/192 (14%), and 43/191 (23%), respectively. Compared with expectant management, the odds ratio for a live birth was 0.79 (95% CI 0.45 to 1.38) after CC and 1.46 (0.88 to 2.43) after unstimulated IUI. Of interest is the fact that patients were less satisfied with the expectant approach. This study did not have a group that included patients on both CC and IUI.[3]

Reindollar et al.[4] randomized patients with unexplained infertility to standard treatment [3 cycles CC with IUI, 3 cycles of gonadotropin [follicle stimulating hormone (FSH)] with IUI and followed by up to 6 cycles of in vitro fertilization (IVF)], or fast track (3 cycles CC with IUI followed by up to 6 cycles of IVF). The pregnancy rate (PR) per cycle with CC, FSH and IVF were 7.6%, 9.8% and 30.7%, respectively. The CC/IUI PRs were high enough to merit initial treatment with CC/IUI for unexplained infertility in lieu of more costly and complex FSH/IUI treatment with the attendant risk of multiple pregnancy.[4]

Zeyneloglu et al.[5] published a meta-analysis of studies, evaluating patients who superovulated with gonadotropins and randomized for timed intercourse or IUI. A total of 980 cycles were evaluated when all seven eligible studies were combined. There were 49 pregnancies in 431 cycles with timed intercourse (11.37%), whereas there were 110 pregnancies in 549 cycles of IUI (20.04%). The PRs following IUI were significantly increased in FSH/IUI cycles (common OR = 1.84; 95% CI = 1.30–2.62) compared with those for timed intercourse.[5]

Endometriosis

Patients with mild or minimal endometriosis and infertility may benefit from the use of IUI.[6] Prado-Perez et al.[7] compared three groups of patients 1) patients without endometriosis, 2) those with minimal or mild endometriosis and, 3) those with moderate or severe endometriosis. The PRs were 25.7%, 22.7%, and 5.6%, respectively. The third group had a significantly lower PR (P = 0.006). Dmowski et al.[8] compared PRs for couples treated with IUI and those treated directly with IVF. The PR after the first IVF cycle was 47%, with a cumulative pregnancy rate of 41% after six FSH/IUI cycles. The authors recommended that in women over 38 years, if the endometriosis is moderate or severe, or if a male or tubal factor coexists, one should consider going directly for IVF.[8]

Male factor

With the advent of intracytoplasmic sperm insertion (ICSI) and the excellent PR achieved, patients with severe male factor should probably bypass IUI and directly consider in vitro fertilization (IVF) with ICSI. These are patients with a total motile sperm concentration of < 5 million, or patients with more than one abnormal semen parameter. In patients with milder forms of male factor, however, IUI may play a role. Zayed et al.[9] in a prospective trial, evaluated the efficacy of controlled ovarian hyperstimulation (COH) with IUI versus IVF in patients

JAYPEE BROTHERS

with mild male factor. Mild male factor was defined as patients with only one abnormal semen parameter and a total motile sperm concentration >5 million, and motility and morphology greater than 5%. They reported a live-birth rate of 19% per cycle, which was comparable to their IVF counterparts (18.4%). Generally speaking, the PR is better when the age of the female partner is < 37 years.[9] Badawy et al.[10] in a prospective observational study, evaluated the effect of sperm morphology and number on IUI success. Three hundred and ninety-three couples underwent 714 IUI cycles with a protocol using a combination of CC and human menopausal gonadotropin (hMG). The overall PR per cycle was 11.06%. The PR per cycle was 5.5% when the number of motile spermatozoa was < 5 million and 24.28% with normal motile sperm > 5 million. The PR in women < 25 years of age, with the number of motile spermatozoa > 5 million was 28.2% per cycle. In women > 35 years of age, no pregnancies were reported when the number of motile spermatozoa was < 5 million, and the PR was very low (0.84%) when the number of motile spermatozoa was > 5 million. The PR was low (6.95%) in patients with abnormal morphology (<30% normal forms) compared to those with normal morphology (16.83%).[10]

Tubal disease

Tubal disease (occlusion, hydrosalpinx) is not an indication for IUI. These patients should be treated surgically or with IVF.

Ejaculatory failure

These include patients with problems such as anatomical, neurological, or psychogenic causes (e.g. severe hypospadias, retrograde ejaculation, and impotence). The success rate of IUI in this group of patients depends alot on the sperm quality. In patients with a progressive sperm motility of at least 20% to 30%, the prognosis with IUI is good. Urry et al.[11] reported pregnancies in six of seven patients within 6 cycles in couples with retrograde ejaculation.[11] Pryor et al.[12] reported their experience with 11 quadriplegic men and their spouses undergoing IUI. Ejaculates were obtained by vibratory stimulation (2 patients) or electroejaculation (9 patients). There were no pregnancies in the first 5 patients who underwent IUI 24 hours after the luteinizing hormone (LH) surge in unstimulated cycles. Patients were then stimulated with CC and human chorionic gonadotropin (hCG). Sperm were inseminated 32 to 34 hours after hCG injection, once again with no pregnancies. The authors then repeated the same protocol with the exception that IUI was delayed to 38 to 40 hours after hCG injection. Ten patients underwent 19 IUI cycles with 6 pregnancies (60% PR).[12] Kathiresan et al.[13] also reported excellent PRs (37.8%) in 82 patients with spinal cord injuries, using both intravaginal as well as intrauterine insemination. Of interest is the fact that 5.7% of IUI pregnancies were obtained when fewer than 4 million total motile sperm were inseminated and a PR of 2.9% was obtained when a total motile sperm count below 3 million was inseminated.[13]

JAYPEE BROTHERS

Cervical factor

Five percent of infertile couples will have a cervical factor during a basic infertility work-up.[14] In a randomized clinical trial Oei et al.[15] assessed the effectiveness of the postcoital test (PCT) by comparing a strategy in which all couples had a PCT with a strategy in which none of the couples had a PCT. They concluded that the performance of the PCT resulted in more interventions, without an increase in PR.[15] This has led to the abandonment of the PCT in many guidelines. Steures et al.[16] in a prospective clinical trial, randomized 99 couples with an isolated cervical factor to IUI for 6 months or expectant management for 6 months. They achieved an ongoing PR of 43% (22) in the IUI group compared to 27% (13) in the expectant group (relative risk, 1.6; 95% CI, 0.91 to 2.8). The number of couples required for treatment with IUI to achieve one additional ongoing pregnancy was 6.2 (95% CI, 3.6 to infinity). They suggest that there is a beneficial effect of IUI in couples with an isolated cervical factor.[16]

Other factors affecting pregnancy rates

Female age

Female age is a significant factor that affects PR. Success rates start to decrease after age 35 and drop dramatically after age 40. Dovey et al.[17] analyzed their data with CC and intrauterine insemination in 1,738 infertility patients that underwent 4,199 cycles.[16] On a per patient treated basis, cumulative PRs were 24.2% under age 35 years, 18.5% within the ages 35 to 37 years, and 15.1% within the ages 38 to 40 years, whereas only 7.4% within the ages 41 to 42 years and 1.8% above age 42 years became pregnant (one pregnancy in 55 patients). Most of the pregnancies with CC in all the age groups were in the first 3 to 4 cycles.[17]

Agarwal and Buyalos[18] evaluated the influence of female age on CC with IUI therapy and compared the efficacy of this therapy between patients with ovulatory and anovulatory infertility. They evaluated 664 CC with IUI cycles in 290 women aged 22 to 48 years. They found a significant decrease in PR in females aged > 35 years as compared to their younger counterparts (Table 3.2). A surprising

TABLE 3.2: Effect of female age on PR with CC and IUI
(modified from Agarwal and Buyalos et al. 1996)[18]

	Age group			
	≤30 y	*31–35 y*	*36–40 y*	*≥41 y*
No. of cycles	96	216	222	130
No. of pregnancies	18	28	16	7
Clinical PR (%)	18.8*!	13.0®#	7.2	5.4
Clinical PR (%)	14.7m		6.5	

* ≤ 30 years versus 36 to 40 years, P <0.003.
! ≤ 30 years versus ≥ 41 years, P < 0.002.
@ 31 to 35 years versus 36 to 40 years, P < 0.05
# 31 to 35 years versus ≥ 41 years, P < 0.03.
m ≤ 35 years versus ≥ 36 years, P < 0.0005.

JAYPEE BROTHERS

finding was that there was no difference in PRs between patients with ovulatory and anovulatory infertility diagnosis. The vast majority of pregnancies occurred within the first four treatment cycles, irrespective of age or ovulatory versus anovulatory infertility diagnoses.

Ovulation induction with CC requires less monitoring and expense than the use of gonadotropins or other assisted reproductive technologies (ART). However, as the results indicate, PR with CC in females > age 35 years are markedly lower. In the long run, it may therefore be more efficacious to proceed with the initial use of the more advanced treatment modalities in older patients.

Does male age have an impact?

It is generally recognized that the aging process in men is subtle as compared to women. This is reflected in the fact that some very famous men (Charlie Chaplin, Anthony Quinn, and more recently, Rod Stewart) have fathered children at advanced ages. This view was, however, challenged by Mathieu et al.[19] who analyzed 901 IUI cycles in 274 couples who obtained 80 pregnancies. The cumulative PR after 3 cycles was 22% and after 6 cycles it was 39%. Univariate analysis disclosed two factors of poor prognosis: duration of infertility > 3 years, and husband age > 35 years. These are provocative data that need to be confirmed by other groups.[19]

Impact of ovulatory status

Park et al.[20] evaluated the impact of ovulatory status and follicular response on PRs in CC-IUI cycles. They evaluated 254 women, who underwent 585 CC-IUI cycles. The overall clinical PR per cycle was 11.1% and the live birth rate (LBR) was 8.7%. In anovulatory women, the clinical PR and LBR were 15.7% and 13.6%, respectively. In ovulatory women, the clinical PR and the LBR were 8.8% and 6.3% respectively. As the number of large follicles increased from one to two, the LBR increased from 6.8% to 10.5%. A multiple follicular response increased PRs in both ovulatory and anovulatory women. Anovulatory women, however, had nearly double the clinical PR and LBR compared to those in ovulatory women, irrespective of the number of large follicles.[20]

Diminished ovarian reserve (DOR)

Patients with DOR are those whose oocytes have decreased reproductive potential. The diagnosis is often made when the cycle day 3 FSH level is elevated.[21] The original work with FSH levels and PRs was done in IVF patients. Recently, the anti-Mullerian hormone level has also been used to assess ovarian reserve. Ovarian responsiveness (that is different from DOR), on the other hand, is evaluated with the measurement of ovarian volumes and antral follicle counts. DOR is often a clinically challenging situation, especially when diagnosed in relatively young patients. It is generally agreed that patients with DOR should be made aware of the prognosis, but an elevated FSH level (especially in patients with regular menses) should not be used as a reason to deny treatment.[22] The issue of the best treatment protocol for these patients (IUI vs IVF) remains unresolved.

JAYPEE BROTHERS

Conclusion

So, what is the current role of IUI in a modern infertility practice? The initial work- up should be directed towards determining the etiology of infertility. In patients with unexplained infertility, minimal or mild endometriosis, mild male factor and cervical factor, the initial approach should be IUI. Unstimulated IUI is useful only in patients with cervical factor and ejaculatory failure. CC-IUI may increase fecundity via a number of proposed mechanisms: (1) increasing the number of oocytes available for fertilization, (2) overcoming subtle ovulatory dysfunction, (3) allowing for more precise timing of insemination, and (4) increasing the number of sperm in the upper female reproductive tract.[20] In patients under age 35 years, the initial approach should be CC and IUI for 3 to 4 cycles. The next step, arguably, should be IVF.[4] In patients above age 35 years (and definitely in patients above age 40 years), the initial approach should be gonadotropins with IUI for 3 to 4 cycles followed by IVF. The couple with the best chance of pregnancy has been described by Merviel et al.[6] as follows: a woman under age 30 years with cervical or anovulatory infertility and a man with a total motile sperm count ≥ 5 million spermatozoa.[6]

References

1. Cohen MR. Intrauterine insemination. Int J Fertil 1962;7:235-40.
2. ESHRE Capri Workshop Group. Intrauterine insemination. Hum Reprod Update 2009;15:265-77.
3. Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay CCK, Harrold A, et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic controlled trial. BMJ 2008;337:716-23.
4. Reindollar RH, Regan MM, Neumann PJ, Levine B-S, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril 2010;94:888-99.
5. Zeyenloglu HB, Arici A, Olive D, Duleba AJ. Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotrophins: a meta-analysis. Fertil Steril 1998;69:486-91.
6. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. Fertil Steril 2010;93:79-88.
7. Prado-Perez J, Perez-Rivadeneira E, Sanon-Julien F. The impact of endometriosis on the rate of pregnancy of patients submitted to intrauterine insemination. Fertil Steril 2002;77:S51
8. Dmowski WP, Pry M, Ding J, Rana N. 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;78:750-6.
9. Zayed F, Lenton EA, Cooke ID. Comparison between stimulated in-vitro fertilization and stimulated intrauterine insemination for the treatment of unexplained and mild male factor infertility. Hum Reprod 1997;12:2408-13.

JAYPEE BROTHERS

10. Badawy A, Elnashar A, Eltotongy M. Effect of sperm morphology and number on success of intrauterine insemination. Fertil Steril 2009;91:777-81.
11. Urry RL, Middleton RG, McGavin S. A simple and effective technique for increasing pregnancy rates in couples with retrograde ejaculation. Fertil Steril 1986;46:1124-8.
12. Pryor JL, Kuneck PH, Blatz SM, Thorp C, Cornwell CE, Carrell DT. Delayed timing of intrauterine insemination results in a significantly improved pregnancy rate in female partners of quadriplegic men. Fertil Steril 2001;76:1130-5.
13. Kathiresan AS, Ibrahim E, Aballa TC, Attia GR, Lynne CM, Brackett NL. Pregannсy outcomes by intravaginal and intrauterine insemination in 82 couples with male factor infertility due to spinal cord injuries. Fertil Steril 2011;96:328-31.
14. Collins JA, van Steirtegham A. Overall prognosis with current treatment of infertility. Hum Reprod Update 2004;10:309-16.
15. Oei SG, Helmerhost FM, Bloemenkamp KW, Hollants FA, Meerpoel DE, Keirse MJ. Effectiveness of the postcoital test: randomized controlled trial. BMJ 1998;317:502-5.
16. Steures P, van der Steeg JW, Hompes P, Bossuyt P, Habbema J, Eijkemans M, et al. Effectiveness of intrauterine insemination in subfertile couples with an isolated cervical factor: a randomized clinical trial. Fertil Steril 2007;88:1692-6.
17. Dovey S, Sneeringer RM, Penzias AS. Clomiphene citrate and intrauterine insemination: analysis of more than 4100 cycles. Fertil Steril 2008;90:2281-6.
18. Agarwal SK, Buyalos RP. Clomiphene citrate with intrauterine insemination: is it effective therapy in women above the age of 35 years? Fertil Steril 1996;65:759-63.
19. Mathieu C, Ecochard R, Bied V, Lornage J, Czyba JC. Cumulative conception rate following intrauterine artificial insemination with husband's spermatozoa: influence of husband's age. Hum Reprod 1995;10:1090-7.
20. Park SJ, Alvarez JR, Weiss G, Hagen SV, Smith D, McGovern PG. Ovulatory status and follicular response predict success of clomiphene citrate-intrauterine insemination. Fertil Steril 2007;87:1102-7.
21. Scott RT, Hofmann GE. Prognostic assessment of ovarian reserve. Fertil Steril 1995;63:1-11.
22. Van Rooij IAJ, de Jong E, Broekmans FJM, Looman CWN, Habbema JDF, te Velde ER. High follicle-stimulating hormone levels should not necessarily lead to the exclusion of subfertile patient from treatment. Fertil Steril 2004;81:1478-85.

JAYPEE BROTHERS

Intrauterine Insemination

Intrauterine Insemination (IUI) has evidently stood the test of time as a simple, safe, relatively non-invasive, 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 Dr Gautam N Allahbadia encompasses everything the reader needs to know about IUI from sperm physiology, the basic set-up required, semen preparation techniques, indications, the IUI technique complications, outcomes, predictors of success and gamete cryopreservation to a comparative evaluation of 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 make it an indispensable technique for the masses, especially in resource, technology and economy-limited settings.

Gautam N Allahbadia MD is the Medical Director of Rotunda–The Center for Human Reproduction, Rotunda IVF and Keyhole Surgery Center, Rotunda Blue Fertility Clinic and Keyhole Surgery Center, Rotunda Fertility Clinic and Keyhole Surgery Center, Mumbai, Maharashtra, India. The development of a highly successful egg donation program at Rotunda has made it possible to achieve pregnancies in women who have premature ovarian failure. The Centers provide a full spectrum of state-of-the-art Medical and Surgical treatment in Reproductive Endocrinology and Gynecology including advanced Laparoscopic Surgery, Tubal Reconstruction, and Minimally Invasive USG-guided Therapeutic Procedures.

Dr Allahbadia and his world-class team of Reproductive Endocrinologists, Embryologists, Andrologists and Infertility Specialists have helped hundreds of couples have babies through Assisted Reproduction. He is a noted world authority on ultrasound guided embryo transfers and one of the pioneers in third party reproduction in South-East Asia, with India's first trans-ethnic surrogate pregnancy involving a Chinese couple's baby delivered by an unrelated Indian surrogate mother, and India's first Same-Sex Couple pregnancy and delivery of twins to his credit. He cherishes 125 peer-reviewed publications, over 125 scientific papers, 114 book chapters and 18 textbooks and is on the Editorial Board of several international journals. He has been instrumental in setting up 17 private IVF Centers in India between 2000-2012 and 8 Rotunda IVF Franchisee units between 2000-2011 as an IVF Consultant. He is the recipient of over 25 prizes and fellowships, the Canadian Young Scientist Fellowship Award for the year 1994, Dr Kumud Tamaskar award and FOGSI-CORION National Research for original research work in infertility in the years 1991 and 1998, respectively, and the prestigious Deutscher Akademischer Austauschdienst fellowship for the year 1996 to train in Assisted Reproductive Techniques in Germany being among the notable few. He is the recipient of six research grants from the International College of Surgeons and the Medical Research Centre of Bombay Hospital Trust. He has been an invited guest speaker or faculty member at over 200 Congresses, Workshops and scientific meetings and has organized several international conferences in the field.

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 (http://www.mumbaitopdocs.com).

Shelving
Recommendation
OBSTETRICS & GYNECOLOGY

ISBN 978-93-5090-403-9

Available at all medical book stores
or buy directly from Jaypee Brothers through online shopping
at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com