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INFERTILITY MANAGEMENT

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INFERTILITY MANAGEMENT SERIES

INTRAUTERINE INSEMINATION

JAYPEE

Contents

1. An Overview of Intrauterine Insemination 1

Nalini Mahajan, Shivani Singh

- Improvement in Technique 2
- Rationale 2
- Indications 2
- Intrauterine Insemination Prerequisites 3
- Investigations 4
- Follicular Monitoring/Determining the Luteinizing Hormone Surge/Ovulation Trigger 5
- Sperm Preparation 5
- Insemination Procedure 6
- Choice of Catheter 7
- Timing of IUI/Single Versus Double IUI/Number of IUIs 7
- Optimal Number of Intrauterine Inseminations 7
- Combining Intrauterine Insemination with Superovulation or Controlled Ovarian Hyperstimulation 8
- Which is the Drug of Choice for Ovarian Stimulation? 8
- Factors that Determine Intrauterine Insemination Outcome 10

2. Ovarian Stimulation for Intrauterine Insemination 13

Manjunath Swamy, Nalini Mahajan, Shalu Gupta

Oral Drugs 13

Manjunath Swamy

- Oral Drugs Used for Ovulation Induction 13
- Clomiphene Citrate 13
- Tamoxifen Citrate 16
- Letrozole 16
- Anastrozole 17
- Role of Adjuvants 17

Ovulation Induction for IUI: Gonadotropins and Analogs 18

Nalini Mahajan, Shalu Gupta

- Physiology 18
- Stimulation Protocols 19
- Choice of Gonadotropin 20
- Gonadotropin only Protocols 20
- Gonadotropin Combined with Oral Ovulogens 25
- Monitoring during Gonadotropin Stimulation 25
- Determinants of Success 26
- Complications and How to Avoid them 26
- Ovarian Stimulation in Non-PCOS Infertility (Unexplained, Male Factor, Tubal Factor and Endometriosis) 27

- Gonadotropin-Releasing Hormone Analogs in Ovulation Induction and IUI 28
- Gonadotropin-Releasing Hormone Antagonist in Intrauterine Insemination Cycle 30

3. Timing of Trigger and Insemination 36

PM Gopinath

- Timing of Trigger 36
- Choice of Trigger 38
- Timing of Insemination 38

4. Monitoring an IUI Cycle: Ultrasonography and Hormonal Parameters 41

Carlos Iglesias Sánchez, Juan A Garcia-Velasco

- Clinical Use of Intrauterine Insemination 41
- Requirements for Intrauterine Insemination 42
- Indications for Intrauterine Insemination 44
- Sperm Collection and Processing 45
- Timing the Insemination 46
- How can Follicle Size be Monitored? 47
- Intrauterine Insemination in Unstimulated Cycles 50
- Intrauterine Insemination in Stimulated Cycles 50
- What are the Advantages of Intrauterine Insemination Compared with Programmed Coitus? 50
- Which Drugs Should be Used to Stimulate Ovulation? 51
- Is a Multifollicular Response Desirable? 53
- How do We Monitor Follicle Development? 54
- Triggering Ovulation and Insemination 54
- Is a Double Insemination Recommended? 54
- Is it Necessary to use Ultrasound-Guided Intrauterine Insemination? 54
- Luteal Phase Support 55
- Are Gonadotropin-Releasing Hormone Antagonists Useful? 55
- Number of Intrauterine Insemination Cycles 56

5. Natural Cycle Intrauterine Insemination: Is it an Option to Couples with Infertility? 62

Thankam Rama Varma

- Rationale for Intrauterine Insemination Treatment 62
- Semen Preparation 63
- Review of Literature 63
- Intrauterine Insemination in Natural Cycles 64
- Costs and Benefits 65

6. Sperm Preparation for Intrauterine Insemination 68

Sunita Kinger

- Purpose of Sperm Preparation 68
- Sperm Preparation Techniques 69
- Density Gradient Centrifugation versus Swim-up/Sperm Wash 73

7. Insemination: Tips and Tricks 76

Rohit Gutgutia, Arindam Rath

- Technique of Intrauterine Insemination 76
- Discussion 78

8. Donor Sperm Insemination: Do's and Don'ts 84

Richa Jagtap, Manjushri Amol Kothekar

- History 84
- Do's 85
- Don'ts 90
- Optimizing Success Rate 90
- Complications 91
- What Next 91

9. Complications of Ovarian Stimulation and Intrauterine Insemination 93

Antonia Tocino Diaz, Manuel Fernández-Sánchez

- Complications of Ovarian Stimulation 93
- Complications of Intrauterine Insemination Technique 96
- Pregnancy Complications after Intrauterine Insemination 98

10. Ethical and Psychosocial Aspects in Intrauterine Insemination 103

Mirudhubashini Govindarajan, Srisaranya Mithra

- Psychosocial Consequences of Infertility Management 103
- Need for Counseling 104
- Ethical Guidelines as Formulated by Indian Council of Medical Research 105

11. Medicolegal Aspects of Intrauterine Insemination 107

Arati Gupte Shah, Manish Banker, Pravin Patel

- Indications for IUI-Husband and IUI-Donor 107
- Code of Practice 108
- Rights of a Child Born through Intrauterine Insemination 112
- Donor for Intrauterine Insemination 112
- Managing Complications 113

- Other Ethical Issues 113
- Posthumous Intrauterine Insemination 114
- Recent Advances 114

12. Design, Equipment and Personnel Management for Intrauterine Insemination Laboratory 115

Yolanda Minguez, Javier Herrero Zapata Irene Rubio Palacios

- Laboratory Design 116
- Equipment 117
- Consumables and Media 118
- Personnel Management 131
- Laboratory Safety and Infection Control 131
- Record Maintenance 133
- Quality Control 133

Index *135*

CHAPTER

3

Timing of Trigger and Insemination

PM Gopinath

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INTRODUCTION

The rationale of intrauterine insemination (IUI) treatment is to increase the chances of pregnancy in the couple by increasing the chance that maximum number of healthy sperm reaches as close to the liberated ovum. Hence, it is very important to time the trigger and to effectively perform the IUI which can yield an optimum success rate.

TIMING OF TRIGGER

The IUI is performed in an unstimulated cycle or stimulated with clomiphene citrate or stimulated cycle with gonadotropin or stimulated with gonadotropin and gonadotropin-releasing hormone (GnRH) analogs.

Unstimulated Cycle

It is illogical to plan an IUI cycle in an unstimulated cycle. However, there are some occasions where we will land up doing IUI in an unstimulated cycle. There is no need to use trigger in this situation. But it is important to predict the precise time of ovulation. Traditional methods for timing insemination were used; basal body temperature charts or cervical mucus assessment. Newer methods involve urine luteinizing hormone (LH) kits such as clearplan (Unipath, Bedford, UK), which provide a convenient and reasonably reliable method.[1-4]

Clomiphene-induced Cycle

In this situation, it is useful to take the guidance of follicular monitoring with ultrasound. The mean follicular diameter and the trilaminar endometrial

thickness are the key factors which guides one to time the trigger. The mean follicular diameter of 18–20 mm and the endometrial thickness of 8 mm will be the appropriate time to trigger.

Gonadotropins-induced Cycle

Induction of ovulation with gonadotropins and IUI are frequently used to treat infertility. Among infertile couple, treatment with induction of ovulation and IUI is three times as likely to result in pregnancy as is intracervical insemination and twice as likely to result in pregnancy as is treatment with either superovulation and intracervical insemination or intrauterine insemination alone. Here again, the ultrasound follicular monitoring will be the key factor in timing the trigger. When the mean follicular diameter of 18–20 mm along with the endometrial thickness of more than 8 mm is achieved, the trigger can be administered.[18]

Gonadotropin-releasing Hormone Analog Cycle

The midcycle LH surge in the reproductive cycle is an intriguing endocrinological phenomenon. The exact details of the mechanism in many species including human are still not known, while it is known that central signaling by hypothalamic GnRH is permissive.[4] Complete blockade of the GnRH receptor terminates the periovulatory LH surge, although alterations in the magnitude of GnRH secretion are not crucial for timing and size of the LH surge.[5]

A premature LH surge can be defined as a premature rise of LH (> 10 IU/L) along with a concomitant rise in progesterone (> 1 μg/l–3.2 nM/L).[6] Premature LH surge in the natural cycle is very rare,[7] but may be more frequent in older women since their maximum follicle diameter at the time of ovulation is substantially smaller.[7,8]

Premature LH surges also occur in 25–30% of stimulated IUI cycles[6,9] and this may interfere with timing of the IUI or result in cancellation of the treatment and increased treatment failures. Administration of a GnRH antagonist almost completely prevents the premature luteinization but does not substantially improve the clinical pregnancy rate. The GnRH antagonists are used in IUI cycle to prevent the premature luteinization and to avoid untimely inseminations in the weekends. The monitoring and the timing of the trigger again depend on the follicular monitoring and endometrial thickness assessment. Probably premature luteinization is not the cause but one of the consequences of the poor quality of the growing follicle.[6] In seven randomized controlled trials (RCTs), the average ongoing pregnancy rate was only 5.3% greater with GnRH antagonist treatment [95% confidence interval (CI): 1.5, 9.2]. This means that it would take 20 cycles of GnRH

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antagonist administration to have one pregnancy more than without GnRH antagonist treatment.

CHOICE OF TRIGGER

The most commonly used agent for trigger in the IUI is injection human chorionic gonadotropin (hCG) 5,000–10,000 IU. Nowadays, the choriogonadotropin alpha 250 μg in 0.5 mL (Ovitrelle®-Merck Serono) or injection ganirelix 0.25 mg (Orgalutran®-Schering-Plough), which is approximately equivalent to 6500 IU of hCG is being used in the place of hCG. When the stimulation is performed with gonadotropins and antagonist there is one more option of using GnRH agonist trigger of injection leuprolide acetate 1 mg or 2 mg (Lupride®-Sun Pharma) instead of hCG.

TIMING OF INSEMINATION

Insemination can be performed at various time points around ovulation and can be done once or repeated several times. In the majority of the published studies, the insemination is done 32–38 hours following injection hCG administration[10] and it is believed that IUI at 32–38 hours post-hCG would provide the best results.[11] The scientific basis for 32–38 hours timing is derived from ultrasonographic and hormonal studies that have shown the occurrence of follicle rupture after day 2 post-hCG in 68% of cases in spontaneous cycles[12] and in 81% in stimulated cycles (95%Cl; 76–86%).[13]

It is assumed that the timing of insemination relative to ovulation is critical for an optimal success rate, so it is rather surprising that few studies were designed to find the optimal time for insemination.[11] A systematic review found no difference in the pregnancy rate per couple with two inseminations compared with one.[9] As shown in this study (Table 1), the incidence of follicular rupture shown by TVS at the time of IUI ranged between 68% and 76%, which agrees with the above studies and lends credence to choosing the timing of IUI at 36 ± 2 hours post-hCG. The effects of timing of intrauterine insemination in relation to ovulation and the number of inseminations on cycle pregnancy rate in common infertility etiologies.

Several retrospective studies have provided conflicting results with regard to the impact of the number of inseminations on clinical pregnancy rate. However, meta-analysis of all cycles of single and double IUI in three randomized trials with the husband's sperm seemed to show an increased probability of pregnancy with double IUI.[14] On the other hand, two systematic reviews found no difference in the pregnancy rate per couple with two inseminations when compared with one.[9,14] Moreover, a more

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Table 1: Cycle outcome related to occurrence of ovulation at IUI 36 ± 2 h post-hCG

Parameter	*All cycles*	*Male*	*Non-male total*	*Ano-vulation*	*Unex-plained*
Cycle outcome known	1146	428	718	226	492
Ovulation status known	1114	422	692	212	480
Ovulation present (*n*)[a]	816	322	494	146	348
Ovulation absent (*n*)[a]	298	100	198	66	132
Ovulation rate (%)	73.2	76.3	71.3	68.3	72.5
All cycles with clinical pregnancy (*n*)[a]	116	30	86	34	52
Overall CPR[b] (%)	10.1	7.1	12.4	16.1	10.8
Pregnancies in positive ovulation cycles (*n*)[a]	96	24	72	28	44
CPR[b] in cycles with positive ovulation (%)	11.7	7.4	14.6	19.1	12.6
Pregnancies in negative ovulation cycles (*n*)[a]	20	6	14	6	8
CPR[b] with negative ovulation (%)	6.7	6	7	9.9	6
OR (95% CI) of pregnancy in positive ovulation versus negative ovulation cycles	1.85 (1.12-3.06)	1.26 (0.52-2.95)	2.2 (1.23-4.08)	2.1 (0.91-4.85)	2.08 (1.01-4.31)
P	0.015[c]	0.82[c]	0.007[c]	0.071[c]	0.047[c]

[a]Number
[b]Cycle pregnancy rate
[c]X^2 test

recent randomized trial of single versus double IUI in multifollicular ovarian hyperstimulation cycles in unexplained and mild male infertility[15] found no difference.

Guzick[16] and Abdelkader and Yeh[17] reviewed the available evidence for single and double IUI and both agreed that double IUI adds more to cost and inconvenience to CPR and recommended a well-timed single IUI. However, we should remember that there are limitations to the use of meta-analysis in the context of IUI studies because of heterogeneity of the published trials.

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INTRAUTERINE INSEMINATION

Intrauterine insemination (IUI) is the most frequently used procedure in infertility management. It is minimally invasive, relatively inexpensive and moderately effective. This book gives a comprehensive account of both the clinical and the laboratory aspects of IUI including the fundamental issue of setting up a good laboratory. The stimulation protocols used, monitoring techniques and the optimal timing and type of drug used for the ovulation trigger are dealt with in detail. There are some tips and tricks to help you optimize results and importantly it guides you on prevention and management of complications. The pros and cons of "Natural Cycle IUI" have also been discussed. We live in litigious times, and it is imperative that we understand the medico-legal implications of both IUI with partner and donor sperm. A chapter has been dedicated to this subject.

The book looks at the ethical and psychological issues surrounding the procedure and will be a very useful tool for gynecologists, embryologists and reproductive medicine specialists.



Juan A Garcia-Velasco MD PhD obtained his medical degree from Complutense University in Spain in 1990. Board Certified in Obstetrics and Gynaecology through residency at La Paz Hospital from 1992 to 1995, he obtained his PhD in Medicine and Surgery through Autonoma University of Madrid in 1995. He did a fellowship in Reproductive Endocrinology and Infertility at Yale University (USA) in 1997–1998. He is now Director of IVI Madrid and Associate Professor of Gynaecology at Rey Juan Carlos University in Madrid, Spain. Active lecturer around the world at major scientific meetings, he has published more than 100 scientific articles published at impact journals, several chapters and edited four books. He is the Principal Investigator of projects funded by the Ministry of Education and the Ministry of Health. He is also a member of the Editorial Committee of Fertility and Sterility and Associate Editor of Reproductive Biomedicine Online as well as active member of SGI, ESHRE, ASRM, SEGO and SEF.



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Nalini Mahajan MD M MedSci(ART) FICOG graduated from Lady Hardinge Medical College, Delhi University in 1974. She was awarded the President's Gold Medal for standing first in MBBS. She was also awarded the "Lala Hardhian Singh Jain Memorial Medal", the "Prashant Chandra Chaudhuri Memorial Prize", and the Pfizer gold medal and postgraduate award for being the best candidate. She went on to do an MD in Obstetrics and Gynecology from Delhi University and then a Master's in ART in 1994 from Nottingham University in UK, being the first Indian to be awarded the degree. She established an IVF center at Mother and Child Hospital in 1995 and took over as Clinical Director of NOVA IVI Fertility in 2012. She has presented many prize winning papers, written chapters for books on infertility management and is invited faculty at all major infertility conferences. She has been the past president of the Indian Fertility Society and is on the executive of the Indian Society for Assisted Reproduction. She is also on the Editorial Board of "Obs & Gyne Today" and the "International Journal of Reproduction, Contraception, Obstetrics and Gynecology (IJRCOG)" and a reviewer for the "Journal of Human Reproductive Sciences".

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ISBN 978-93-5152-212-6
9 789351 522126