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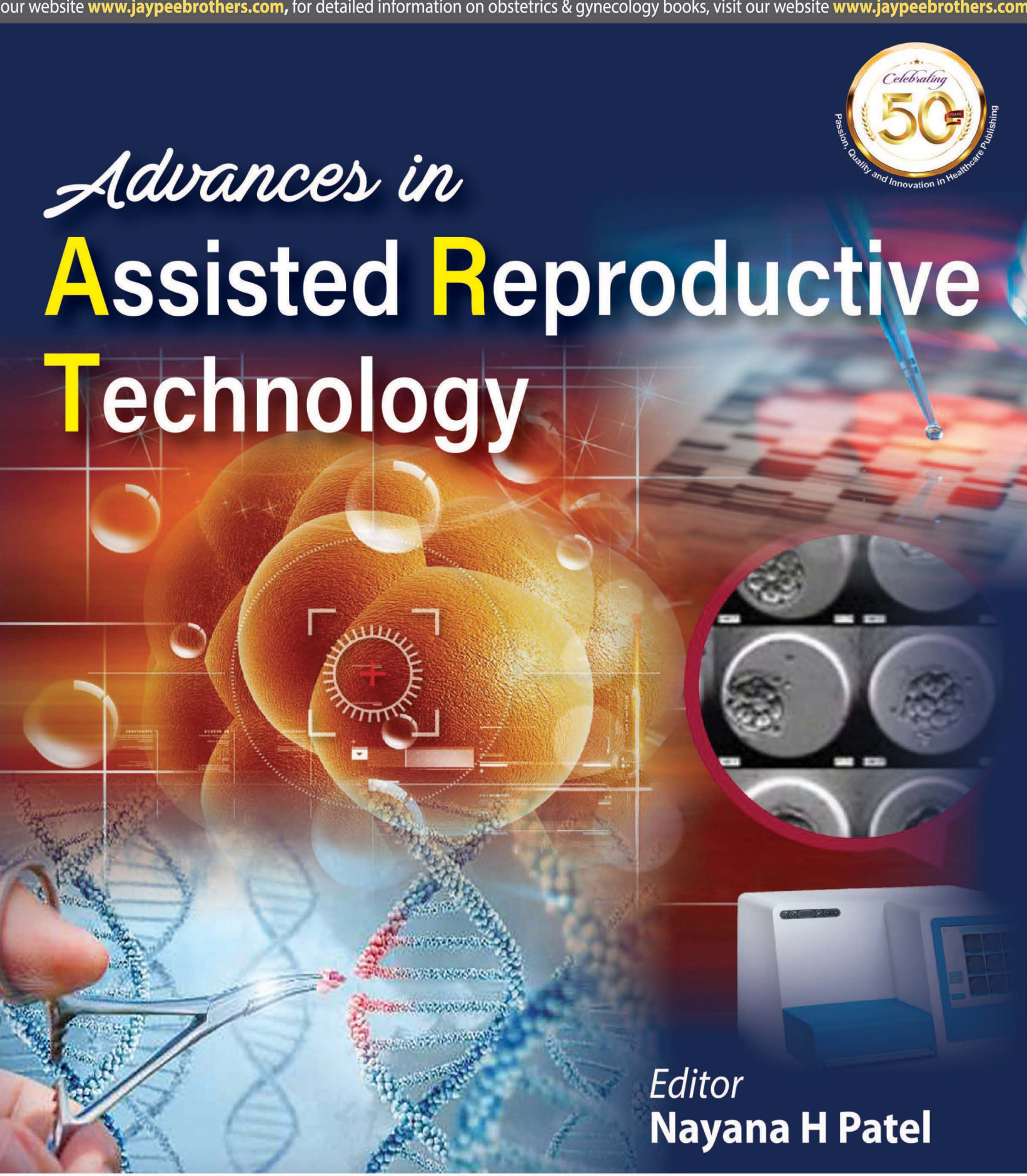
Advances in Assisted Reproductive Technology



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Contents

1. Controlled Ovarian Hyperstimulation for IVF Embryo Transfer and its Influence on Outcomes 1

Manchi Bharucha, Faram E Irani

- Recent Advancements *1*
- Endocrine Regulation of Ovarian Function and Folliculogenesis *3*
- Unexpected Low or Poor Response in Women with Normal Baseline Hormonal Levels *5*
- Exploring Uncharted Territories in Controlled Ovarian Hyperstimulation *5*
- Newer Developments in Gonadotropin Research for Controlled Ovarian Hyperstimulation *8*
- Frozen versus Fresh Embryo Transfer *10*
- Correlation between Embryo Developmental Stage and Endometrial Status *10*
- Maximizing Live Birth with Single Embryo Transfer *11*

2. Individualized Controlled Ovarian Stimulation 16

Abha Majumdar, Roshi Satija

- Patient Profile *16*

3. Treatment for Poor Responders: Recent Consensus 24

Trupti Mehta, Sangeeta Deshmukh, Meenal Khandeparkar, Firuza R Parikh

- The POSEIDON Stratification for Women with Poor Ovarian Response *24*
- Etiopathology of Poor Ovarian Response *25*
- Defining Ovarian Reserve *28*
- Ovarian Reserve Tests *28*
- Biological Markers *29*
- Anti-Müllerian Hormone *29*
- Discussion *30*
- Management of Poor Ovarian Responders *31*
- Pretreatment and Adjunctive Therapy *31*
- Results of IVF Cycles with Full Dose Gonadotropins versus Natural Cycles versus Clomiphene Alone versus Letrozole Alone *33*
- Future Prospects *35*

4. IVF Lite: Is this the Future of Assisted Reproductive Technology? 40

Gautam Nand Allahbadia, Goral Gandhi, Akanksha Allahbadia Gupta, Maham AS

- UAE Perspective *41*
- Rationale of Deferred Embryo Transfer *41*
- Modified Natural Cycle IVF *42*
- Clomiphene Citrate or Letrozole *42*
- Mild Stimulation versus Conventional Stimulation for IVF *43*
- Poor Ovarian Reserve *43*
- Older Women *44*
- Minimal Stimulation and Single-embryo Transfer with Segmented IVF *45*

- Mild Stimulation using Corifollitropin Alfa *45*
- Neonatal Outcome after Minimal Stimulation *46*
- Preimplantation Genetic Screening *46*
- Interesting Case Reports *47*
- Recent Advances *47*

5. Luteal Phase Stimulation 50
Markus Eckart Nitzschke, Nisha Bhatnagar, Payal Bajaj
- Luteal Phase Ovarian Stimulation *50*
- Luteal Phase Stimulation Protocol *52*
- Case Study *54*
- Future Prospects *55*

6. Downregulation in IVF Cycles 56
Pratap Kumar
- Agonist Protocol by Long Suppression Method *56*
- Antagonist Protocol *57*
- Review of Literature *58*

7. Role of Adjuvants in Controlled Ovarian Hyperstimulation: Recent Evidences 60
Purnima Nadkarni, Aditi Nadkarni, Anuradha Rathi, Urmila Sunda
- Adjuvants in Poor Responders *60*
- Adjuvants in Hyper-responders *61*
- Adjuvants in Normal Responders and Clomiphene Citrate Resistance *61*
- Adjuvants for Endometrial Receptivity *61*
- Adjuvants to Prevent Complications *63*

8. Ovarian Hyperstimulation Syndrome 65
Asha Baxi, Dhaval Baxi
- Pathophysiology *65*
- Classification *66*
- Risk Factors and Prediction of Ovarian Hyperstimulation Syndrome *67*
- Prevention of Ovarian Hyperstimulation Syndrome *68*
- Clinical Features *71*
- Management *71*
- Investigations *71*
- Treatment *72*
- Ovarian Hyperstimulation Syndrome and Pregnancy Outcome *73*

9. Luteal Phase Support: Current Evidence 77
Sadhana Desai, Partha Guha Roy
- Luteal Phase Deficiency *77*
- Luteal Phase Support in ART Cycles *77*
- Adjuvants in Luteal Phase Support *79*

10. Endometrial Receptivity: Recent Advances 84
Diksha Goswami, Narendra Malhotra, Jaideep Malhotra, Neharika Malhotra, Shally Gupta, Rishabh Bora
- What is Endometrial Receptivity? *84*
- Impact of IVF Stimulation on Endometrial Receptivity *86*

- Impact of Various Pathologies on Endometrial Receptivity *86*
- Assessment of Endometrial Receptivity *87*
- Measures to Improve Endometrial Receptivity *89*

11. Influence of Endometrial Preparation Protocols on Embryo Implantation in Frozen Embryo Transfer 91
Arunima Halder, Kamini A Rao
- Window of Implantation *91*
- Role of Estrogen and Progesterone in Generation of the Endometrium *91*
- Indications for Frozen Embryo Transfer *92*
- Endometrial Preparation Protocols in Frozen Embryo Transfer *92*
- Adjuvants used in Frozen Embryo Transfer Cycles *95*

12. Deciding on the Moment of Embryo Transfer: Discovering the Window of Implantation in ART 100
Mackens Shari, Racca Annalisa, Santos-Ribeiro Samuel, van de Vijver Arne, Christophe Blockeel
- The Window of Implantation in Assisted Reproductive Technology *100*
- Molecular Endometrial Receptivity Testing *104*

13. Freeze-all Strategy for All 108
Jatin P Shah
- How did the "Freeze-all" Strategy Begin? *108*
- Other Indications for "Freeze-all" *109*
- Author's Recommendations *111*

14. Procedure in Assisted Reproductive Technology 114
Kaberi Banerjee, Bhavana Singla
- What is Assisted Reproductive Technology? *114*
- Artificial Insemination *114*
- *In Vitro* Fertilization *116*
- Preimplantation Genetic Screening or Preimplantation Genetic Diagnosis *117*
- Assisted Hatching *118*
- Cryopreservation *118*
- Third-party Reproduction *118*
- What is the Success Rate for ART? *119*

15. Genetic Testing in Male Infertility 121
Rahul Gajbhiye
- Male Infertility *121*
- Genetic Basis of Sperm Motility Defects and Testing *126*
- Recent Advances in Genetic Evaluation of Male Infertility *126*

16. Medical Management of Male Infertility 129
Niket Patel, Yuvraj Jadeja
- Pretreatment Investigations *130*
- Medications *130*
- Optimizing Surgical Sperm Extraction *134*

17. Advances in Sperm Retrieval Techniques in Azoospermic Men 135
Rupin Shah
- Indications for Operative Sperm Retrieval *135*
- Sperm Retrieval Techniques *135*
- Choice of Sperm Retrieval Method *137*
- Complications of Operative Sperm Retrieval *138*
- Hormonal Stimulation before Sperm Retrieval *139*
- Predictors of Sperm Retrieval *139*

18. Ultrasound in Infertility 142
Asha Rao, Padmashri, C Rathi Lavanya, Vedapriya
- Evaluation of Uterine, Ovarian, and Adnexal Pathology *142*
- Evaluation of the Uterus *142*
- Evaluation of Ovaries *146*
- Evaluation of other Adnexal Pathologies *148*
- Role of Ultrasound in ART *148*
- 3D US in Endometrial Receptivity *149*
- Ultrasound-guided Procedures *149*

19. Color Doppler in Infertility 151
Sonal Panchal
- Baseline Scan and Deciding the Stimulation Protocol *151*

20. Hysteroscopy in ART 160
Divyesh V Shukla, Shilpi Shukla
- Investigations for Evaluation of Uterine Cavity *160*
- Why Hysteroscopy? *161*

21. Fertility-enhancing Surgeries in ART 172
Sanjay Patel
- Hysteroscopic Tubal Cannulation *172*
- Laparoscopic Tubal Microsurgery *172*
- Laparoscopic Salpingo-ovariolysis, Fimbrioplasty, and Adhesiolysis *175*
- Role of Salpingectomy Before IVF *175*
- Role of Laparoscopy in Endometriosis *175*
- Role of Laparoscopy in Fibroid of Uterus *176*
- Laparoscopy for Polycystic Ovary Syndrome and Infertility *177*

22. Newer Concepts in the Management of PCOS 181
Duru Shah, Sabahat Rasool
- Diagnostic Criteria *181*
- PCOS and Subfertility *181*
- Ovarian Hyperstimulation Syndrome *183*

23. Recent Advances in Endometriosis in ART 188
Kanthi Bansal, Sugandha Goel
- Epidemiology *188*
- Endometriosis and Infertility *188*

- Medical versus Surgical Treatment: What is the Best Choice and What Comes First? *188*
- Management of Ovarian Endometrioma *190*
- Assisted Reproduction and Endometriosis *192*
- Future Thoughts *193*

24. Recurrent Implantation Failure 196
Hrishikesh Pai, Unnati Mamtora
- Acquired Uterine Abnormalities *197*
- Sperm DNA Fragmentation *198*
- Gamete Donation and Surrogacy *199*

25. Recurrent Pregnancy Loss: What's New 202
Mala Arora
- Incidence *202*
- Etiology *202*
- Evaluation, Workup, and Treatment *207*
- Hormonal Causes *209*
- Unexplained Recurrent Miscarriage *210*
- Prognostic Factors in Early Pregnancy Transvaginal Scan *211*

26. Fertility Preservation: Newer Concepts 214
Nalini Mahajan
- Effect of Chemotherapy and Radiotherapy on Gonads *214*
- Fertility Protection and Preservation *215*
- Fertility Preservation Techniques 216
- Future Directions *218*

27. Third-party Reproduction 225
Molina Patel, Nayana H Patel
- Egg Donation *225*
- Embryo Donation *230*
- Sperm Donation *231*
- Surrogacy *231*
- ICMR Code of Practice and Ethical Considerations in Gestational Surrogacy (Salient Points) *233*
- Reproductive Tourism *233*
- Disclosure to Children *233*

28. Laparoscopic-assisted Uterus Retrieval from Live Organ Donors for Uterine Transplant: The Next Step in Infertility and a Giant Leap in Surgery 235
Shailesh Puntambekar, Sambit Nanda
- Formulation of Team and Patients *235*
- Presurgical Procedures *235*
- Postoperative Procedures *240*
- Discussion *241*

29. Regenerative Medicine in Infertility 245
Nayana H Patel, Molina Patel
- Platelet-rich Plasma *245*
- Stem Cells *247*

- Application of Regenerative Medicine in Infertility *249*
- Future Prospects of Regenerative Medicine *252*
- Issues Related to Use of Stem Cells *252*
- Current Status of Stem Cells in India *252*
- Clinical Studies at Akanksha Hospital and Research Institute *253*

30. Quality Control in Embryology Laboratory 255
Priya Kannan
- Importance of Quality Management *255*
- Quality Management in IVF Laboratory *255*
- Quality Control of Culture Systems *256*
- Key Performance Indicators for Assisted Reproductive Technology Program *257*
- Quality Control of IVF Laboratory Environment *257*
- Quality Control of Equipment *258*
- Quality Control IVF Laboratory Personnel *259*

31. Newer Media in Embryology Laboratory 261
Pankaj Talwar, Pooja Awasthi
- The Composition of Embryo Culture Media *261*
- Advances in the Media *263*
- Advances in Oils *263*
- Type of Embryo Culture Media and Cell Culture *265*
- Future of Embryo Culture System *266*

32. Oocyte Quality and Markers 273
Vijay Mangoli
- Morphological Assessment *274*
- Oocytes with Abnormal Size and Shape *279*
- Cellular Parameters and Oocyte Maturity *281*

33. Influence of Controlled Ovarian Stimulation on Oocyte Quality 283
Matheus Roque
- Does Ovarian Stimulation Exert an Effect on Oocyte/Embryo Quality? *284*
- Does the Number of Retrieved Oocytes Affect the IVF Outcomes? *285*

34. Optimizing Sperm Selection Methods 290
Alpesh Doshi
- Considerations for Treatment Selection *290*
- Sperm Selection Methods *292*

35. Cryopreservation in ART 299
Rajvi H Mehta
- Principles of Cryopreservation *299*
- Removing Water from Cells *299*
- Mechanisms of Cell Damage during Freezing *300*
- Ideal Rate of Cooling *300*
- Mitigating the Detrimental Effects of Freezing *300*
- Factors Determining the Success of Cryopreservation *301*

- Vitrification *301*
- Mechanisms of Cooling during Vitrification *301*
- Factors Determining the Success of Cryopreservation *302*
- Cryopreservation in Assisted Reproductive Technology *302*
- Cryopreservation of Embryos *303*
- Cryopreservation of Oocytes *303*
- India's Contribution to Human Embryo Cryopreservation *303*
- Cryopreservation of Human Reproductive Tissues: The Purpose *303*
- Purpose for Cryopreservation of Semen/Spermatozoa *303*
- Purpose for Cryopreservation of Oocytes *304*
- Purpose for Cryopreservation of Zygotes *304*
- Cryopreservation Protocols *304*
- Comparison of Slow Freezing versus Vitrification *305*

36. Morphokinetics in ART 307
Keshav Malhotra
- Time-lapse Technology: Different Systems Available Right Now *307*
- Time-lapse Imaging: A Predictive as well as a Selective Tool *309*
- Limitations of Existing Models *311*
- Limitation of Morphokinetics *311*

37. Preimplantation Genetic Screening and Diagnosis 314
Yuvraj Jadeja, Niket Patel, Piyush Chudasama
- History of Preimplantation Genetic Diagnosis *315*
- Indications for Preimplantation Genetic Testing *315*
- Preimplantation Genetic Testing *315*
- Sources of Genetic Material for Preimplantation Genetic Testing *315*
- Protocols for Genetic Analysis *316*
- Diagnostic Methods for PGD/PGS *317*
- Mosaicism Challenge *319*
- Recommendations for the Laboratory *319*
- Recommendations for Clinicians *319*
- Suggested Guidelines to Prioritize the Transfer of Mosaic Embryos *320*

38. *In Vitro* Maturation 322
Devika Gunasheela, Rajam Murali
- History *322*
- Definition of IVM and its Controversies *323*
- Physiology of Oocyte Maturation *323*
- Why IVM and in Whom? *324*
- Laboratory and Embryological Aspects of IVM *326*
- Endometrial Preparation in IVM Cycles *327*
- Safety of IVM *327*
- The Gunasheela Experience *328*
- Results *329*
- IVM in Fertility Preservation *329*

39. Microfluidics in ART 334
Manish Pandya
- What is our Goal in Assisted Reproductive Technology? *334*
- Embryologist Compatibility *336*
- Andrology and Microfluidics *336*
- Embryology and Microfluidics *336*
- Embryo Culture *337*

40. Co-culture Techniques in ART 342
Harsha Bhadarka, Kruti Patel
- Mechanisms *343*
- Autologous Endometrial Co-culture *343*
- Autologous Cumulus Cell Co-culture *345*
- Cumulus Co-culture Method *345*
- Co-culture with Fallopian Tube Epithelial Cells *346*

41. Oocyte Activation 349
Takashi Yamaguchi, Keiji Kuroda, Masahiko Ito, Atsushi Tanaka
- Fertilization and Oocyte Activation *349*
- Fertilization Failure *350*
- Treatment of Fertilization Failure *350*

42. Triple Parenting 355
Harsha Bhadarka, Arpita Patel
- Indications *355*
- Prevention in Next Generation *356*

Index 363

4

CHAPTER

IVF Lite: Is this the Future of Assisted Reproductive Technology?

Gautam Nand Allahbadia, Goral Gandhi, Akanksha Allahbadia Gupta, Maham AS

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INTRODUCTION

Infertility is one of the major medical problems in the western world caused by genetic or epigenetic factors, or both, which has led to continuous research and advancements in the field of assisted reproductive technology (ART). Many stimulation protocols are available for controlled ovarian hyperstimulation (COH) in *in vitro* fertilization (IVF). An inverse relationship between oocyte efficiency and ovarian response was reported in conventional IVF. The purpose of a new study by Zhang et al. was to report metaphase II (MII) oocyte efficiency according to oocyte yield in minimal/mild-stimulation IVF (mIVF) and to assess whether oocyte yield affects live birth rate (LBR). Infertile women (n = 264) aged <39 years old with normal ovarian reserve who had mIVF were recruited. All participants received the same protocol for ovarian stimulation. All the embryos were cultured to the blastocyst stage and vitrified using a freeze-all approach. This was followed by a single blastocyst transferred to each participant in subsequent cycles over a 6-month period. Ovarian response was categorized according to the number of MII oocyte yield (low: 1–2, intermediate: 3–6, and high: ≥7 MII oocytes). MII oocyte utilization rate was calculated as the number of live births divided by the number of MII oocytes produced after only one oocyte retrieval and subsequent transfers of vitrified/warmed blastocysts. The main outcome measure was cumulative LBR over a 6-month period. Among all the participants, 1,173 total retrieved oocytes (4.4 ± 0.2 per patient) resulted in 1,019 (3.9 ± 0.2 per patient) total MII oocytes, a clinical pregnancy rate (PR) of 48.1% and a LBR of 41.2%. Oocyte utilization rate was inversely related to ovarian response where it was 30.3% in the "low" versus 9.3% in the "intermediate" versus 4.3% in the "high" oocyte yield groups ($p < 0.05$). Implantation rate significantly dropped as the number of MII oocytes increased and was highest in the "low" oocyte yield group ($p < 0.0001$). Cumulative LBR was similar in "low", "intermediate", and "high" oocyte yield groups ($p > 0.05$). The number of MII oocytes had poor sensitivity and specificity for predicting a live birth. These data extend the hypothesis of oocyte efficiency reported in conventional IVF protocols to mIVF protocols.

Why more is less and less is more?

It has been proven that the use of high-gonadotropin dose does not necessarily improve the final outcome of IVF. Mild ovarian stimulation is based on the principle of optimal utilization of competent oocytes/embryos and endometrial receptivity. There is growing evidence that the pregnancy or LBRs with mild-stimulation protocols are comparable to those with conventional IVF; the cumulative pregnancy outcome has been shown to be no different, despite having fewer numbers of oocytes or embryos available with milder ovarian stimulation. Although equally effective, mild-stimulation IVF is associated with a greater safety profile, in terms of the incidence of ovarian hyperstimulation syndrome (OHSS) and venous thromboembolism. It is also found to be better tolerated by patients and less expensive. Emerging research evidence may lead to widespread acceptance of mild IVF, by both patients and IVF providers, and make IVF more accessible to women and couples worldwide.

Blumenfeld searched the pertinent English literature (PubMed) addressing mild stimulation for IVF/ART and

publications addressing "mild" or "soft" controlled ovarian stimulation (COS) versus conventional COS for IVF, OHSS, natural cycle IVF, and IVF outcome in association with COS. Four possible mechanisms can be put forward to explain the apparent paradox of "less is more". (1) In the natural- or mild-stimulation cycles, the healthiest follicles are selected by the principle of "quality for quantity"; (2) high estradiol (E2) in the late follicular phase significantly correlated with higher rates of small for gestational age (SGA) and low-birth-weight (LBW) neonates; (3) anti-Müllerian hormone (AMH), luteinizing hormone (LH), testosterone, and E2 are significantly higher in natural cycle (NC)-IVF than in stimulated IVF follicles, suggesting an alteration of the follicular metabolism in stimulated cycles; and (4) supraphysiological E2 may increase the growth hormone-binding protein (GHBP) by neutralizing GH and diminishing the resultant insulin-like growth factor (IGF) levels, necessary for optimal synergism with follicle-stimulating hormone (FSH). The author suggested to aim at the retrieval of around eight to ten eggs. Mild stimulation should be the common practice for IVF. In cases where more than ten ova are retrieved or high E2 levels are reached, either intentionally or unintentionally, "freeze-all policy" should be considered and embryo transfer (ET) done in a subsequent natural cycle.

Baker et al. published a retrospective study to evaluate the correlation between total gonadotropin dose and LBR. A total of 658,519 fresh autologous cycles of IVF were reported to the Society for Assisted Reproductive Technology from 2004 to 2012. Logistic regression models were fitted to LBRs with the use of categorized values for total FSH dose and number of oocytes retrieved as the primary predictor variables. To reduce the effect of the most significant confounders that may lead physicians to prescribe higher doses of FSH, additional analyses were performed limited to good-prognosis patients (<35 years of age, body mass index <30 kg/m^2, and no diagnosis of diminished ovarian reserve, endometriosis, or ovulatory disorder) and including duration of gonadotropin treatment. LBR significantly decreased with increasing FSH dose, regardless of the number of oocytes retrieved. The statistically significant decrease in LBR with increasing FSH dose remained in patients with good prognosis, and regardless of female age, except for women aged ≥35 years with 1–5 oocytes retrieved. This analysis suggests that physicians may wish to avoid prescribing a high dose of FSH.

UAE PERSPECTIVE

In the UAE, for the last decade, IVF clinics were allowed to cryopreserve only gametes and not embryos. This law has changed this year and the clinics can now take individual patient permissions to freeze embryos from the Ministry of Health, UAE. Over the past decade in contradiction to the world, IVF laboratories were vitrifying oocytes and accumulating them in cases of poor responders and older women. IVF Lite in the country was done using oocyte accumulation and segmented IVF with or without genetic screening. When the requisite number was collected over multiple egg retrievals, the oocytes were thawed and injected and the generated embryos were either transferred directly or subjected to preimplantation genetic screening (PGS) and then screened euploid embryos transferred. The efficiency of a good vitrification system continued giving the UAE clinics results comparable to embryo vitrification over the last decade. The rate-limiting step was the method used and the training and experience of the laboratory staff. From 2014, we were using published data to counsel our patients about the noninferiority status of oocyte vitrification at the time of recruiting them for IVF Lite.

The aim of a prospective observational study by Herero et al. was to compare multiple embryological and pregnancy outcomes for vitrified oocytes against the same outcomes using vitrified embryos in patients at risk for OHSS. 96 patients were included and allocated to vitrification of oocytes (Group 1) or embryos (Group 2). No statistical differences in baseline characteristics between groups were detected. No differences were observed in outcomes according to vitrification timing. Oocyte vitrification achieved the same LBR as embryo vitrification.

The aim of an American study was to report the oocyte-freezing experience in women aged 40 years and older at a single fertility center. 158 women (mean age 43.9 ± 0.2) who underwent minimal ovarian stimulation IVF were enrolled. IVF protocol included the use of clomiphene citrate (CC) (50 mg/day) or letrozole (2.5 mg/day) with or without low-dose gonadotropins (started at 75 IU/day and increased as needed to 150 IU/day). 584 retrieved oocytes (2.1 ± 0.15 per patient) yielded 532 mature MII oocytes that were frozen. After thawing and fertilization by ICSI, a total of 344 embryos (1.9 ± 0.1 per patient) were formed. A total of 57 relatively good embryos were transferred and yielded three live births (5.3% per embryo transfer), three spontaneous abortions, and one chemical pregnancy. These data are important in counseling older women who desire autologous oocyte freezing.

RATIONALE OF DEFERRED EMBRYO TRANSFER

The rationale of a deferred ET whether following a conventional stimulation of a minimal stimulation is the

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same. Roque et al. setup a prospective study to compare IVF outcomes between fresh ET and frozen-thawed ET (the "freeze-all" policy), with fresh ET performed only in cases without progesterone (P) elevation. A total of 530 patients submitted to COS with a gonadotropin-releasing hormone (GnRH) antagonist protocol, and cleavage stage, Day 3 ET. A total of 530 cycles were included in the analysis: 351 in the fresh ET group (when P levels were ≤1.5 ng/mL on the trigger day); and 179 cycles in the freeze-all group (ET performed after endometrial priming with estradiol valerate, at 6 mg/day, taken orally). For the fresh ET group versus the freeze-all group, the implantation rate was 19.9% and 26.5%; clinical PR was 35.9% and 46.4%, respectively; and ongoing PR was 31.1% and 39.7%. The IVF outcomes were significantly better in the group using the freeze-all policy, compared with the group using fresh ET. These results suggest that even in a selected group of patients who underwent fresh ET (P levels ≤1.5 ng/mL), endometrial receptivity may have been impaired by COS, and outcomes may be improved by using the freeze-all policy.

MODIFIED NATURAL CYCLE IVF

The first live birth after IVF was achieved in a purely natural cycle. Because early attempts at IVF were associated with low efficiency, ovarian stimulation was added to achieve a greater margin for error in oocyte retrieval, fertilization, and thus, overall pregnancy success. As technology improved, the intuitive appeal of the natural cycle led investigators to once again attempt IVF without antecedent gonadotropin stimulation. Triggering of ovulation with human chorionic gonadotropin (hCG) was added to allow for accurate scheduling of oocyte retrieval and thus increased oocyte yield. When GnRH antagonists became available, premature ovulations could be prevented, albeit at the cost of adding some form of ovarian stimulation to continue follicle development until ovulation triggering. This type of cycle came to be known as the "modified natural cycle" (MNC-IVF). These modified natural IVF cycles are associated with decreased medication costs; they produce acceptable PRs and they may be particularly appropriate for patients at increased risk of OHSS, poor responders, and those wishing to avoid supernumerary embryo production. In MNC-IVF, spontaneous ovulation is prevented with a minimal amount of hormones and spontaneous monofollicular growth is supported. As a result, there is no risk of OHSS, and the risk of a multiple pregnancy is low. There is a 9.1% chance of pregnancy after one MNC-cycle and the cumulative PR after a maximum of six MNC-IVF cycles is 33.4%. The cumulative results of a maximum of six MNC-IVF cycles are comparable to those of the first COS-IVF treatment cycle including transfer of cryopreserved embryos produced as a result of the treatment (33.4% versus 37.7%). The risk of a twin pregnancy following MNC-IVF is 0.1%, and 18.3% following COS-IVF. This means that MNC-IVF is a good alternative for COS-IVF.

A Korean prospective randomized study was performed to investigate the effectiveness of minimal stimulation using recombinant human FSH (rhFSH) and GnRH antagonist compared with GnRH antagonist multiple-dose protocol (MDP) in low responders undergoing IVF/ICSI. The study demonstrated that minimal stimulation in natural cycles provides similar PRs to the GnRH antagonist MDP with fewer dose and days of rhFSH used and thus can be a cost-effective alternative as a last chance before oocyte donation in low responders.

CLOMIPHENE CITRATE OR LETROZOLE

There has been increasing interest in combining the oral agents CC and letrozole with gonadotropins in IVF—for poor responders to reduce the amount of gonadotropins used, and in normal responders to reduce the incidence of OHSS. In normal responders, mild stimulation with the use of CC and gonadotropins was found to decrease the number of oocytes retrieved and result in good PRs, but in most studies, the cumulative PR was lower compared with conventional ovarian stimulation when frozen embryo transfers were considered. Coadministration of letrozole and gonadotropins has mainly been used in patients with breast cancer to prevent the massive elevation of serum E2 concentrations with the use of standard COH. CC and letrozole have both been used with gonadotropins in poor responders and have been shown to reduce the amount of gonadotropin used without reducing the PR. Letrozole use with gonadotropins in IVF cycles may increase endometrial receptivity by increasing integrin expression in the endometrium and by lowering estrogen concentrations to more physiologic levels.

The objective of study by Rose et al. was to compare the use of CC and letrozole in an IVF setting in which the objective was to produce only one or two embryos. Either CC or letrozole was used in conjunction with gonadotropins without the use of GnRH antagonists. Sixty-two patients received either CC or letrozole with low-dose gonadotropins in 128 non-randomized treatment cycles. hCG was given when one follicle was at least 17 mm. Oocyte retrieval was done 34 hours later and fertilization was performed using ICSI. There were no statistically significant differences in the number of large follicles produced, oocytes fertilized,

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endometrial thickness, clinical PRs, or delivery rates in patients taking letrozole compared to CC. More mature oocytes were retrieved after CC, but a subset analysis of patients undergoing both treatments did not support this difference. The only statistically different finding in both analyses was the peak estradiol levels during treatment, which averaged 516 pg/mL with letrozole and 797 pg/mL with CC (p = 0.005). Overall, the cancellation rate due to a premature LH surge was 5%. An average of 2.8 mature oocytes were recovered, 2.1 oocytes were fertilized, and 1.6 embryos were transferred. The overall clinical PR per transfer was 25% [95% confidence interval (CI) 17.7–33.3%] and the overall LBR per transfer was 19.2% (95% CI, 11.6–26.8%). Other than peak estradiol levels, there were no clinically significant differences when letrozole or CC was used for mild ovarian stimulation for IVF. There were only rare cancellations because of premature LH surges.

MILD STIMULATION VERSUS CONVENTIONAL STIMULATION FOR IVF

Lazer et al. examined whether treatment with minimum-dose stimulation (MS) protocol enhances clinical PRs compared to high-dose stimulation (HS) protocol. A retrospective cohort study was performed by comparing IVF and pregnancy outcomes between MS and HS gonadotropin-antagonist protocol for patients with poor ovarian reserve. Inclusion criteria included patients with an AMH ≤8 pmol/L and/or antral follicle count (AFC) ≤5 on Days 2–3 of the cycle. Patients in 2008 exclusively had a HS protocol treatment, while patients in 2010 had treatment with a MS protocol exclusively. The MS protocol involved letrozole at 2.5 mg over 5 days, starting from Day 2, overlapping with gonadotropins, starting from the 3rd day of letrozole at 150 units daily. GnRH antagonist was introduced once one or more follicles reached 14 mm or larger. The HS group received gonadotropins (≥300 IU/day) throughout their antagonist cycle. Clinical PR was significantly higher in the MS protocol compared to the HS protocol (p = 0.007). Furthermore, the live birth rate was significantly higher in the MS group compared to the HS group (p =0.034). In conclusion, the MS IVF protocol is less expensive (lower gonadotropin dosage) and resulted in a higher clinical PR and LBR than a HS protocol for poor responders.

Zhang et al. performed a randomized noninferiority controlled trial with a prespecified border of 10% that compared 1 cycle of mini-IVF with single-embryo transfer (SET) with 1 cycle of conventional IVF with double-embryo transfer. Around 564 infertile women (<39 years old) who were undergoing their first IVF cycle were allocated randomly to either mini-IVF or conventional IVF. The primary outcome was cumulative LBR per woman over a 6-month period. Secondary outcomes included OHSS, multiple PRs, and gonadotropin use. The primary outcome was cumulative live birth per randomized woman within a time horizon of 6 months. 564 couples were assigned randomly between February, 2009 and August, 2013 with 285 couples allocated to mini-IVF and 279 couples allocated to conventional IVF. The cumulative LBR was 49% (140/285) for mini-IVF and 63% (176/279) for conventional IVF [relative risk (RR), 0.76; 95% CI, 0.64–0.89]. There were no cases of OHSS after mini-IVF compared with 16 moderate/severe OHSS cases (5.7%) after conventional IVF. The multiple PRs were 6.4% in mini-*IVF* compared with 32% in conventional IVF (RR, 0.25; 95% CI, 0.14–0.46). Gonadotropin consumption was significantly lower with mini-IVF compared with conventional IVF (459 ± 131 vs 2079 ± 389 IU; p < 0.0001). Compared with conventional IVF with double-embryo transfer, mini-IVF with SET lowers LBRs, completely eliminates OHSS, reduces multiple PRs, and reduces gonadotropin consumption.

POOR OVARIAN RESERVE

Pilehvari et al. setup a study to compare the pregnancy outcomes achieved by IVF between minimal stimulation and conventional antagonist protocols in poor ovarian responders (PORs). In this randomized controlled trial, 77 PORs undergoing IVF were selected and divided into two groups. First group was the minimal stimulation group (n = 42) receiving 100 mg/day CC on Day 2 of the cycle for 5 day that was followed by 150 IU/day human menopausal gonadotropin (hMG) on Day 5 of the cycle. Second group was the conventional group (n = 35) receiving at least 300 IU/day gonadotropin on Day 2 of the cycle. GnRH antagonist protocol was applied for both groups according to flexible protocol. Number of retrieved oocytes and chemical PR were the main outcomes. There was no difference in number of retrieved oocyte and PR (2.79 ± 1.96 vs 2.20 ± 1.71 and 5.6% vs 4.1%; p > 0.05) between both groups. The gonadotropin dose used in the minimal stimulation group was lower than conventional group (1,046 ± 596 vs 2,806 ± 583). Minimal stimulation protocol with lower gonadotropin used is likely to be considered as a patient-friendly and cost-effective substitute for PORs.

A recent study compared the IVF outcomes of letrozole/antagonist and microdose GnRH agonist flare up protocols in PORs undergoing ICSI. 60 proven POR patients were randomized by computer-generated list to receive either

JAYPEE BROTHERS

letrozole/antagonist (mild stimulation) n = 30 or GnRHa protocol (microdose flare) n = 30. Both groups were similar with respect to background and hormonal characteristics (age, duration of infertility, BMI, FSH, LH, and E2). The clinical PR per cycle was similar in both groups (13.3 vs 16.6%; OR = 0.769; 95% CI = 0.185, 3.198). The doses of used gonadotropins and the number of stimulation days were significantly lower in the letrozole/antagonist protocol. The peak E2 level on the day of hCG, the endometrial thickness, the retrieved oocytes, the number of fertilized oocytes, the number of transferred embryos, and the cancellation rate were statistically similar in both groups. The letrozole/antagonist protocol is a cost-effective and patient-friendly protocol that may be used in PORs for IVF/ICSI.

The objective of a French study was to assess the reproductive competence of oocytes obtained by follicular flushing in poor responder patients. This prospective comparative study, at the University of Paris XI, Assistance Publique des Hopitaux de Paris, INSERM Unit 782, was performed on 165 infertile IVF embryo transfer candidates. A total of 271 consecutive minimal stimulation IVF (msIVF) cycles were studied. Oocyte retrieval was performed 34 hours after hCG administration and oocytes were allocated into two groups according to their retrieval method: oocytes obtained in the first follicular aspiration (FA, n = 127) and oocytes retrieved in the subsequent follicular flushing (FF, n = 102). The principal outcome was to evaluate clinical pregnancy and embryo implantation rates. Thus, patient characteristics, fertilization rate, and clinical PR per oocyte were comparable in both of groups. In contrast, embryo morphology (41% vs 59%, $p < 0.01$) and implantation rates (20.4% vs 34.8%, $p < 0.04$) were better in the FF group. In conclusion, an optimal reproductive competence was observed in oocytes retrieved by follicular flushing in msIVF in poor responder patients.

The use of progestin (P) during ovarian stimulation is effective in blocking the LH surge in women with normal ovarian reserve; however, its effects have not been determined in poor responders. A recent study by Chen et al. aimed to explore the follicular dynamics in P-primed minimal stimulation in poor responders. A total of 204 infertile women with diminished ovarian reserve were allocated into the medroxyprogesterone acetate (MPA) group or the natural cycle control group in an alternating order. MPA (10 mg) was administered daily beginning from the early follicular phase and a low dose of hMG was added in the late follicular phase, if the serum FSH level was lower than 8.0 mIU/mL. When a dominant follicle reached maturity, triptorelin 100 μg and hCG 1,000 IU were used for trigger, and oocytes were retrieved 34–36 hours later. All viable embryos were cryopreserved for subsequent frozen embryo transfer. Natural cycle IVF was used as controls. Compared with the natural cycle group, the MPA group exhibited a larger preovulatory follicle (18.7 ± 1.8 mm vs 17.2 ± 2.2 mm), a longer follicular phase (13.6 ± 3.6 days vs 12.3 ± 3.2 days), and higher peak estradiol values (403.88 ± 167.16 vs 265.26 ± 122.16 pg/mL), while maintaining lower LH values ($p < 0.05$). The incidences of spontaneous LH surge and premature ovulation decreased significantly (1.0% vs 50% and 2% vs 10.8%, respectively; $p < 0.05$). A greater number of oocytes and viable embryos were harvested from the MPA group than from the natural cycle group ($p < 0.05$). Moreover, the clinical PR was slightly higher in the MPA group than in the natural cycle controls, but the difference was not significant (11.8% vs 5.9%, $p > 0.05$). This study supported the hypothesis that P-primed minimal stimulation achieved ovulation control of the dominant follicle and did not adversely affect the quality of oocytes in poor responders. Therefore, P-priming is a promising approach to overcome premature ovulation in minimal stimulation for poor responders.

OLDER WOMEN

There were few reports about infertile women aged 45 years and above undergoing IVF/ICSI. Yan et al. reported the case of a 49-year-old woman who delivered twins after ICSI using autologous oocytes with mild ovarian stimulation. The patient was presented with 26-year primary infertility caused by bilateral fallopian tube obstruction and severe oligoasthenozoospermia in her husband. She was given a mild ovarian stimulation cycle of CC and low-dose FSH with ICSI, and two blastocysts were transferred. Twins were delivered by cesarean section at 37 weeks for moderate pregnancy-induced hypertension.

For women of advanced age with abnormally increased FSH levels, standardized hormonal stimulation often represents a cost-intensive procedure with a low success rate. It is well established now that with mild ovarian stimulation, there is a greater percentage of good-quality eggs (although a smaller number) than with higher-dose conventional stimulation. Mild-stimulation protocols reduce the mean number of days of stimulation, the total amount of gonadotropins used, and the mean number of oocytes retrieved. The proportion of high-quality and euploid embryos seems to be higher compared with conventional stimulation protocols, and the PR per embryo transfer is comparable. Moreover, the reduced costs, the better tolerability for patients, and the less time needed to complete an IVF cycle make mild approaches clinically and cost-effective over a given period of time. The low number

JAYPEE PROOFERS

of embryos available for transfer poses a great challenge in the management of older women going in for IVF. A potential management of these older women is to create a sufficient pool of embryos by accumulating vitrified good-grade embryos over several minimal stimulation and modified natural cycles. At the end of the accumulation process, these embryos can be subjected to a PGS using next-generation sequencing and then the pool would have only chromosomal normal embryos with maximal chances of implantation. This would potentially make the chances of success for older women similar to normal responders. This management, however, is unthinkable without an outstanding vitrification program. The option of accumulating embryos has become a promising reality with the advent of vitrification technologies.

MINIMAL STIMULATION AND SINGLE-EMBRYO TRANSFER WITH SEGMENTED IVF

In Zhang's series, patients were not denied the treatment based on their Day 3 FSH value or ovarian reserve. Yet, very acceptable PRs were achieved (20% for fresh embryo transfers and 41% for cryopreserved embryo transfers). These results strengthen the argument for a mini-IVF protocol and vitrification as an alternative to standard conventional IVF stimulation protocols.

A retrospective, cohort study was performed in private infertility center to evaluate the embryological and clinical results of a large exclusively SET program according to patient's age (≤29, 30–34, 35–39, 40–44, and ≥45 years). A total of 7,244 infertile patients had undergone 20,244 cycles with a clomiphene-based minimal stimulation or natural cycle IVF protocol during 2008. Following oocyte retrieval, fertilization, and embryo culture, a total of 10,401 fresh or frozen SET procedures were performed involving cleavage-stage embryos or blastocysts. Successful oocyte retrieval rate (78.0%) showed no age-dependent decrease until 45 years. Fertilization (80.3%) and cleavage (91.1%) rates were not significantly different between age groups. Blastocyst formation (70.1–22.8%) and overall LBRs (35.9–2%) showed an age-dependent decrease. Frozen-thawed blastocyst transfer cycles gave the highest chance of live birth per embryo transfer (41.3–6.1%). High-fertilization and cleavage rates were obtained regardless of age, whereas blastocyst formation and LBRs showed an age-dependent decrease. An elective SET program based on a minimal ovarian stimulation protocol yields acceptable LBRs per embryo transfer in infertile patients up until their mid-40s. However, in very advanced age patients (≥ 45 years old), success rates fall below 1%.

A 3-year, retrospective, single-center cohort study was conducted in a private infertility center to determine cumulative LBRs per scheduled oocyte retrieval following minimal ovarian stimulation/natural cycle IVF in unselected infertile patients. A total of 727 consecutive infertile patients were analyzed who underwent 2,876 (median 4) cycles with scheduled oocyte retrieval from November, 2008 to December, 2011. Natural cycle IVF or clomiphene-based minimal ovarian stimulation was coupled with SET and increased use of delayed vitrified-warmed blastocyst transfer. Main outcome measures were crude and expected age-specific cumulative LBR per scheduled oocyte retrieval. Crude cumulative LBRs were 65%, 60%, 39%, 15%, and 5% in patients aged 26–34, 35–37, 38–40, 41–42, and 43–44 years, respectively. No live births occurred in patients aged ≥ 45 years. Dropout rates per cycle were 13–25%. Success rates gradually reached a plateau, with few additional live births after six cycles. Most of the expected success rate was reached within 6 months with almost maximal rates within 15 months of the first oocyte retrieval. Acceptable cumulative LBR are reached with an exclusive minimal ovarian stimulation/SET policy, especially in patients aged <38 years but also in intermediate aged patients (38–40 years).

MILD STIMULATION USING CORIFOLLITROPIN ALFA

Mild COH, combined with oocyte retrieval (OR) under local anesthesia (LA), may provide low-impact IVF. Since a single injection of corifollitropin alfa (CFA) provides 7 days of COH, the authors hypothesized that CC followed by CFA may provide adequate COH response from one single FSH injection. Their aim was to assess IVF outcomes after a novel CC/CFA protocol, compared to women undergoing standard rFSH COH protocols (good prognosis comparative cohort: GPCC) in a 1:2 matched design. In this pilot study of 25 patients, they examined the effectiveness of oral clomiphene (100 mg; days 2–6) followed by CFA in a GnRH antagonist protocol producing a single injection COH stimulation regime. All ORs were conducted under LA preovarian block. Cycle outcomes were compared to a matched GPCC undergoing standard rFSH COH. Mild stimulation was achieved with less oocytes being collected compared to the GPCC (6.4 ± 0.7 vs 10.7 ± 0.9, $p < 0.001$), resulting in a reduced number of good-quality embryos available for transfer/cryopreservation (3.7 ± 0.6 vs 5.7 ± 0.5, $p = 0.01$). While embryo quality was similar between the two groups, endometrial thickness was

JAYPEE BROTHERS

significantly lower in the group receiving CC/CFA. PRs were significantly lower in the CC/CFA cohort compared to GPCC (31.8 vs 57.1%, $p = 0.04$) and 44% of CC/CFA participants required supplemental rFSH in order to achieve the hCG trigger criteria. Sequential clomiphene CFA protocol does not appear to be an optimal regime for low-impact IVF treatment, as it does not provide adequate COH from a single CFA injection and results in lower fresh embryo transfer PRs and fewer embryos for cryopreservation.

NEONATAL OUTCOME AFTER MINIMAL STIMULATION

Kato et al. compared neonatal outcome between children born after vitrified versus fresh SET. This was a retrospective, single-center cohort study of 6,623 delivered singletons following 29,944 SETs. Patients underwent minimal ovarian stimulation/natural cycle IVF followed by SET of fresh or vitrified-warmed cleavage-stage embryos or blastocysts. Gestational age (38.6 ± 2 weeks vs 38.7 ± 1.9 weeks) and preterm delivery rate (6.9% vs 6.9%, aOR: 0.96 95% CI: 0.76–1.22) in singletons born after the transfer of vitrified embryos were comparable to those born after the transfer of fresh embryos. Children born after the transfer of vitrified embryos had a higher birth weight (3,028 ± 465 vs 2,943 ± 470 g, $p < 0.0001$) and lower LBW (8.5% vs 11.9%, aOR: 0.65, 95% CI: 0.53–0.79) and SGA (3.6% vs 7.6% aOR: 0.43, 95% CI: 0.33–0.56) rates. Total birth defect rates (including minor anomalies) (2.4% vs 1.9%, aOR: 1.41, 95% CI: 0.96–2.10) and perinatal mortality rates (0.6% vs 0.5%, aOR: 1.02, 95% CI: 0.21–4.85) were comparable between the vitrified and fresh groups. Vitrification of embryos/blastocysts did not increase the incidence of adverse neonatal outcomes or birth defects following SET.

PREIMPLANTATION GENETIC SCREENING

The aim of a Russian study was to investigate, with FISH, the frequency of aneuploidies of the PB-I and PB-II of oocytes in women participating in IVF programs. The study included 93 women, 82 of them were after COS and 11 in natural cycles. FISH in 238 PB-I and PB-II was done. The study revealed that the frequency of aneuploidies in oocytes after COS was higher than in the natural cycle and also was higher after COS in women with infertility compared to women stimulated because of male infertility and egg donors. Aneuploidies of oocytes after COS are more common in patients after 35 years old.

De Sutter et al. compared fertilization and aneuploidy rates after two stimulation protocols in an IVF program. In 349 treatment cycles, CC and human menopausal gonadotropin (hMG) were used in one group ($n = 233$) and hMG after treatment with a GnRHa in two other groups (long protocol): goserelin ($n = 73$) and buserelin ($n = 43$). Cytogenetic analysis was performed on all unfertilized oocytes in both groups. Fertilization rates were significantly higher in the GnRHa/hMG group than in the CC/hMG group, but cleavage rates and embryo quality were not different. Out of 736 oocytes prepared for cytogenetic analysis, 256 were karyotyped—172 were found to be euploid and 84 were aneuploid. More oocytes were aneuploid in the GnRHa/hMG group than in the CC/hMG group and this difference was statistically significant.

A study by Rubio et al. aimed to test the influence of gonadotropin doses on embryo aneuploidy rates. A total of 32 young oocyte donors with a high response to ovarian stimulation were included in the study. Two subsequent stimulation treatments were performed in each donor: first, a standard dose cycle using a 225 IU starting dose of recombinant FSH (r-FSH) and second, a reduced dose cycle with a starting dose of 150 IU r-FSH. In both cycles, GnRHa cotreatment was used for downregulation. Ovarian response, embryo development, and aneuploidy for chromosomes 13, 15, 16, 17, 18, 21, 22, X, and Y were the main outcomes of the study. A total of 22 donors completed both treatments with different gonadotropin doses. In the remaining 10 donors, the reduced dose cycle was canceled due to low-ovarian response. In those donors who completed both regimens, significant increases in rates of fertilization and chromosomally normal blastocysts were observed in the reduced dose cycle. No differences were observed in pregnancy and implantation rates in recipients who received oocytes from standard and reduced doses cycles. Despite the limited numbers in the study, the authors concluded that in high responder donors, a decrease in the gonadotropin dose could improve fertilization rates and embryo quality.

To test whether ovarian stimulation for IVF affects oocyte quality and thus chromosome segregation behavior during meiosis and early embryo development, PGS of embryos was employed in a prospective, randomized controlled trial, comparing two ovarian stimulation regimens by Baart et al. in 2007. Infertile patients under 38 years of age were randomly assigned to undergo either a mild-stimulation regimen using GnRH antagonist cotreatment (67 patients), which does not disrupt secondary follicle recruitment, or a conventional high-dose exogenous gonadotropin regimen and GnRHa cotreatment (44 patients). Following IVF, embryos were biopsied at the eight-cell stage and the copy number of

JAYPEE PROOFERS

10 chromosomes was analyzed in one or two blastomeres. The study was terminated prematurely after an unplanned interim analysis (which included 61% of the planned number of patients) found a lower embryo aneuploidy rate, following mild stimulation. Compared with conventional stimulation, significantly fewer oocytes and embryos were obtained following mild stimulation ($p < 0.01$ and < 0.05, respectively). Consequently, both regimens generated on average a similar number (1.8) of chromosomally normal embryos. Differences in rates of mosaic embryos suggest an effect of ovarian stimulation on mitotic segregation errors. The authors summarized that future ovarian stimulation strategies should avoid maximizing oocyte yield but aim at generating a sufficient number of chromosomally normal embryos by reduced interference with ovarian physiology.

INTERESTING CASE REPORTS

Xu and Li reported a novel strategy of continuous ovarian stimulation in a poor responder with two oocyte retrievals within the follicular and luteal phases of the same menstrual cycle. A patient, aged 41 years, diagnosed as infertile with low ovarian reserve sought IVF treatment. A minimal ovarian stimulation protocol was commenced with use of low-dose urinary FSH (150 IU/day) from Day 3, combined with using CC (50–100 mg) when the biggest follicle reached 10 mm in diameter to prevent ovulation. GnRH agonist was administered on Day 15 when the lead follicles reached 18 mm in diameter. The first ultrasound-guided oocyte retrieval was performed 21 hours later; however, no ovum was obtained. Luteal-phase ovarian stimulation was started 2 days later. The second oocyte retrieval was performed 25 hours after hCG administration. Finally, one mature oocyte resulting in a cleavage embryo (8-cell, grade 2) was obtained. The case demonstrates that it is feasible to obtain mature oocytes and good embryos from luteal-phase stimulation. Continuous stimulation during the follicular and luteal phase can be a solution for poor ovarian response. Ovarian stimulation may be performed flexibly in special circumstances. This was the first report on a novel strategy of continuous ovarian stimulation on a poor responder during the follicular and luteal phases of the same menstrual cycle with two oocyte retrievals. In the reported case, a patient, aged 41 years, who was diagnosed with very poor ovarian function, sought therapy for IVF. Antral follicles and basic hormones were evaluated on Day 2 of the menstrual cycle. The stimulation cycle was commenced with use of 150 IU/day urinary FSH from Day 3, combined with CC and ibuprofen in the late follicular and luteal phases to prevent ovulation. Oocyte retrieval was attempted twice. The authors performed luteal-phase ovarian stimulation continuously 2 days after the first failed oocyte retrieval during the follicular phase. Finally, one mature oocyte resulting in a cleavage embryo (8-cell, grade 2) was obtained after the luteal phase stimulation and retrieval, redeeming the previous unsuccessful oocyte retrieval. The case demonstrates that it is practical to obtain mature oocytes and good embryos from maintaining luteal-phase stimulation. For poor ovarian response, continuous stimulation during the follicular and luteal phases can be a solution.

In vitro fertilization–embryo transfer with ICSI was performed for a 45-year-old woman with a peak serum FSH level of 29 mIU/mL and a history of failing to conceive in five previous IVF-ET cycles at a younger age. A minimal FSH stimulation protocol was used. A fresh transfer of a 7-cell embryo was performed on Day 3. A successful pregnancy and delivery ensued. This case report establishes a precedent that a successful pregnancy following IVF-ET is possible in a woman whose serum FSH is >15 mIU/mL and is age of 45 years.

RECENT ADVANCES

There is an ever-increasing trend in ARTs to reduce the intensity of ovarian stimulation for IVF and to restrict the number of embryos that are transferred into the uterine cavity. Recent findings suggest that the magnitude of ovarian stimulation affects the proportion of euploid embryos. Ovarian stimulation regimens for IVF seem to have a deleterious effect on oocyte quality and embryo aneuploidy in a dose-dependent manner. We are moving to a global era of SET and now it becomes more important than ever before to ensure that this single embryo has the highest implantation potential. Strategies are being adopted to improve the accuracy for selecting euploid, viable embryos for transfer.

One such strategy involves further refinement of morphological criteria associated with improved viability by considering, for example, pronuclei disposition, nucleolar organization, and identification of the fast-cleaving embryos, with only mononucleated blastomeres and trying to correlate morphokinetics with cytogenetics. Another strategy employs preimplantation genetic diagnosis whereby a biopsied blastomere is tested for ploidy using next-generation sequencing. Even in older patients, lower oocyte yields may represent a more appropriate response to ovarian stimulation, allowing the most competent follicles and oocytes to develop and thereby reducing the occurrence of embryo aneuploidy. IVF Lite plus ACCU-VIT by repeated

JAYPEE BROTHERS

mild-stimulation cycles with subsequent vitrification of blastocysts, combined with PGS, is a promising new approach for poor responders as well as women of advanced maternal age.

CONCLUSION

Mild ovarian stimulation for IVF minimizes OHSS and multiple gestations without compromising the PR. Gentle ovarian stimulation protocols, such as "mini-IVF", have several potential advantages over conventional IVF protocols, including less medication and fewer injections, producing fewer eggs, but eggs of higher quality. IVF Lite involves a soft stimulation protocol with lesser amount of fertility drugs. When combined with Embryo ACCU-VIT, it provides a very efficient and cost-effective alternative to conventional IVF. It is designed to retrieve only a few eggs in each ovarian stimulation cycle. Stimulation in this manner has been associated with better quality eggs and hence better quality embryos. In other words, it is a simpler treatment schedule with lower doses of drugs, fewer risks (from multiple pregnancy and overstimulation), and consequently reduced cost.

During ART interventions, COS is used to obtain several oocytes in attempts to increase the likelihood of having at least one developmentally competent embryo available for transfer. Conventional ovarian stimulation regimens for IVF seem to have a deleterious effect on oocyte quality and embryo aneuploidy in a dose-dependent manner. Chromosome abnormalities are common in oocytes derived from patients undergoing IVF treatment. Future ovarian stimulation strategies should avoid maximizing oocyte yield but aim at generating a sufficient number of chromosomally normal embryos by reduced interference with ovarian physiology.

The proportion of oocytes displaying aneuploidy is closely related to maternal age and may exceed 80% in patients over 40 years old. Even in older patients, lower oocyte yields may represent a more appropriate response to ovarian stimulation, allowing the most competent follicles and oocytes to develop and thereby reducing the occurrence of embryo aneuploidy.

EDITORS' COMMENTS

1. The IVF Lite protocol consisting of msIVF + ACCU-VIT + remote embryo transfer (rET) may be explored as an approach to poor responders, larger study groups and more number of studies will land confidence to this form of IVF.
2. The IVF Lite protocols may be consecutively used without a testing cycle. The back-to-back stimulations may give a favorable pregnancy rate per time spent by the patient.
3. Due to the lesser amounts of fertility drugs used in this soft stimulation, cost-effectiveness is a major advantage in low-dose protocol.
4. Minimal stimulation protocols are also gaining momentum in patients with PCO and even normoresponders these days.

SUMMARY

The IVF Lite involves a soft stimulation protocol with lesser amount of fertility drugs. When combined with embryo Accumulation using the Cryotech™ Vitrification Technology (ACCU-VIT), it provides a very efficient and cost-effective alternative to conventional IVF. It is designed to retrieve only a few eggs in each ovarian stimulation cycle. Stimulation in this manner has been associated with better quality eggs and, hence, better quality embryos. In other words, it is a simpler treatment schedule with lower doses of drugs, fewer risks (from multiple pregnancy and overstimulation), and consequently reduced cost. Today, we can offer IVF Lite to almost everyone requiring IVF. The groups, which traditionally benefited from minimal stimulation IVF (msIVF), are poor responders, older patients (above age of 40), women with multiple previous conventional IVF failures, and hyper-responders [like patients with polycystic ovarian syndrome (PCOS) who go repeatedly into ovarian hyperstimulation]. Today, because of the cost advantages and much higher success rates, we have extended the indications of IVF Lite to almost all patients requiring IVF/intracytoplasmic sperm injection (ICSI).

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JAYPEE BROTHERS

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Being academically oriented, she has been an invited speaker at a number of national and international conferences, published numerous research articles in both national and international journals. She philanthropes various trusts like SurroMa, Savita Chhaya and SRT-IVF (aids in low cost IVF cycles for surrogates). Other than that, the center has a developed Human Breast Milk Bank, which is first of its kind in any private IVF setup in India.

Her huge ART centre at Anand, Gujarat, has many feathers to its cap such as Asia 1st grandmother surrogate, west India's 1st preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) babies, the centre has in-house preimplantation genetic testing (PGT) facility with next generation sequencing (NGS) platform and its own molecular department and also has an advanced research department which is approved by Department of Scientific and Industrial Research (DSIR) and is known for its constant ground-breaking researches.

Sandro C Esteves MD PhD is Medical and Scientific Director, ANDROFERT—Andrology and Human Reproduction Clinic, Center for Male Reproduction, Campinas, Brazil. He has published over 200 scientific papers in peer-reviewed journals, authored over 70 book chapters, and presented over 150 papers at both national and international scientific meetings. His current Hirsch index (h-index) is 41 while his citation count is over 4,800 (Google Scholar). He is Faculty Member of F1000Prime in the area of reproductive endocrinology and infertility, Member of the Society for Translational Medicine's Male Infertility Cooperative Group, and Co-founder of the POSEIDON Group (*www.groupposeidon.com*).

He has served as an Editor of several textbooks related to male infertility, reproductive medicine, and assisted reproductive technology. He is also the Guest Editor of many special issues in scientific journals on topics related to reproductive medicine. He is currently working as an Associate Editor of International Brazilian Journal of Urology and Frontiers in Endocrinology (Reproduction), and serves the Editorial Board of Andrology, International Urology and Nephrology, Asian Journal of Andrology, Translational Andrology and Urology, Journal of Evidence-based Women's Health Society, and MedicalExpress.

He has been invited as guest speaker at many international meetings in over 35 countries. He is the recipient of the Alumni of the Year Award from the Cleveland Clinic Center for Reproductive Medicine, and consecutive Star Awards from the American Society for Reproductive Medicine.

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