IFS CONVERSATIONS

Volume 12 (2020)

UNIVERSAL FREEZING

"Are we Ready As Yet?"

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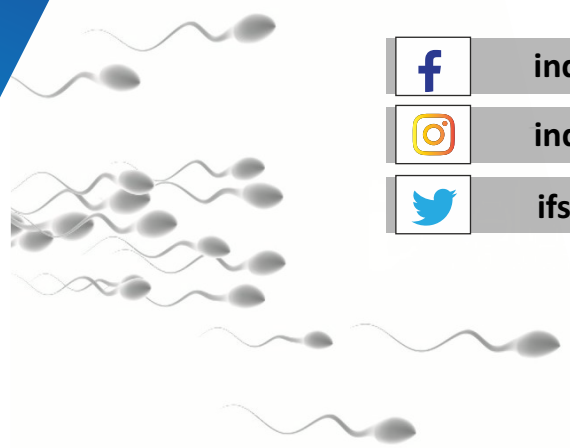
IFS SECRETARIAT

+91 11 40018184
+91 9899308083
+91 9667742015
indianfertilitysocietydelhi@gmail.com
www.indianfertilitysociety.org
302, 3rd Floor, Kailash Building,
26, Kasturba Gandhi Marg,
C.P. New Delhi - 110001



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9968604341
drsprasad@yahoo.com

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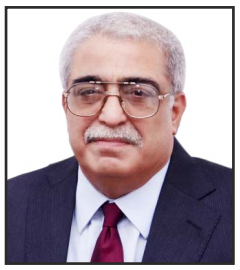
9810023111



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swetagupta06@yahoo.com

Dr Shweta Mittal
Editor
9910303056
mshwets@hotmail.com

Dr Rashmi Sharma
Jt. Editor
9810252619
drrashmisharma73@gmail.com

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Web Editor
9818331760
rupalibassi@hotmail.com

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8860295298
saumya.87in@gmail.com

TEAM IFS

Dr M Kochhar
Patron
9810018277 / 24352514
drmkochhar@yahoo.com

Dr M Telang
Founder President
9811030476/25822454
drmangalatelang@gmail.com

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9810315807
abhamajumdar@hotmail.com

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Past President
9810087666
dr.nalinimahajan@gmail.com

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Past President
9810018951, 22443069
jainravi6@rediffmail.com

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9810122337
sm_doc@southendivf.com

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9810116623
drsohaniverma@gmail.com

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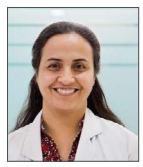
9873855738
nymphaea2006@yahoo.co.in



Dr Vandana Bhatia
9891967417
vandanabhatia1971@yahoo.com

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9810794610
gaurav1979@hotmail.com

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MESSAGE FROM THE PRESIDENT DESK

Dr Sudha Prasad
President - IFS

Dear Friends,

It is indeed a great privilege and pleasure for me to present this "IFS Conversation". The sole purpose of getting these conversations is to showcase the various recent academic activities conducted by our extremely enthusiastic and committed members spread over 27 chapters across India and abroad.

The topic of this conversation is "Universal Freezing: Are we ready as yet?". Freeze-All is the term used to define the strategy of cryopreserving all the embryos formed after in vitro fertilization and transferring them in segmented cycle into a more physiologic endometrium. This strategy has been practiced traditionally in cycles at risk of OHSS, PGT cycles, poor maternal health on the day of transfer or endometrial issues. However, Universal Freeze-All strategy involves the freezing of all embryos despite the above mentioned causes. This strategy as we know was devised in order to overcome a possible negative influence of supraphysiological steroids witnessed in fresh transfers on implantation and live births.

The aim of this conversation is to deduce whether this strategy is beneficial in high responders, intermediate or in low responders with respect to the outcomes of live births so as to get a clear picture whether the freeze-all cycles are preferable for all patients.
In the end, I congratulate the editorial team for their excellent hard work and dedication to plan and prepare this news bulletin and wish all readers a very rewarding and pleasant reading.
Long live IFS!

Warms Regards and best wishes,

Sudha Prasad

Dr. Sudha Prasad
President- IFS

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MESSAGE FROM THE SECRETARY DESK

Dr Neena Malhotra
Secretary - IFS

Dear Members and Friends

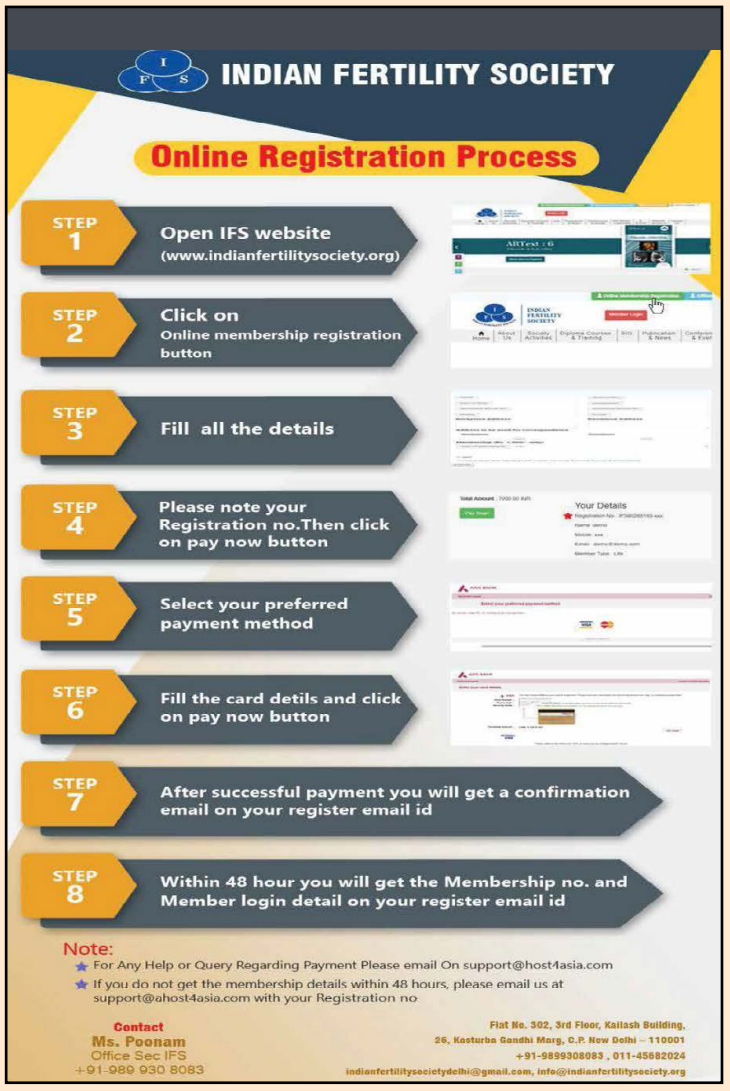
It gives me pleasure to forward yet another volume of IFS Conversation, upholding the academic commitments of the society. The promising editorial team have appreciably kept the deadlines in bringing out the volume despite the tribulations of the present times.

The theme **"Universal Freezing: Are we ready as yet?"** is very aptly thought and delivered in a time when we have mastered the Art and Science of Vitrification, with excellent survival of frozen embryos, yet evidence on improved live birth rate comes significantly for hyper-responders and patients undergoing PGT-A. Whether we translate it to normo- responders comes at a cost of procedure, besides putting the mothers at risk of pre-eclampsia and new-borns to macrosomia , adding further financial burden from perinatal morbidity. This issue contributes to the upcoming developments on the subject of Elective freezing unfolding the many dilemmas and controversies on the subject. Hope our readers will find this issue resolving some of the controversies and dilemmas. Congratulations to the sustained team efforts of the editorial committee and the contributors of this issue of IFS Conversation.

Good wishes

Neena Malhotra

Dr. Neena Malhotra
Secretary - IFS



MESSAGE FROM THE EDITOR'S DESK

Dr. Shweta Mittal Gupta
Editor - IFS

Dr Rashmi Sharma
Jt. Editor - IFS

Dear Members & Friends,

Please accept greetings from the editorial team . We present before you the second issue of IFS conversation this year .

As we are aware that our nation is facing unprecedented covid-19 pandemic situation and the outbreak has disrupted life of billions around the globe, we at IFS are determined to face the challenge by ensuring that relevant academic content reaches all our members online . We believe in going green and the IFS Conversation will be circulated digitally.

This issue of IFS conversation is dedicated at " Universal Freezing - are we ready as yet ?" The improvements in vitrification technology and the good outcomes obtained in assisted reproductive technologies have supported new indications for freezing and segmentation of treatment. Still there are some controversies regarding evidence that suggest that freeze-all is not "for all," but should be individualized.

We are thankful to experts who have given their valuable contribution. on this topic of fresh versus frozen embryo transfers . You will also find all the academic activities done under the aegis of IFS during the period between July – Sept 2020 . Many of these are still available online for you to access . Many of our members presented their work this year at virtual ESHRE 2020 . You will get a glimpse some of these presentations .

We welcome our members to contribute scientific content in forth coming issues of IFS conversation. we will be more than happy to publish all your academic achievements & awards at national or international level.

Happy reading !

Dr. Shweta Mittal Gupta
Editor, IFS

Dr. Rashmi Sharma
Joint Editor, IFS

INVITED ARTICLES

Should we "cool off" all embryos? indications for segmental IVF

Dr Shweta Mittal
Senior consultant, Centre of IVF & Human Reproduction
Sir Ganga Ram Hospital
Email: mshwets@hotmail.com

The freeze-all strategy ia a popular alternative to fresh embryo transfer (ET) during in vitro fertilization (IVF) cycles. Success of IVF depends not only on embryo quality, but also on endometrial receptivity. Embryo-endometrium interaction and alteration in uterine milieu due to supraphysiological hormonal levels, which occurs during ovarian stimulation, may bring about reduction in IVF results due to change in histological pattern of endometrium,stromal glandular dyssynchrony and altered expression of adhesion molecules like integrins1,2 especially after fresh embryo transfer, when compared to frozen embryo transfers (FET). This would ultimately lead to not only reduction in pregnancy rates but also poorer obstetrical & perinatal outcomes.The concept of delaying embryo transfer to a frozen cycle can overcome the deleterious effects of controlled ovarian stimulation over the endometrium , therby improving outcomes 3,4.In the freeze-all strategy, the entire cohort of embryos is cryopreserved (not just the "second best"), and the best embryos are transferred in a later cycle into a more physiologic endometium5

Indications for "Freeze all "

A fresh cycle in which all suitable embryos are frozen is known as a 'freeze-all' or 'freeze-only' cycle. With improved success of embryo cryopreservation, the indications for embryo freezing have widened.

One of the commonest reasons for an freeze-all strategy is hyperresponders with increased risk of ovarian hyperstimulation syndrome (OHSS). If during an IVF cycle despite having high estradiol levels, hCG was administered or in case of a downregulated cycle showing hpyper response,no other alternative would be left other than administering hCG. These cycles would impose greater risk of OHSS, if in a fresh cycle embryos are transferred, resulting in pregnancy and release of endogenous hCG6. This is associated with an increase in the inflammatory mediator vascular endothelial growth factor and a prolonged, more severe clinical course of OHSS.Thus freeze-all approach prevents in such cases development of late OHSS. Cochrane meta-analysis suggests that if the rate of OHSS is 7% following fresh transfer, in the freeze-all approach it is 1–3% when triggered with hCG even in normal responder group7.

All IVF cycles triggered with GnRH agonist without low dose hCG supplementation,would require elective freezing of embryos so as to optimize pregnancy rates and to avoid low pregnancy rates subsequent to premature demise of corpus luteum and defective luteal phase without presence of hCG in circulation leading to profound LH deficiency and progesterone secretion by corpus luteum.8

Blastocyst transferred on day five is more physiolgical as compared to slow-developing embryos, which become blastocysts on day 6. These day 6 embryos, if transferred in a fresh embryo transfer cycle will result in lower pregnancy rates due to advanced endometrium, out of synchrony with the endometrial window of implantation. Several studies demonstrate higher pregnancy rates when day-6 embryos are cryopreserved and resynchronised with the endometrium in a subsequent FET cycle compared with fresh transfer on day 6.9

Other indications for elective freezing of all embryos are uterine abnormality identified during ovarian stimulation (e.g. endometrial polyp identified during the cycle, fluid in the endometrium,thick or thin endometrium).Complications of egg-collection procedure (e.g. intraperitoneal bleeding, damage to viscera, pelvic infection.Social factors (unable to attend embryo transfer or need to defer pregnancy).Raised progesterone on day of trigger injection is a commonly practised strategy for elective cryopreservation of all embryos in a particular cycle.10,11

Moving towards selective single embryo transfer would further defer fresh embryo transfers as improved outcomes after embryo cryopreservation and FET have allowed IVF centres to adopt to a policy of elective single embryo transfer, while maintaining cumulative live-birth rates.This would tremendously reduce chance of multiple pregnancy. 12

Planned freeze-all is a commonly practised policy in patients undergoing IVF with the use of pre-implantation genetic testing, wherein embryos can be biopsied and cryopreserved, while genetic analysis is undertaken.It also allows accumulating more embryos especially in cases of PGT for monogenic disorders and in advanced maternal age before proceeding for genetic analysis. Elective cryopreservation of all embryos is a viable option for fertility preservation in those due to undergo gonadotoxic therapy. There has been an increasing trend towards freezing all embryos when dealing with cases of recurrent implantation failure.

Unplanned elective freezing	Planned elective freezing
Risk of ovarian hyperstimulation	Preimplantation genetic testing
Uterine abnormality like endometrial polyp,fluid,thick/thin endometrium etc	Fertility preservation
High progesterone of day of trigger	Recurrent implantation failure
GnRH agonist trigger without hCG rescue	
All blastocysst formed on day 6	

Table 1: Summary of indications for elective freezing of all embryos

Why has embryo freezing increased ?

Improved embryology techniques 13,14,15

Moving from initial technique of slow freeze for embryos to vitrification has changed the embryo survival rates. Vitrification is faster and more convenient, taking only minutes and not requiring large, expensive equipment. Moreover, a cohort study of more than 30 000 FET demonstrated a higher live-birth rate per cycle started for vitrified versus slow frozen embryos, with meta-analysis data supporting these findings.

In order to reduce multiple pregnancies and to observe embryo growth beyond the stage of embryonic arrest,more embryos are frozen at blastocyst stage. Evidence suggests improved live-birth rates following transfer of embryos cryopreserved at the blastocyst stage compared with embryos at cleavage stages.

To conclude:

IVF practices have changed tremendously over a period of last decade. Though there are valid indication for freeze all policy for embryos, though not all patients should be offered freeze all strategy barring indications, which absolutely makes it essential to freeze so as to either bring better health and safety to the patient or to improve cahnce of pregnancy16. Additionally all legal & ethical issues pertaing to embryo cryopreservation should be kept in mind before offering this strategy.

References:

1. Nikas G, Develioglu OH, Toner JP, Jones HW. Endometrial pinopodes indicate a shift in the window of receptivity in IVF cycles. Hum Reprod 1999; 14: 787– 92.

2. Thomas K, Thomson A, Wood S, Kingsland C, Vince G, Lewis-Jones I. Endometrial integrin expression in women undergoing in vitro fertilization and the association with subsequent treatment outcome. Fertil Steril 2003; 80: 502– 7.

3. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. Fertil Steril 2011; 96: 516– 8.

4. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Ross R. Contrasting patterns in in vitro fertilization pregnancy rates among fresh autologous, fresh oocyte donor and cryopreserved cycles with the use of day 5 or day 6 blastocysts may reflect differences in embryo-endometrium synchrony. Fertil Steril 2008; 89: 20– 6.

5. Roque M, Lattes K, Serra S, Solà I, Geber S, Carreras R, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril 2013; 99: 156– 62

6. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med 2016; 375: 523– 33.

7. Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. Cochrane Database Syst Rev 2017; 3: CD011184.

8. Lass A, Peat D, Avery S, Brinsden P. Histological evaluation of endometrium on the day of oocyte retrieval after gonadotrophin-releasing hormone agonist-follicle stimulating hormone ovulation induction for in-vitro fertilization. Hum Reprod1998; 13: 3203– 5.

9. Shapiro BS, Richter KS, Harris DC, Daneshmand ST. A comparison of day 5 and day 6 blastocyst transfers. Fertil Steril 2001; 75: 1126– 30.

Shapiro BS, Garner FC. Recurrent implantation failure is another indication for the freeze-all strategy. Fertil Steril 2017; 108: 44.

10. Ochsenkühn R, Arzberger A, von Schönfeldt V, Gallwas J, Rogenhofer N, Crispin A, et al. Subtle progesterone rise on the day of human chorionic gonadotropin administration is associated with lower live birth rates in women undergoing assisted reproductive technology: a retrospective study with 2,555 fresh embryo transfers. Fertil Steril 2012; 98: 347– 54

11. Healy MW, Patounakis G, Connell MT, Devine K, DeCherney AH, Levy MJ, et al. Does a frozen embryo transfer ameliorate the effect of elevated progesterone seen in fresh transfer cycles? Fertil Steril 2016; 105: 93– 9.e1.

12. McLernon DJ, Harrild K, Bergh C, Davies MJ, De Neubourg D, Dumoulin JCM, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ 2010; 341: c6945.

13. Li Z, Wang YA, Ledger W, Edgar DH, Sullivan EA. Clinical outcomes following cryopreservation of blastocysts by vitrification or slow freezing: a population-based cohort study. Hum Reprod 2014; 29: 2794– 801.

14. Edgar DH, Gook DA. A critical appraisal of cryopreservation (slow cooling versus vitrification) of human oocytes and embryos. Hum Reprod Update 2012; 18: 536– 54.

15. Rienzi L, Gracia C, Maggiulli R, LaBarbera AR, Kaser DJ, Ubaldi FM, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum Reprod Update 2017; 23: 139– 55.

16. Maheshwari A, Pandey S, Amalraj Raja E, Shetty A, Hamilton M, Bhattacharya S. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? Hum Reprod Update 2018; 24: 35– 58.

Opportunities and threats presented by " Universal freeze all policy ".

Dr Rashmi Sharma
Director, Origyn Fertility and IVF
Joint Editor, Indian Fertility Society
Email: drrashmisharma73@gmail.com

Opportunities

The Biggest benefit of freeze all strategy or segmental IVF is that Segmentation can profoundly eliminate the risk of OHSS. With the use of GnRH agonist trigger and freeze-all strategy ,there is no doubt that it leads to drastic decrease in OHSS.(1)

However the question is that, If the OHSS risk is within acceptable limits with a low or intermediate oocyte yield (<15 oocytes retrieved) than is it ok to overgeneralize the results to the entire population ? So, the other proposed but controversial benefits of freeze all strategy are better live birth rates and better maternal and perinatal outcomes in frozen embryo transfers. Dr Ruma has beautifully compiled the outcome of various studies in her article regarding live birth rates in fresh vs frozen embryo transfers. The consensus till now is that freeze all policy leads to better live birth rates in hyper responder patients, but there is no difference in normal or poor responder patients.

Possible proposed mechanism for lower pregnancy rate in fresh transfers in hyper-responder patients is negative impact of controlled ovarian stimulation due to supraphysiological estradiol (E2) and progesterone (P) levels, on endometrial receptivity. Many molecular, genetic and morphological studies have supported this suggestion . Another proposed mechanism for better ART outcome in frozen cycles is that physical effects of freezing and thawing may filter out embryos with borderline quality. This would allow more robust embryos to survive and develop, also resulting in more optimal fetal growth .

Another argument given in favour of freeze all policy is better maternal and perinatal outcomes . Dr Renu has compiled evidence about this in her article .Pregnancies resulting from FET are associated with lower relative risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality compared with fresh ET but with increased risks of pregnancy-induced hypertension, postpartum hemorrhage, and large for gestational age compared with fresh ET. (2,3) Absence of corpus luteum in endometrial preparation with hormone replacement therapy has been suggested as the reason of increased risk for PIH , because corpus luteum does not only produce estrogen and progesterone but also produces lots of metabolites and vasoactive products which may be essential for proper placentation .

large retrospective cohort studies have shown that frozen-thawed embryo transfers, both at cleavage and blastocyst stages, significantly reduce the rate of ectopic pregnancy.(4,5,6,)

Side benefits of "freeze all policy" -

1. It offers possibility of initiating ovarian stimulation on any given day of the menstrual cycle as we are not bothered with taking care of endometrial receptivity in that particular cycle (7,8).It has been seen that there is no difference in reproductive outcomes when stimulation was initiated in the luteal phase(9).This makes more room for logistical treatment changes to accommodate both the scheduling restrictions of physicians, IVF lab and the patient
2. Another side benefit is that it allows for a different approach to prevent premature LH surge and avoidance of injection shots like use of oral medroxyprogesterone acetate (MPA) or Clomiphene in place of antagonist injections .Less injections and cost consequent to avoidance of antagonist injections means an enormous improvement in the quality of life for women undergoing IVF. (10)

Threats presented by freeze all policy

1. Generalization of results to normal and poor responders as well in the absence of evidence
2. Cost increment due to additional freezing and thawing .
3. Increased time to pregnancy
4. Many patients may discontinue treatment without transfer at all – patient drop out.
5. More PIH, PPH, Macrosomia
6. Centre specific – robust cryopreservation program is a must before going for universal freezing .

References

1. Bosdou JK, Venetis CA, Tarlatzis BC, Grimbizis GF, Kolibianakis EM (2019) Higher probability of live-birth in high, but not normal, responders after first frozen-embryo transfer in a freeze-only cycle strategy compared to fresh-embryo transfer: a meta-analysis. Hum Reprod 34: 491–505.

2. Sha T,Yin X ,Cheng W, Massey IY .Pregnancy-related complications and perinatal outcomes resulting from transfer of cryopreserved versus fresh embryos in vitro fertilization: a meta-analysis. Fertil Steril,2018 Feb;109(2):330-342.

3. Maheshwari A, Pandey S, Raja EA, Shetty A, Hamilton M, Bhattacharya S.Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? Hum Reprod Update 2018 Jan 1;24(1):35-58.

4. Ishihara, Kuwahara A ,Saitoh H. Frozen-thawed blastocyst transfer reduces ectopic pregnancy risk: an analysis of single embryo transfer cycles in Japan.Fertil Steril ,2011;95:1966–1969.

5. Shapiro BS, DaneshmandST, De Leon L, Garner FC, Aguirre M, Hudson C. Frozen-thawed embryo transfer is associated with a significantly reduced incidence of ectopic pregnancy. Fertil Steril.2012;98:1490–1494.

6. Z. Li, E.A. Sullivan, M. Chapman, C. Farquhar, Y.A. Wang .Risk of ectopic pregnancy lowest with transfer of single frozen blastocyst .Human Reproduction, Volume 30, Issue 9, September 2015:Pages 2048–2054,

7. Sonmezer M , Turkuoglu I , Coskun U , Oktay K.Random start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles .Fertil Steril ,May 2011;Vol 95,Issue 6: P2125.

8. Ozkaya E , Roman GS , Oktay K .J Assist Reprod Genet. 2012 Jun; 29(6): 503–505.

9. Chen H, Wang Y, Lyu Q, Ai A, Fu Y, Tian H, Cai R, Hong Q, Chen Q, Shoham Z, Kuang Y. Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovarian stimulation for in vitro fertilization and vitrified embryo transfer cycles. Fertil Steril. 2015;103:1194–1201

10. Kuang YP, Chen QJ, Fu YL, et al. Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Fertil Steril 2015; 104:62–70.

Universal freeze-all policy and its association with live-births. A critical review of literature

Dr Ruma Satwik
Consultant, Centre of IVF and Human Reproduction, Sir Gangaram Hospital, New Delhi
Email: rumasatwik@gmail.com

Freeze-all is a term used to define the strategy of cryopreserving the entire cohort of embryos formed after in vitro fertilization and transferring them in a later cycle into a more physiologic endometrium. [1] Freeze-all has been practised traditionally in cycles at-risk for OHSS, asynchronous donor-recipient-cycles, PGT cycles, poor maternal well-being on the day of transfer, endometrial issues, (cavity fluid, too thick or too thin) or inability to transfer on account of cervical stenosis. However, the UNIVERSAL FREEZE-ALL strategy advocates freezing the entire embryo cohorts despite the absence of aforementioned causes. The UNIVERSAL FREEZE-ALL strategy as we know it today, was conceived in order to overcome a possible negative influence of supraphysiological steroids witnessed in fresh transfers on implantation and live births. This review article looks at the available evidence on whether a strategy of UNIVERSAL FREEZE-ALL would benefit couples with respect to the outcomes of live births and whether it works equally in different profiles of women undergoing frozen embryo transfer. It also attempts to critically look at evidence on what are the possible short-term and long-term harms of such a strategy.

Rationale of Universal Freeze-all

Controlled Ovarian Stimulation (COS) aiming at multiple folliculogenesis is an inseparable part of modern In Vitro Fertilization (IVF) programmes. This helps in optimizing results for the couple since it is known that livebirths after IVF have a strong correlation with the numbers of retrieved oocytes. [2] However, altering the norm of monofollicular ovulation is not without adverse effects. Multiple follicular development as a result of COS leads to supraphysiological estrogen levels, which on an average reach ten times than what is seen in natural cycles. Similarly, progesterone, a product of corpus luteum is secreted in higher quantities after COS than in a natural cycle, corresponding with the numbers of corpora lutea formed. It is known that endometrial development under the influence of estrogen followed by progesterone is highly synchronized with the arrival of a competent blastocyst by day five or six of ovulation.[3] This synchrony between the endometrium and embryo is vital to successful implantation. [4] It has been observed that supraphysiological steroid levels induced by COS, cause endometrial development to be accelerated, possibly via altered steroid receptor expression in late follicular phase [5]. This amounts to an incremental degree of embryo endometrial asynchrony that is likely to negatively affect implantation. Indeed, in clinical situations, evidence from various retrospective studies suggests that frozen transfers yield higher implantation, ongoing pregnancies and live births than fresh transfers –––– –''–––––––[1,68].

The adverse effects of supraphysiological steroids in fresh embryo transfer cycles is not restricted to implantation alone but also extends to the perinatal

period. Higher peri-implantation progesterone, responsible for endometrial advancement, also causes alterations in trophoblastic differentiation, expansion and invasion leading to sub-normal placentation in COS cycles.[9][10]. The results of a meta-analysis involving 11 observational studies in singleton pregnancies have shown that adverse perinatal outcomes occur at a higher frequency in pregnancies resulting from fresh embryo transfers versus frozen embryo transfers. The relative risks (RR) of antepartum hemorrhage (RR = 0.67, 95% CI 0.55–0.81), preterm birth (RR = 0.84, 95% CI 0.78–0.90), small for gestational age (RR = 0.45, 95% CI 0.30–0.66), low birth weight (RR = 0.69, 95% CI 0.62–0.76), and perinatal mortality (RR = 0.68, 95% CI 0.48–0.96) were lower in women who received frozen embryos.[11]

What are the indicators of embryo-endometrial asynchrony?

It has been seen that endometrial advancement by 3 days or more seems to affect endometrial receptivity and subsequent likelihood of achievement of pregnancy [12][13]. It is also known that natural cycles have a window of implantation that can stretch over three to four days. The question to be answered is whether the level of embryo-endometrial asynchrony in stimulated cycles is always such that the broad window of implantation is unable to adjust for endometrial advancement. Is it possible to identify then, which IVF cycles after COS, would suffer an extreme level of asynchrony to affect implantation and what are the indicators of this asynchrony?

Progesterone elevation (PE), erroneously referred to earlier as premature luteinization, is defined as high hCG day serum progesterone, and has been used as a surrogate marker widely for determining embryo-endometrial asynchrony, with threshold values varying widely from 0.4ng/ml to 2.5ng/ml in various studies. Lower threshold values have been used for low responders and higher values for high responders [14]. Additionally, some authors have found the use of progesterone to estrogen ratio to be theoretically reasonable over using hCG day progesterone alone. [15,16] Many others have not considered the issue of progesterone elevation significant enough to effect a change in their transfer policy.[17-20]

What is the quantum of effect of progesterone elevation on live births?

We get our first detailed insight into the association of PE with achievement of pregnancy in fresh transfers, through Venetis et al 's superbly conducted synthesis of all available evidence on the matter in 2013. [21] That this study should be compulsory reading for all reproductive medicine specialists as an exercise in research methods is a matter for another piece, but what can be said for the purpose of this review is that it synthesized evidence from 68 studies (eleven prospective and remaining retrospective) published between 1990-2012, involving more than 60,000 cycles of fresh and frozen embryos. The criteria for studies to be included were that it should have reported on 1) controlled ovarian stimulation with gonadotropins alone either in agonist or antagonist cycles in IVF, 2) hCG day progesterone levels and 3) clear outcomes of either clinical pregnancies, ongoing pregnancies or live births. Till then PE thresholds for attaining clinical pregnancies reported in various studies ranged from anywhere between 0.4ng/ml to 2.5ng/mL, chosen either arbitrarily or based on previous study thresholds. This metaanalysis found a negative association between PE and achievement of pregnancy, the strongest risk existing for PE above 1.5ng/mL. They quantified this risk as a 10% absolute reduction in clinical pregnancies when women having hCG day progesterone above 1.5ng/ml, underwent a fresh transfer versus when a freeze-all approach was adopted. The incidence of PE varied with the threshold chosen being 17% for PE > 1.5ng/ml. To give a clinically meaningful interpretation to this finding, they said that if the annual pregnancy rate of a centre were to be 40%, and progesterone elevation occurred in 17% of cycles totally and all underwent fresh transfers, the pregnancy achievement rate would drop from 40% to 38.3% for that centre in that year.

Amongst the secondary outcomes studied, there was a significant positive corelation of PE with agonist cycles versus antagonist, dose of gonadotropins, hCG day estradiol levels and retrieved oocyte numbers. The authors however failed to find an association between duration of gonadotropin treatment, whether hyper, average or poor responder, or type of gonadotropin used (rec FSH, hMG, LH addition) with PE.

It is left to the readers to discern how significant that change in annual live births from 40% to 38.3% in their practice is, but as it happened, the trend of universal-freeze all spread like wild-fire in most centres of the world through the middle of last decade.

Like most meta-analysis involving retrospective studies, this one too suffered from heterogeneity and although the authors attempted to tackle different confounders in a very systematic way, evidence from large, randomized controlled clinical trials dealing with a uniform population and uniform intervention on the subject at hand was still lacking. Data on progesterone elevation threshold so far, had been derived from retrospective studies, non-randomized prospective studies or from retrospective analysis of data collected for an RCT evaluating a different research question. As of now, any threshold value of PE does not seem reasonable enough to pursue a freeze-all policy. And decisions based on progesterone estrogen ratio, rate of progesterone rise and progesterone threshold values based on ovarian response will have to wait till large scale RCTs are undertaken on that subject.

Does freeze-all benefit a specific category of patients?

Two landmark randomized controlled trials, both adequately powered, employing a homogenous population (same patient characteristics), using uniform intervention (receiving the same type of protocol and gonadotropin, embryo transfers at the same stage) and having uniform outcomes (live births) addressing the issue were published in 2016 and then in 2018. These trials changed the way we thought about Universal freeze-all policy. . The first study asked the question whether in PCOS women defined by Rotterdam's criteria, the policy of universal freeze-all followed by transfer of embryos in a subsequent cycle would yield higher live births than when transferring embryos in fresh cycles. It randomized a total of 1508 PCOS women on the day of oocyte retrieval who were not at risk of ovarian hyperstimulation syndrome (OHSS) to receive up to two day 3 embryos in fresh cycle or in frozen cycle using hormone replacement. A significant improvement in live births was found in favour of women undergoing frozen embryo transfers in this population. (49% vs. 42%, RR: 1.17; 95%CI= 1.05-1.31). This was attributable largely to a significant lowering of miscarriages in frozen transfers versus fresh transfers. (22.0% vs. 32.7%, RR: 0.67; 95% CI= 0.54-0.83).

The second trial conducted by the same group asked the question whether the policy of freeze all would increase live births over fresh transfers in OVULATORY women. They randomized 2158 ovulatory women, on the day of oocyte retrieval who were not at risk of developing OHSS to receive fresh

day3 embryos or frozen day 3 embryos in subsequent NATURAL cycles. The results changed the existing perception about frozen embryo transfers. The live-birth rate did not differ significantly between the frozen-embryo group and the fresh-embryo group (48.7% and 50.2%, respectively; RR: 0.97; 95% CI 0.89-1.06).

As expected, frozen transfers resulted in a significantly lower rate of OHSS vs. fresh transfers in both PCOS women (1.3% vs. 7.1%, RR: 0.19; 95% CI=0.10 to 0.37) and in ovulatory women (0.6% vs. 2.0%; RR:0.32; 95% CI=0.14-0.74).

However, there appeared to be a three times higher rate of preeclampsia in the frozen embryo transfer group of PCOS women. (4.4% vs. 1.4%, RR: 3.12; 95% CI=1.26-7.73). The study also found a higher rate of neonatal death and still births in the frozen transfer group, attributable to prematurity, although this was not significantly so. The adverse perinatal outcomes were not any different amongst ovulatory women undergoing fresh or frozen ET.

This trend of elevated risk for preeclampsia with frozen embryo transfers is worrying and merits a discussion. There is increasingly accumulating evidence, that this risk exists in hormonally replaced cycles '[24] and not in natural cycles, exonerating the embryo freezing process as being responsible in its pathogenesis. In cycles where uterine preparation with exogenous estrogen and progesterone is undertaken, processes involved in natural ovulation are suppressed leading to a lack of corpus luteum. One of the corpus luteal product is relaxin which is responsible for maternal cardiovascular adaptation to pregnancy. Absence of corpus luteum and therefore relaxin leads to a blunted maternal cardiovascular adaptation to pregnancy resulting in a higher risk of preeclampsia. [25,26] This finding should encourage reproductive medicine specialists to move from transferring frozen embryos in artificially prepared uterus to naturally prepared uterus amongst the population of ovulatory women.

How does the rate of embryonic development or embryo-stage affect their performance in fresh and frozen cycle?

The window of receptivity in fresh transfers is expected to close early due to endometrial advancement. This phenomenon might affect slow growing embryos more, so that day six blastocysts might have poorer implantation rates in fresh cycles than in frozen cycles. [27] In a retrospective

The data on childhood cancer is for now scarce, considering the rarity of this condition and it can only come from stringently maintained population-based data over several decades. A retrospective cohort study based on Danish population-based registry data and the Danish Infertility Cohort (individual record linkage) that included 1085172 children born in Denmark between January 1, 1996, and December 31, 2012, has found that the risk of childhood cancer, mainly leukemia and sympathetic nervous system tumours, increases by an average of 2.4 times after frozen embryo transfer versus after natural conception. [31] The study duration suggests enrolment at a time when slow freezing was the norm in most clinics of the world. There have been concerns raised with the study's findings in that this risk might not be applicable to vitrification, the current standard in most IVF clinics. But as of now there is no hard data to exonerate vitrification from any long term adverse effects on offspring health.

analysis of 3391 single blastocysts transfers, the sustained implantation rates of slow growing D5 blastocysts were significantly lower than normally growing D5 blastocysts in fresh cycles. (44% versus 64% in women <35 years of age (P < 0.001) and 18% versus 56% in women ≥35 years of age (P < 0.001)). However, when slowly blastulating embryos underwent vitrification and then ET, they had implantation rates which were equivalent to their normally blastulating counterparts. [28] This normalization in cryopreserved ETs indicates that dyssynchrony may be a major adverse factor limiting outcomes with late blastulating embryos in fresh cycles.

A large randomized controlled trial that enrolled 1650 OVULATORY women assessed the benefit of freeze-all strategy with single BLASTOCYST transfers. ––[29] Earlier trials had shown no difference in live births with the adoption of freeze-all in ovulatory women undergoing day 3 embryo transfers. Could Day 5 embryos perform differently in the frozen cycle versus the fresh? This trial's findings contrasted with those done for day3 embryos in that the live births were significantly higher in ovulatory women undergoing FROZEN SINGLE BLASTOCYST transfers versus those undergoing fresh single blastocyst transfers. (50% vs 40%; RR 1·26, 95% CI 1·14-1·41). Thus supporting the hypothesis that the window of implantation might close early for some blastocysts in fresh cycles but continues to remain open to day 3 embryos.

Long term Adverse effects of embryo freezing

As data on babies born after embryo freezing accumulates, two negative observations about the embryo freezing process have come to fore. The first is an increased risk of fetal macrosomia [30] and second is a small but significant increase in the risk of childhood cancers [31]. The risk of fetal macrosomia with frozen transfers has been the subject of over twelve studies and a synthesis of evidence from these studies reveals the odds for fetal macrosomia with frozen embryo transfers to be increased 1.7-fold compared to fresh transfer (AOR = 1.71 95% CI 1.59–1.83 p< 0.001) and 1.4-fold compared to natural cycle (AOR = 1.42 95% CI 1.17–1.71 p< 0.001) ––––[32]. This risk has been seen in large population based studies too (derived from the Nordic database) and exists irrespective of the freezing

technique whether slow or vitrification. [33] Epigenetic modifications induced in the embryo during the culture and freezing process have been thought to be responsible for this.

Conclusions

This review concludes that

- Universal freeze-all policy does not benefit all subsets of women in terms of improving live-births. The hyper-responding PCOS woman, benefits from the universal freeze-all policy not only in terms of an improved chance of live births (+17% over baseline), but largely through an approximately 80% reduction in OHSS. That should be something to strive for. There is no advantage gained in the ovulatory woman however, with the universal freeze-all policy, barring prevention of OHSS.
- As of now, there are no reliable markers such as hCG day progesterone, progesterone-estrogen ratio etc. to determine embryo-endometrial asynchrony.
- Slow growing blastocysts or day 6 blastocysts would probably do poorly in fresh transfers and it is wiser to pursue a freeze-all policy especially if a single blastocyst is all that is available for transfer.
- One would also have to consider the increased costs involved, the increased time to pregnancy, the logistics of storing extra embryos and certainly not the least of all, the long term effects of embryo freezing process on the offspring before offering freeze-all approach in any category of patients.
- The experience of a laboratory with embryo freezing either slow or vitrification, is an important factor determining success of the freeze-all policy. Unless a clinic audits their own data and prove beyond reasonable doubt that their frozen transfer results are vastly improved over fresh transfers, they should not advocate the universal freeze-all policy uninhibitedly.

BIBLIOGRAPHY

[1] Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Freeze-all policy: Fresh vs. frozen-thawed embryo transfer. Fertil Steril 2015;103:1190–3. https://doi.org/10.1016/j.fertnstert.2015.01.045.
[2] Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011;26:1768–74. https://doi.org/10.1093/humrep/der106.
[3] Bergh PA, Navot D. The impact of embryonic development and endometrial maturity on the timing of implantation. Fertil Steril 1992;58:537–42. https://doi.org/10.1016/s0015-0282(16)55259-5.
[4] K. Diedrich, B.C.J.M. Fauser, P. Devroey GG. Role of the endometrium and embryo in human implantation | Human Reproduction Update | Oxford Academic. Hum Reprod Update 2007;13:365–77. https://doi.org/https://doi.org/10.1093/humupd/dmm011.
[5] Papanikolaou EG, Bourgain C, Kolibianakis E, Tournaye H, Devroey P. Steroid receptor expression in late follicular phase endometrium in GnRH antagonist IVF cycles is already altered, indicating initiation of early luteal phase transformation in the absence of secretory changes. Hum Reprod 2005;20:1541–7. https://doi.org/10.1093/humrep/deh793.
[6] Boynukalin FK, Turgut NE, Gultomruk M, Ecemis S, Yarkiner Z, Findikli N, et al. Impact of elective frozen vs. fresh embryo transfer strategies on cumulative live birth: Do deleterious effects still exist in normal & hyper responders? PLoS One 2020;15. https://doi.org/10.1371/journal.pone.0234481.
[7] Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. Fertil Steril 2011;96:516–8. https://doi.org/10.1016/j.fertnstert.2011.02.059.
[8] Liu X, Bai H, Shi W, Shi J. Frozen-thawed embryo transfer is better than fresh embryo transfer in GnRH antagonist cycle in women with 3–10 oocytes retrieved: a retrospective cohort study. Arch Gynecol Obstet 2019;300:1791–6. https://doi.org/10.1007/s00404-019-05373-9.
[9] Mainigi MA, Olalere D, Burd I, Sapienza C, Bartolomei M, Coutifaris C. Peri-implantation hormonal milieu: Elucidating mechanisms of abnormal placentation and fetal growth. Biol Reprod 2014;90:26. https://doi.org/10.1095/biolreprod.113.110411.

[10] E Labarta 1, J A Martínez-Conejero, P Alamá, J A Horcajadas, A Pellicer, C Simón EB. Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis - PubMed. Hum Reprod 2011;26:1813–25.
[11] Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment:

A systematic review and meta-analysis. Fertil Steril 2012;98:368-377.e9. https://doi.org/10.1016/j.fertnstert.2012.05.019.
[12] Ubaldi F, Bourgain C, Tournaye H, Smitz J, Van Steirteghem A, Devroey P. Endometrial evaluation by aspiration biopsy on the day of oocyte retrieval in the embryo transfer cycles in patients with serum progesterone rise during the follicular phase. Fertil Steril 1997;67:521–6. https://doi.org/10.1016/S0015-0282(97)80080-5.
[13] Kolibianakis E, Bourgain C, Albano C, Osmanagaoglu K, Smitz J, Van Steirteghem A, et al. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pick-up. Fertil Steril 2002;78:1025–9. https://doi.org/10.1016/S0015-0282(02)03323-X.
[14] Xu B, Li Z, Zhang H, Jin L, Li Y, Ai J, et al. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: An analysis of more than 10,000 cycles. Fertil Steril 2012;97. https://doi.org/10.1016/j.fertnstert.2012.03.014.
[15] Lee FK, Lai TH, Lin TK, Horng SG, Chen SC. Relationship of progesterone/estradiol ratio on day of hCG administration and pregnancy outcomes in high responders undergoing in vitro fertilization. Fertil Steril 2009;92:1284–9. https://doi.org/10.1016/j.fertnstert.2008.08.024.
[16] Mariano Mascarenhas 1, Mohan Shashikant Kamath 1, Achamma Chandy 1 ATK. Progesterone/Estradiol Ratio as a Predictor in the ART Cycles with Premature Progesterone Elevation on the Day of hCG Trigger - PubMed. J Reprod Infertil 2015;16:155–61.
[17] Hofmann GE, Bentzien F, Bergh PA, Garrisi GJ, Williams MC, Guzman I, et al. Premature luteinization in controlled ovarian hyperstimulation has no adverse effect on oocyte and embryo quality. Fertil Steril 1993;60:675–9. https://doi.org/10.1016/S0015-0282(16)56221-9.
[18] Hofmann GE, Khoury J, Johnson CA, Thie J, Scott J. Premature luteinization during controlled ovarian hyperstimulation for in vitro fertilization-embryo transfer has no impact on pregnancy outcome. Fertil Steril 1996;66:980–6. https://doi.org/10.1016/S0015-0282(16)58693-2.
[19] Martínez F, Coroleu B, Clua E, Tur R, Buxaderas R, Parera N, et al. Serum progesterone concentrations on the day of HCG administration cannot predict pregnancy in assisted reproduction cycles. Reprod Biomed Online 2004;8:183–90. https://doi.org/10.1016/S1472-6483(10)60514-7.
[20] Ubaldi F, Camus M, Smitz J, Bennink HC, Van Steirteghem A, Devroey P. Premature luteinization in in vitro fertilization cycles using gonadotropin-releasing hormone agonist (GnRH-a) and recombinant follicle- stimulating hormone (FSH) and GnRH-a and urinary FSH.
[21] C.A. Venetis, E.M. Kolibianakis, J.K. Bosdou BCT. Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles | Human Reproduction Update | Oxford Academic. Hum Reprod Update 2013;19:433–57.
[22] Chen Z-J, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome. N Engl J Med 2016;375:523–33. https://doi.org/10.1056/NEJMoa1513873.
[23] Shi Y, Sun Y, Hao C, Zhang H, Wei D, Zhang Y, et al. Transfer of Fresh versus Frozen Embryos in Ovulatory Women. N Engl J Med 2018;378:126–36. https://doi.org/10.1056/NEJMoa1705334.
[24] Dall'Agnol H, García Velasco JA. Frozen embryo transfer and preeclampsia: where is the link? Curr Opin Obstet Gynecol 2020;32.
[25] Singh B, Reschke L, Segars J, Baker VL. Frozen-thawed embryo transfer: the potential importance of the corpus luteum in preventing obstetrical complications. Fertil Steril 2020;113:252–7. https://doi.org/10.1016/j.fertnstert.2019.12.007.
[26] Von Versen-Hoÿnck F, Schaub AM, Chi YY, Chiu KH, Liu J, Lingis M, et al. Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. Hypertension 2019;73:640–9. https://doi.org/10.1161/HYPERTENSIONAHA.118.12043.
[27] Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Ross R. Contrasting patterns in in vitro fertilization pregnancy rates among fresh autologous, fresh oocyte donor, and cryopreserved cycles with the use of day 5 or day 6 blastocysts may reflect differences in embryo-endometrium synchrony. Fertil Steril 2008;89:20–6. https://doi.org/10.1016/j.fertnstert.2006.08.092.
[28] Franasiak JM, Forman EJ, Patounakis G, Hong KH, Werner MD, Upham KM, et al. Human Reproduction Open. Hum Reprod Open 2018;2018:1–6. https://doi.org/10.1093/hropen/hoy022.
[29] Wei D, Liu JY, Sun Y, Shi Y, Zhang B, Liu JQ, et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. Lancet 2019;393:1310–8. https://doi.org/10.1016/S0140-6736(18)32843-5.
[30] Pinborg A, Henningsen AA, Loft A, Malchau SS, Forman J, Andersen AN. Large baby syndrome in singletons born after frozen embryo transfer (FET): is it due to maternal factors or the cryotechnique? Hum Reprod 2014;29:618–27. https://doi.org/10.1093/humrep/det440.
[31] Hargreave M, Jensen A, Hansen MK, Dehlendorff C, Winther JF, Schmiegelow K, et al. Association between Fertility Treatment and Cancer Risk in Children. JAMA - J Am Med Assoc 2019;322:2203–10. https://doi.org/10.1001/jama.2019.18037.
[32] Berntsen S, Pinborg A. Large for gestational age and macrosomia in singletons born after frozen/thawed embryo transfer (FET) in assisted reproductive technology (ART). Birth Defects Res 2018;110:630–43. https://doi.org/10.1002/bdr2.1219.
[33] Ernstad EG, Spangmose AL, Opdahl S, Henningsen AKA, Romundstad LB, Tiitinen A, et al. Perinatal and maternal outcome after vitrification of blastocysts: A Nordic study in singletons from the CoNARTaS group. Hum Reprod 2019;34:2282–9. https://doi.org/10.1093/humrep/dez212. Fertil Steril 1996;66:275–80. https://doi.org/10.1016/S0015-0282(16)58453-2.

Maternal and Perinatal Outcomes in Fresh vs Frozen Embryo Transfer

Dr Renu Tanwar
Professor & IVF Consultant
Deptt of Obs & Gyn
Maulana Azad Medical College
Email: drrtanwar@gmail.com

Priyanka Khandey

Introduction

Frozen embryo transfer (FET) has become a successful technique for in vitro fertilization (IVF) cycles. The use of frozen embryo transfer is increasing worldwide in last decade for the treatment of infertility, so the proportion of children conceived after FET is steadily increasing.[1] With the improvements in cryopreservation techniques, introduction of vitrification method and different frozen embryo transfer (FET) regimes, the success rate has rapidly increased, and earlier evidences suggested that FET may increase pregnancy rates and improve favourable perinatal outcomes. However, the outcome of interest should be the safety of the mother and offspring and need to be evaluated cautiously.

Fresh embryo transfers cycle to Freeze-all-approach

Till date, fresh embryo transfer is the most conventional strategy in IVF cycles as it leads to shorter time interval to become pregnant. Fresh cycles are associated with increased hormonal levels due to controlled ovarian stimulation (COS). These supra-physiological hormone levels during COS result in a suboptimal uterine environment that may negatively impact embryo implantation and placentation, as potentially disrupting normal synchronous development between the endometrium and the embryo, eventually culminating to untoward obstetrical and perinatal outcomes.[2]

The number of embryos transferred during an IVF cycle is directly related to the high incidence of multiple births, which are the culprit of perinatal morbidity. Therefore, the single fresh embryo transfer (ET) strategy, or freeze-all, followed by a single frozen-thawed embryo transfer (FET) cycle, may reduce the rate of multiple births, without compromising the cumulative live birth rates (LBRs). By ensuring that any

cumulative live birth rates (LBRs). By ensuring that any surplus embryos are available for future use, it reduces pressure on patients and clinicians to transfer more than one embryo at a time and relieve stress of the couples, as additional embryos are available for future use.

Fresh embryo transfers are associated with risk of ovarian hyper-stimulation syndrome (OHSS) in hyper-responder patients. Exposure to the rising serum βhCG levels during an early pregnancy can aggravate the risk of OHSS in these women. Ovulation triggering by GnRH agonist can be a safer option, but this has been shown to affect the endometrial receptivity and lower the chances of implantation, necessitate freeze-all policy.

A newer vitrification technology has become the dominant method now a days with significantly improved embryo cryo-survival rates as compared to slow-freezing method. Studies suggest that children born after FET have similar or in most areas even better perinatal outcome compared to children born after fresh embryo transfer.[3]

Preimplantation genetic testing for aneuploidy (PGT-A) allows for better embryo selection, which improves implantation rates with single embryo transfer and reduces miscarriage rates. These IVF cycles require freezing of embryos. Advancements in extended embryo culture, blastocyst biopsy techniques, and 24-chromosome aneuploidy screening platforms have made PGT-A safe and accessible for all patients who undergo invitro fertilization.

Although an elective frozen ET strategy may appear to be a risky option specially in poor responders, as not all frozen embryos may survive the freeze-thaw process. The technical skill of the embryology laboratory is a key factor in shaping future policy for FET cycles. Freeze all approach causes financial burden over the couples and increases time to pregnancy.

A large number of studies have demonstrated that FET may lead to more favourable perinatal and neonatal outcomes but more number of randomized studies of larger size are needed to prove the superiority of FET over fresh embryo transfer cycles in term of perinatal and maternal outcomes.

Live birth rates: Fresh Vs FET cycles

Earlier studies demonstrated improved clinical pregnancy rate per transfer in the FET vs. the fresh cycles in normal responders.[4] Later, studies evaluating the effectiveness and safety of the freeze-all approach compared to the conventional IVF/ICSI didn't prove superiority of one strategy to the other in terms of cumulative LBRs.[5] Recent meta-analysis observed a significantly higher probability of live birth observed in high responders in the FET group when compared with the fresh ET group, while the probability of live birth was not significantly different between the FET group and the fresh ET group in normal responders.[6,7]

To summarize, elective FET might have an advantage in first ETs over fresh ET in good prognosis – hyper-responder patients, but not in average and certainly not in poor prognosis patients, and with no difference in cumulative LBRs.

Perinatal Outcomes: FRESH vs FET cycles

Several studies comparing children born following FET with fresh ET showed similar or even better perinatal outcomes. FET was shown to be associated with lower risk of prematurity and LBW (low birth weight) in singletons, when compared with fresh ET, whereas there is an increasing concern that children born after FET have increased risk of large for gestation age (LGA) (>90th percentile for gestational age) and/ or macrosomia (birthweight ≥4000 g).[8] Macrosomia/ LGA births have a higher risk of fetal hypoxia, stillbirth, shoulder dystocia, caesarean section, postpartum haemorrhage, perineal lacerations and neonatal metabolic disorders.[9] A meta-analysis studied the association between FET and LGA and/or macrosomia, consisting of 10 studies on LGA and six studies on macrosomia has revealed that the risk of LGA in FET was increased 1.5-fold and 1.3-fold compared to fresh cycles and natural cycles (NC) respectively. Similarly, there was 1.7-fold and 1.4-fold increased risk of macrosomia in FET compared to fresh ET and NC, respectively.[10] Whether the increased risk of LGA and macrosomia is associated with higher long-term health risks remains uncertain.

The underlying pathophysiology of increased risk of LGA and macrosomia in FET singletons remains uncertain. Several possible factors may play a role, i.e., improved uterine environment with better synchronization between embryo and endometrium, the parental characteristics and the freezing-thawing procedures per se, which might induce epigenetic changes during early embryonic stages that alter the intrauterine growth potential in FET offspring.[11]

Maternal Outcomes: Fresh vs FET cycles

Freeze all approach has few additional obstetric complications associated with FET cycles. Singleton pregnancy after FET has a higher risk of caesarean section. Relative risk of hypertensive disorders in pregnancy in the FET group was higher than in the fresh ET group (RR 1.29).[12] Another study concluded that pregnancies resulting from FET were associated with lower relative risks of placental abruption, placenta previa, LBW, PTB, SGA and perinatal mortality, as compared with fresh ET. Nonetheless, pregnancies occurring from FET were associated with increased risks of pregnancy-induced hypertension, postpartum haemorrhage and LGA, as compared with fresh ET. There were no between-group differences in the risks of gestational diabetes mellitus, preterm premature rupture of the membranes, and PTB.[13] A retrospective cohort study on endometrial preparation methods for frozen-thawed embryo transfer cycles found that patients who conceived by hormone replacement cycle/ artificial cycles (AC) had increased risks of hypertensive disorders of pregnancy and placenta accreta and a reduced risk of gestational diabetes mellitus in comparison to those who conceived by FET during a natural-cycle FET.[14] The preparation of the endometrium in hormonal replacement cycle requires medication (exogenous estrogen and progesterone), this condition might be less 'physiological' than a natural ovulatory cycle, it may modulate the risk of obstetrical complications through changes in the endometrial condition and subsequent placental development. During the implantation period, progestin plays important role in decidualization of estradiol-primed human endometrium. It also assists with extravillous trophoblast (EVT) invasion and vascular remodelling, which is essential for development of normal pregnancy. Defects or aberrance in EVT invasion can lead to obstetrical complications such as preeclampsia and placenta accreta

Conclusion

Elective FET might increase LBRs compared to fresh ET in hyper responders, but not in normal/poor responders, with comparable cumulative LBR in the overall population and lower risk of moderate/severe OHSS. Moreover, the relative risk of hypertensive disorders in pregnancy, as well as perinatal mortality due to macrosomia/ LGA were also shown to be increased in FET cycles compared with singletons from fresh ET and NC.

When considering elective freeze-all policy, in addition to LBR and the risk of OHSS, physicians should consider the aforementioned increased FET cycles' pregnancy complications including LGA/macrosomia, caesarean section, hypertensive disorders of pregnancy, postpartum haemorrhage as well as, perinatal mortality. Hence freeze all policy should not be offered to all patients but only to those patients who may benefit from this strategy.

References

1. Pereira N, Rosenwaks Z. A fresh(er). Perspective on frozen embryotransfers. Fertil Steril. 2016;106(2):257–8.

2. Roque M, Valle M, Kostolias A, Sampaio M, Geber S. Freeze all cycle inreproductive medicine: current perspectives. JBRA Assist Reprod. 2017; 21:49-53

3. Roque M, Lattes K, Serra S, Sola I, Geber S, Carreras R, et al. Freshembryo transfer versus frozen embryo transfer in in vitro fertilization cycles:a systematic review and meta-analysis. Fertil Steril 2013; 99: 156-162.

4. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinicalrationale for cryopreservation of entire embryo cohorts in lieu of freshtransfer. Fertil Steril. 2014. 102:3–9.

5. Wong KM, vanWelyM, Mol F, Repping S, Mastenbroek S. Fresh versus frozenembryo transfers in assisted reproduction. Cochrane Database Syst Rev. (2017)2017:CD011184. doi: 10.1002/14651858

6. Bosdou JK, Venetis CA, Tarlatzis BC, Grimbizis GF, Kolibianakis EM. Higherprobability of live-birth in high, but not normal, responders after firstfrozen-embryo transfer in a freeze-only cycle strategy compared to fresh embryotransfer: ameta-analysis. Hum Reprod. 2019; 34:491–505.

7. Roque M, Haahr T, Geber S, Esteves SC, Humaidan P. Fresh versus electivefrozen embryo transfer in IVF/ICSI cycles: a systematic review and metaanalysisof reproductive outcomes. Hum Reprod Update. 2019; 25:2–14.

8. Zhang J, Du M, Li Z,Wang L, Hu J, Zhao B, et al. Fresh versus frozenembryo transfer for full-term singleton birth: a retrospective cohort study. JOvarian Res. 2018; 11:59.

9. Bukowski R, Hansen NI, Willinger M, Reddy UM, Parker CB, Pinar H, et al.Human Development Stillbirth Collaborative Research Network. Fetal growth andrisk of stillbirth: a population-based case-control study. PLoSMed. 2014; 11: e1001633.

10. Berntsen S, Pinborg A. Large for gestationalage and macrosomia in singletons born after frozen/thawed embryo transfer (FET)in assisted reproductive technology (ART). Birth Defects Res. 2018; 110:630–43.

11. Orvieto R, Kirshenbaum M and Gleicher N(2020) Is Embryo Cryopreservation Causing Macrosomia—and What Else? Front.Endocrinol. 11:19. doi: 10.3389/fendo.2020.00019

12. Maheshwari A, Raja EA, Bhattacharya S.Obstetric and perinatal outcomes after either fresh or thawed frozen embryo transfer:an analysis of 112,432 singleton pregnancies recorded in the humanfertilisation and embryology authority anonymized dataset. Fertil Steril. 2016;106:1703–8.

13. Sha T, Yin X, Cheng W, Massey IY.Pregnancy-related complications and perinatal outcomes resulting from transferof cryopreserved versus fresh embryos in vitro fertilization: a meta-analysis.Fertil Steril. 2018; 109:330–42.

14. Saito K, Kuwahara A, Ishikawa T, Morisaki N, Miyado M,Miyado K, et al. Endometrial preparation methods for frozen-thawed embryotransfer are associated with altered risks of hypertensive disorders ofpregnancy, placenta accreta, and gestational diabetes mellitus. Hum

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VIBRATE MEETINGS

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Genital Tuberculosis

Dr. Neena Malhotra
MD, DNB, FRCOG (UK)
Consultant Reproductive Medicine and Infertility Professor
Department of Obstetrics and Gynecology -
All India Institute of Medical Sciences,
New Delhi-110029

Date:- 14th July 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Genital Tuberculosis**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **14th July 2020** for LIVE Event.
6. Already registered members can directly sign in, click on **"Genital Tuberculosis"** and view the LIVE Event

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WHEN TO OFFER IVF TO YOUR PATIENTS

Dr. K. D. Nayar
MD, DGO, Dip. Obst (Ireland), FICOG
Chief Consultant & HOD - Akanksha IVF Centre
Mata Chanan Devi Hospital, New Delhi
President Elect, IFS (2020-2022)
Chair Scientific Committee - Fertivision 2020

Date:- 28th July, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click **"When to offer IVF to your Patients"**
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **28th July 2020** for LIVE Event.
6. Already registered members can directly sign in, click on **"When to offer IVF to your Patients"** and view the LIVE Event

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AZOOSPERMIA

Dr. Prof (Col) Pankaj Talwar, VSM
Designation - Head medical services (Fertility and IVF) CK Birla Hospital, Gurgaon
Director - ARTech Director
Director - i-HOMaa Fertility and Child Care
Sr. Vice President - Indian Fertility Society
Founder Secretary General - Fertility Preservation Society of India
Honorary Senior Consultant & Professor Department of Reproductive Medicine of Pacific Medical College & Hospital, Udaipur.

Date:- 05th Aug, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click **"Azoospermia"**
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **05th August 2020** for LIVE Event.
6. Already registered members can directly sign in, click on **"Azoospermia"** and view the LIVE Event

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ULTRASOUND HOW USEFUL IN INFERTILITY ?

Dr. Sonal Panchal
MD. (Radiology).
Master of Ultrasound in Obstetrics and Gynecology
Consultant Sonography Specialist at Dr. Nagori's Institute for Infertility and IVF, Ahmedabad
Professor - Dubrovnik International University, Croatia

Date:- 11th Aug, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click **"Ultrasound - How useful in infertility ?"**
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **11th August 2020** for LIVE Event.
6. Already registered members can directly sign in, click on **"Ultrasound - How useful in infertility ?"** and view the LIVE Event

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Fibroids And Infertility

Dr. Renu Misra
MBBS, MS, MNAMS
Senior Consultant
Endoscopic surgery & IVF
Sitaram Bhartia Institute of Science & Research
Miracles Fertility & IVF, Gurgaon
Former Additional Professor, All India Institute of Medical Sciences, New Delhi

Date:- 19th Aug, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Fibroids And Infertility**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **19th August 2020** for LIVE Event.
6. Already registered members can directly sign in, click on "**Fibroids And Infertility**" and view the LIVE Event

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Poor Responders

Dr. (Mrs.) Umesh N. Jindal
MD OBGYN PGI Chandigarh 1980
Director : Jindal IVF, Chandigarh
Former Asst. Professor : PGIMER, Chandigarh
Former fellow : University of Washington, Seattle & RSA Kansas city, USA
Organizing Secretary on National Conferences: ISAR 2007, Fertivision 2008, Fertiprotect 2019
Organizing chairperson for Fertivision 2020

Date:- 25th Aug, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Poor Responders**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **25th August 2020** for LIVE Event.
6. Already registered members can directly sign in, click on "**Poor Responders**" and view the LIVE Event

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Endometriosis and Infertility

Dr. K.U. Kunjumoideen
MD, DNB
Consultant - IVF Specialist
ARMC IVF Kozhikode & Perinthalmanna
Joint Secretary, Indian Fertility Society
President, Perinthalmanna OG Society

Date:- 02nd Sep, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Endometriosis and Infertility**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **02nd September 2020** for LIVE Event.
6. Already registered members can directly sign in, click on "**Endometriosis and Infertility**" and view the LIVE Event

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Common errors in infertility practice management : How to tackle?

Dr Bharati Dhorepatil
DNB, DGO, FICS, FICOG, Dip Endoscopy (Germany)
IVF Consultant : NOVA IVF , Fertility Pune
Head of gynecology Dept. - Shree Hospital, Pune
Vice President - IFS
National Vice President - FOGSI India, 2016
Past President - POGS
Past President - IMA, Pune
Ex Chairperson - Clinical Research Committee, FOGSI
Natiobal Corresonding Ediot - Indian OD & GYN Journal
Founder Executive Member - Gyn Endocrine Society, India
Founder Chapter Secrretary - West. Maharashtra Chapter, IFS
Executive Editor - Journal FSR
FOGSI Star Awardee - 2016

Date:- 08th Sep, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Common errors in infertility practice management : How to tackle?**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **08th September 2020** for LIVE Event.
6. Already registered members can directly sign in, click on "**Common errors in infertility practice management : How to tackle?**" and view the LIVE Event

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Intrauterine Insemination

Dr. Shweta Mittal Gupta
Senior Consultant
Centre of IVF and Human Reproduction
Sir Ganga Ram Hospital
New Delhi-110060
Editor: Indian Fertility society (IFS)
Treasurer: AOGD,2020

Date:- 16th Sep, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Intrauterine Insemination**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **16th September 2020** for LIVE Event.
6. Already registered members can directly sign in, click on "**Intrauterine Insemination**" and view the LIVE Event

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Gonadotropins in infertility

Prof Surveen Ghumman Sindhu
Director and Head - IVF & Reproductive Medicine Centre
Max multispeciality hospitals, Delhi and Gurgaon
Professor, School of Health Sciences, Ansal University
Treasurer IFS

Date:- 22nd Sep, 2020 **Time:-** 3:00pm IST.

Steps to view the Webinar

Go to Link:- www.docmode.org/ifs

1. Scroll down and under "ALL LECTURES" Click on the desired lecture.
2. Click "**Gonadotropins in infertility**"
3. This will take you to the lecture page. Now click on **"Enroll"**.
3. Register as Doctor and fill all * Required Details
4. Verify by clicking on Link sent to you by Email
5. Once registered - You can Login on **22nd September 2020** for LIVE Event.
6. Already registered members can directly sign in, click on "**Gonadotropins in infertility**" and view the LIVE Event

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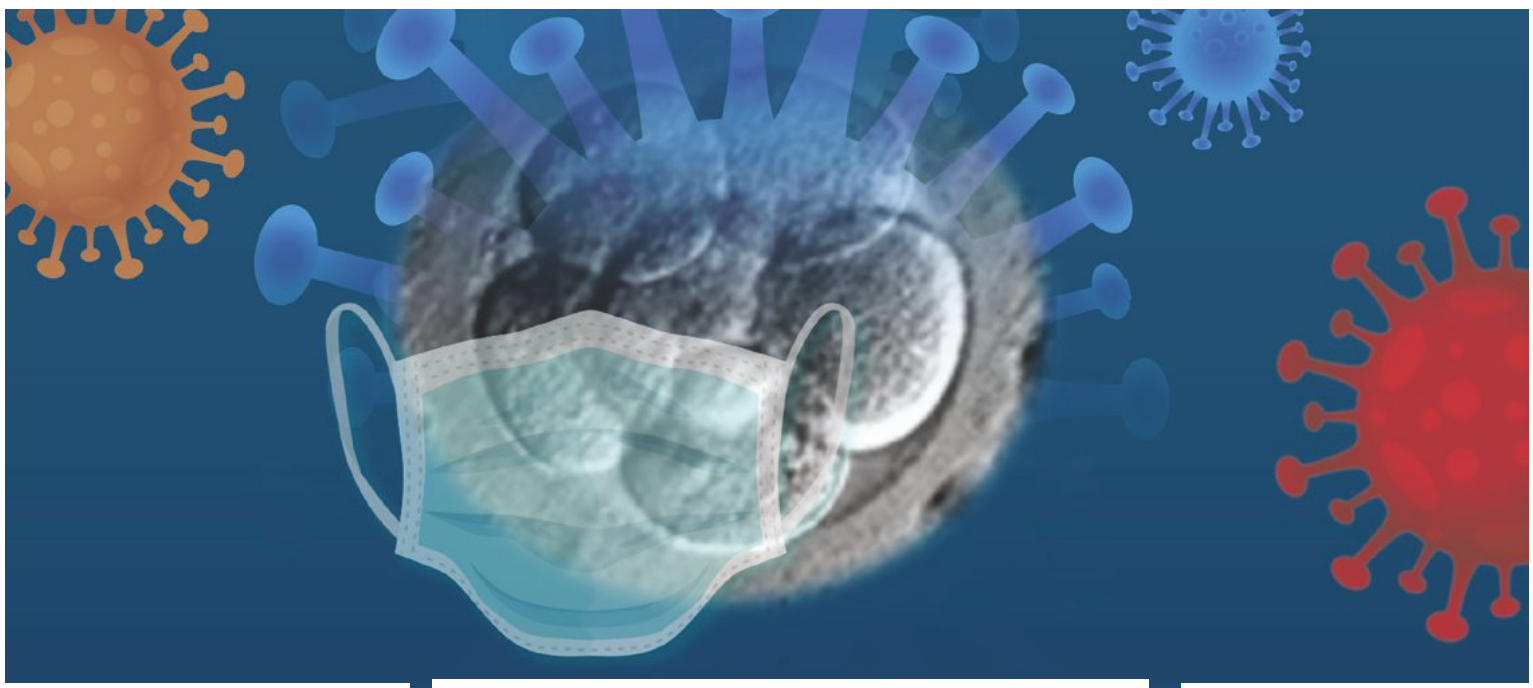
JOINT IFS-ISAR-ACE RECOMMENDATIONS ON RESUMING/OPENING UP ART SERVICES



Indian Society for Assisted Reproduction

For Details Visit
www.indianfertilitysociety.org

IFS ACTIVITIES 2020
CHAPTER ACTIVITIES

Tamil Nadu Chapter
Date: 3 July, 2020

Chhattisgarh Chapter
Date: 8 July, 2020

Rajasthan Chapter
Date: 11 July, 2020

Punjab Chapter
Date: 22 July, 2020

Karnataka Chapter
Date: 31 July, 2020

Bihar Chapter
Date: 23 August, 2020

IFS ACTIVITIES 2020
CHAPTER ACTIVITIES

Uttarakhand Chapter
Date: 27 August, 2020

UP Chapter
Date: 29 August, 2020

Gujarat Chapter
Date: 30 August, 2020

Rajasthan Chapter
Date: 1 September, 2020

Western UP Chapter
Date: 20 September, 2020

Chhattisgarh Chapter
Date: 26 September, 2020

IFS ACTIVITIES 2020
SIG ACTIVITIES

IFS SIG- Ultrasound
Date: 1 July, 2020

IFS SIG- Research Methodology
Date: 3rd and 4th September, 2020

IFS SIG- PCOS
Date: 12 September, 2020

IFS SIG- Endoscopy
Date: 13 September, 2020

IFS ACTIVITIES 2020
INTERNATIONAL WEBINAR

Abbott

INDIAN FERTILITY SOCIETY

ARTiculating EXPERT VIEWS ON IVF

TOPIC: **Decoding Luteal Phase Support**

DATE: **SAT, 4th JULY, 2020** TIME: **6.00 - 7.30** P. M. (IST)

Indian expert

PROF. DR. SUDHA PRASAD
MD, FICOG, FICMCH
President, IFS
Past Vice President FOGSI 2019
Director Matritava, Advanced IVF & Training Centre, New Delhi

Speaker

Program moderator

DR. SONIA MALIK
DGO, MD, FICOG, FIAMS
Director, Southend Fertility & IVF Centres, New Delhi
Past President, IFS (2014-16)

International Expert

PROF. DR. JOHNNY. T. AWWAD
MD, FASC, HCLD/TS (ABB)
Professor of Obstetrics and Gynecology
American University of Beirut Medical Center

AGENDA

TOPIC	SPEAKER	DURATION
Introduction of Speakers & Context setting	Dr. Sonia Malik	5 mins
Optimizing controlled ovarian stimulation in IVF: Impact on oocyte number and quality	Prof. Dr. Sudha Prasad	20 mins
Decoding luteal phase support: Impact of the right progesterone on success rates	Prof. Dr. Johnny. T. Awwad	40 mins
Q& A	Prof. Dr. Johnny. T. Awwad, Prof. Dr. Sudha Prasad, Dr. Sonia Malik	20 mins
Vote of Thanks	Dr. Sonia Malik	5 mins

CLICK ON THE LINK TO REGISTER
https://webstream.streamcart.com/live/abbottint040720

INDIAN FERTILITY SOCIETY
Presents
"THE STALWARTS SPEAK"
INTERNATIONAL WEBINAR ON OVARIAN STIMULATION (OS)

Pioneers in REPRODUCTIVE MEDICINE Go Live to Discuss

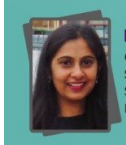
- ESHRE Guidelines for OS in High Responders
- OS In Low Reserve Patients.
- How Many Eggs Do We Need For Fertility Preservation?
- A Quality Management Approach To OS In ART

SAVE-THE-DATE
Saturday
18 July, 2020
06:00 - 08:00 PM IST
12:30 - 02:30 PM GMT
2:30 - 04:30 PM CET

SPEAKERS

Dr. Robert Fischer
Medical Director,
Fertility Center
Hamburg, Germany

Dr. Michael Grynberg
Head, Reproductive Medicine & Fertility Preservation,
University Hospital Antoine Béclère
Clamart, France



Dr. Sesh Kamal Sunkara
Consultant Gynecologist &
Sub-specialist Reproductive Medicine,
Senior Clinical Lecturer in Reprodictive Medicine,
King's College , London, UK

Dr. Mathues Roque
Scientific Director
MATER PRIME - Reproductive Medicine
São Paulo, Brazil

Members of **POSEIDON GROUP**

R.S.V.P.

Dr. Sudha Prasad
President, IFS
Matritava- Advance IVF and Training Centre, New Delhi | India

Dr. Neena Malhotra
Secretary General, IFS
ART Centre AIIMS
New Delhi | India

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Meeting ID: 867 9567 4666
Password: 753611

IFS SECRETARIAT
302, 3rd Floor, Kailash Building, 26, Kasturba Gandhi Marg C.P. New Delhi - 110001
www.indianfertilitysociety.org indianfertilitysocietydelhi@gmail.com indianfertilitysociety

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IFS ACTIVITIES 2020
MISCELLANEOUS

INDIAN FERTILITY SOCIETY

eCME Organized by Abbott In Collaboration with Indian Fertility Society (North Zone)

Abbott

Dr. Sudha Prasad
President, IFS

Dr. Neena Malhotra
General Secretary, IFS

Date: 30th JULY 2020 (Thursday)

Time: 04:00pm to 05:00pm

Recurrent Pregnancy Loss and Thrombophilia: Case Based Discussion

Moderators

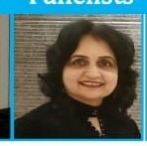
Dr. Leena Wadhwa
Additional Joint Secretary, IFS

Dr. Rashmi Sharma
Joint Editor, IFS

Panelists

Dr. KD Nayar
President Elect, IFS

Dr. Swati Verma
Secretary, Chandigarh IFS



Dr. Bharti Joshi
Assistant Prof, OBG, Chandigarh

Dr. Surveen Ghumman
Treasurer, IFS

Dr. Pikee Saxena
Professor, ObGyn Delhi

Updates in Dydrogesterone Use in Clinical Practice
Dr. Gautam Arora
Regional Medical Advisor
Women's Health Division
Abbott India Limited

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Join

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SANOFI

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INDIAN FERTILITY SOCIETY

Dr. Sudha Prasad
IFS President

Dr. Neena Malhotra
IFS General Secretary

A power packed session to share insights on

'MANAGEMENT OF MALE INFERTILITY – AN OVERVIEW'

Moderator & Chairperson

Dr. M Gouri Devi
MD – Obstetrics, Gynae and Infertility specialist,
Director, Gouri Hospitals Ltd, Ridge Fertility & IVF Centre, Delhi
President Indian Fertility Society (2018-2020)

Speakers

Dr. Kuldeep Jain
Director, KJIVF and laparoscopy centre Delhi
Past President, IFS

Dr. Vineet Malhotra
MS, DNB(Urology)
Clinical Director – Urology, Andrology and Male Health Specialist,
Diyos Hospital, New Delhi

Block your date

10th July, 2020 | 4:00 PM – 5:00 PM

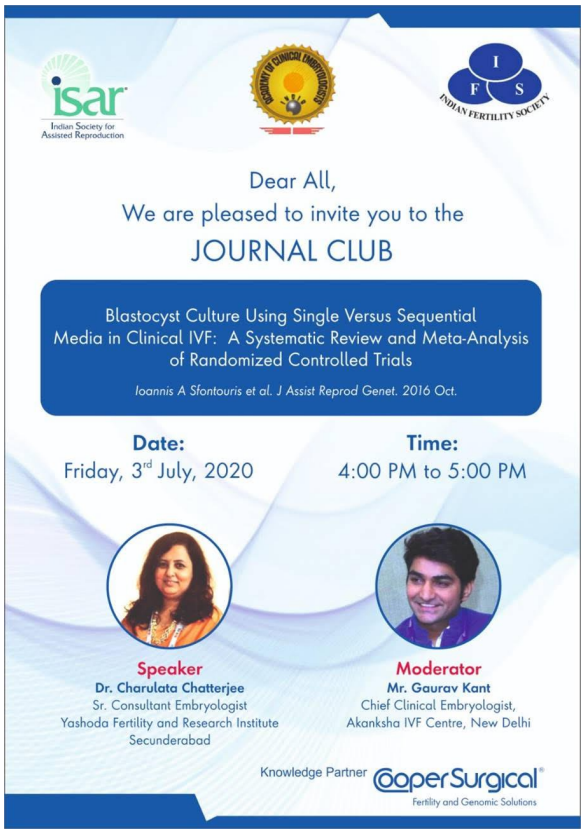
Agenda

Topic	Speaker	Time
Introduction	Dr. M Gouri Devi	4:00 PM – 4:10 PM
Medical management of male infertility	Dr. Kuldeep Jain	4:10 PM – 4:30 PM
Surgical intervention in male infertility	Dr. Vineet Malhotra	4:30 PM – 4:50 PM
Q & A session	Dr. Kuldeep Jain & Dr. Vineet Malhotra	4: 50 PM – 5:00 PM

JOURNAL CLUB
ISAR-ACE-IFS, JOINT ACTIVITY

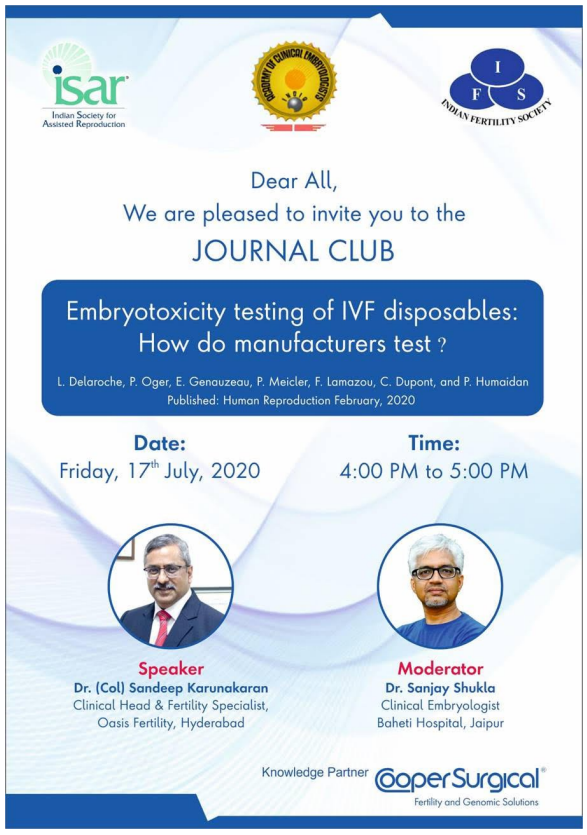
Date: 3rd July, 2020
Presented By: Dr Charulata Chatterjee
Moderator: Mr Gaurav Kant

Topic: "Blastocyst Culture Using Single Versus Sequential Media in Clinical IVF: A Systematic and Meta-Analysis of Randomized



Date: 17th July, 2020
Presented By: Dr Sandeep Karunakaran
Moderator: Dr Sanjay Shukla

Topic: "Embryotoxicity testing of IVF disposables: How do manufacturers



Date: 3rd July, 2020
Presented By: Dr Keshav Malhotra
Moderator: Dr Rutvij Dalal

Topic: "The effects of Storage time after vitrification on pregnancy and Neonatal outcomes among 24,698 patients following the first embryo transfer cycles."

IFS ACTIVITIES 2020
OTHER JOINT ACTIVITY

Date: 28th August, 2020
Convener - Dr Roya Rozati
Co-Convener - Dr Ambuja

Topic: "Managing Infertility in Aged Women"

INTERNATIONAL PRESENTATION FROM IFS MEMBERS

ESHRE Poster 1

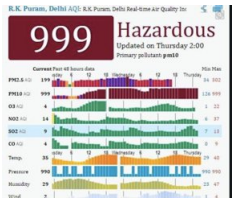
AKANKSHA IVF CENTRE

Effect of Hazardous Air Quality Index on Embryo Development in an IVF laboratory in New Delhi, INDIA

G. Kant1, K.D. Nayar1, M. Singh1, S. Draboo1, H. Sharma1, F. Khan1, S. Gupta1, R. Bhattacharya1, D. Nayar1.
1Akanksha IVF Centre, Reproductive Medicine, New Delhi, India.

QUESTION: Does the hazardous atmospheric air can impact embryo development in the IVF laboratory even after standard air quality management and use of air filters?

STUDY ANSWER: There was a decrease in key performance indicators of IVF lab with increased fragmentation, poor embryo development and reduced reproductive outcome.

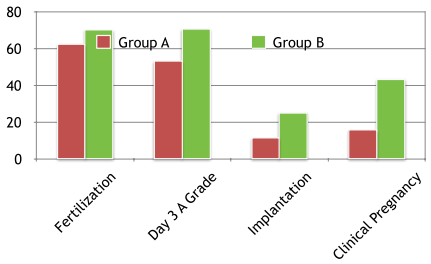


AQI in November 2019 New Delhi India

WHAT IS KNOWN ALREADY:According to WHO survey amongst 1650 cities in the world, Delhi the capital has worst air quality. With the air quality index falling drastically from Moderate (101-200) level between January to September to severe or hazardous (500+) level from October to December. The factors for poor air quality is stubble burning, road dust, cold weather and vehicle pollution.

Studies have supported that air quality is critical to embryo development and for overall success of IVF. Both animal and human studies have suggested an association between poor air quality conditions and impaired embryo development, resulting in decreased implantation and pregnancy rate.

DESIGN: A retrospective study was conducted from 1st January to 31st December 2019. Patients were divided in 2 groups. Group (A) from October to December, when atmospheric air quality was hazardous and Group (B) patients from January to September, when atmospheric air quality was within normal range. Both groups were compared on the basis of fertilisation rate, fragmentation rate, Day 3 grade A embryo development rate, implantation rate and clinical pregnancy rate.



PARTICIPANTS/ MATERIALS, SETTING, METHODS: All patients undergoing fresh day 3 embryo transfers from the month of January to December were included. Out of the total 276 patients, 60 patients had their embryo transfer in the month of October to December (study group), while 216 were those from month of January to September (control group). Same culture media was used throughout the period. There was no change in clinical or embryology team.

Image of pollution in New Delhi

MAIN RESULTS AND THE ROLE OF CHANCE: The average AQI in Delhi was recorded around 500 between October to December 2019, while the maximum was recorded more than 1200. The quality of atmospheric air was correlating with the quality of embryo development. In group A (Oct-Dec), higher fragmentation rate was observed over Group B. Fragmentation rate was significantly higher in Group A <10% : 53.03% vs 70.6%; p= 0.00001), 10-20% (30.80% vs. 18.78%; p=0.0002), >20% (16.16% vs 10.6%; p=0.029) than Group B. There was also a statistically significant decline in fertilization rate (62.5% vs. 70.07%, p=0.008), Day 3 A grade embryo formation rate (53.03% vs 70.6%; p=0.00001), Implantation rate (11.6% vs 25%; p=0.011), Clinical Pregnancy rate (15.7% vs 43.1%; p=0.025).

LIMITATIONS, REASONS FOR CAUTION: Multi centric studies are needed to strengthen these results.

WIDER IMPLICATIONS OF THE FINDINGS: We have demonstrated that poor atmospheric air during October to December in Delhi INDIA has a negative impact on embryo development which also decreases reproductive outcome even after standard air quality management. During this period either case can be avoided or more stringent air quality should be maintained.

REFERENCES:
1. Esteves SC, Bento FC. Air quality control in the ART laboratory is a major determinant of IVF success. Asian J Androl. 2016;18(4):596-599. doi:10.4103/1008-682X.166433

2. Morbeck DE. Air quality in the assisted reproduction laboratory: a mini-review. J Assist Reprod Genet. 2015;32(7):1019-1024. doi:10.1007/s10815-015-0535.

ESHRE Poster 2

AKANKSHA IVF CENTRE

A prospective randomised control study comparing reproductive outcome of day 5 Quarter laser zona thinning assisted hatching (qLZT-AH) in frozen thawed embryo transfers.

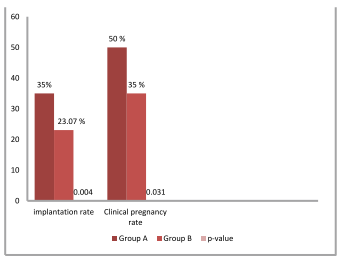
H. Sharma[1], K.D. Nayar[1], G. Kant[1], S. Draboo[1], M. Singh[1], R. Bhattachrya[1], S. Gupta[1], K.D. Nayar[1].
[1]Akanksha IVF Centre- Mata Chanan Devi Hospital, Reproductive Medicine, New Delhi, India.

QUESTION: Can quarter zona laser thinning assisted hatching (qLZT-AH) improve reproductive outcome in day 5 frozen embryo transfer cycles?

STUDY ANSWER: Quarter Laser thinning assisted hatching on day 5 frozen thawed embryos is associated with improved implantation rate, clinical pregnancy rate over no assisted hatching.

WHAT IS KNOWN ALREADY: Hatching is a process where blastocyst escape the Zona pellucida(ZP) membrane prior to implantation. This is accomplished in-vivo by secretion of hatching factors and lysine production by trophectoderm of embryo but in in-vitro fertilisation when embryos are frozen under ultra low temperature may lead to zona hardening. This may inhibit or reduce the chances of spontaneous hatching. With the advent of laser assisted hatching (LAH), this complication could be overcome with focussed laser light to produce opening in ZP with a single pulse of few millisecond, with no mechanical, thermal or mutagenic side effect.

DESIGN: A prospective randomised control study was conducted from 1st January to 31st December 2019. All patients whose embryos were frozen on day 5 were included. Two hundred patients were randomised by computer generated list and divided into 2 groups. Group A (n=100), in which embryos were thawed on day 5 and Quarter laser zona thinning assisted hatching (qLZT-AH) was done while in group B (n=100) no laser assisted hatching was done after thawing.



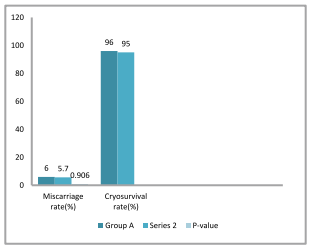
MATERIALS AND METHODS: All normoresponder patients whose embryos were frozen on day 5 were included in this study and patients with endometrium pathologies were excluded. Quarter laser zona thinning assisted hatching (qLZT-AH) was performed after thawing in group A, where 25% of surface area and 50% thickness is removed by using laser while in group B no laser assisted hatching was done. Groups were compared on the basis of implantation rate, clinical pregnancy rate and miscarriage rate.

RESULTS: None of the Frozen embryo transfer cycle was cancelled and no loss of embryo was reported during thawing process. The cryosurvival rate was 96% in group A and 95% in group B which is in the range of cryopreservation key performance indicators. No significant difference in female age, BMI and AMH was observed between the two groups.

There was a statistically significant increase in implantation rate (35% vs. 23.07%, p=0.004) and clinical pregnancy rate (50% vs. 35%, p=0.031) in group A, when day 5 frozen thawed transfers assisted with qLZT-AH was done, while no difference in miscarriage rate (6% vs. 5.70%, p=0.906) was found.

LIMITATIONS: Larger randomised control studies are needed to strengthen these results.

WIDER IMPLICATION: We have demonstrated that day 5 frozen thawed transfers assisted with quarter laser zona thinning assisted hatching is better over no hatching. This study can strengthen the current trend of freezing more potent blastocyst stage and applying qLZT-AH can further improves the results.



REFERENCES: Ali J, Rahbar S, Burjaq H, Sultan AM, Al Flamerzi M, Shahata MA. Routine laser assisted hatching results in significantly increased clinical pregnancies. J Assist Reprod Genet. 2003;20:177–181.

INTERNATIONAL PRESENTATION FROM IFS MEMBERS

ESHRE Poster 3

AKANKSHA IVF CENTRE

Transdermal testosterone vs oral dehydroepiandrosterone (DHEA) pre-treatment in improving IVF outcomes in diminished ovarian reserve patients (POSEIDON group 3 and 4): A randomized controlled trial

N. Sharma[1], K.D. Nayar[1], S. Gupta[1], M. Singh[1], R. Bhattacharya[1] , G. Kant[1] , R. Gahlot[1], K.D. Nayar[1]
[1]Akanksha IVF Centre - Mata Chanan Devi Hospital, Reproductive Medicine, New Delhi, India

INTRODUCTION

Diminished ovarian reserve (DOR) is associated with poor ovarian response, higher cycle cancellation rate and lower clinical pregnancy rate following IVF cycles. Use of adjuvants like androgens in the form of oral tablets or transdermal gel has been advocated. Androgens improve follicular response to gonadotropin stimulation, increase the FSH receptor expression in granulosa cells, leading to better oocyte yield and pregnancy rates. With the introduction of POSEIDON classification, selection of expected poor responders has been made uniform and universal and helps to compare outcomes among various clinical trials being conducted on the same patient group. Oral DHEA has been found to improve clinical pregnancy rate in the recent metanalysis when given in dose of 75mg/day for 3months and more. The efficacy of bioactive androgen, testosterone, has also been evaluated and found to improve clinical outcomes when given for minimum 3-4 weeks prior to stimulation. Transdermal route delivers testosterone in a more physiological way than the oral route, maintaining steady concentration of plasma testosterone for 24 h following application. There has been no study comparing efficacy of oral DHEA with transdermal testosterone in patients who are expected poor responders because of low ovarian reserve.

OBJECTIVES

Our aim was to compare the effect of transdermal testosterone gel with oral DHEA on the ART outcomes in POSEIDON group 3 and 4 patients.

MATERIALS AND METHODS

A prospective, randomised controlled trial was carried out from 1st January 2019 to 31st October 2019 at a tertiary infertility centre in India. Fifty patients fulfilling the criteria of Group 3 and Group 4 of POSEIDON classification were included in the study. Patients with endocrine disorders (thyroid, prolactin), endometrioma, history of surgery on the ovaries, sensitivity to testosterone gel, male factor infertility and deranged liver and renal function tests were excluded. Patients were randomized into two groups of 25 patients each, one group was pre-treated with transdermal testosterone gel (TTG group),12.5 mg/day from day 6th of previous cycle to day 2nd of stimulation cycle while patients in other group took DHEA tablet,75 mg/day for three months (DHEA group) before stimulation.

GnRH antagonist fixed protocol was followed for COH in all patients. Recombinant HCG (250µg) was used as ovulation trigger followed by ovum pick up 34-36 hours later. It was followed by fresh day 3 embryo transfer.

RESULTS

Baseline characteristics like age, BMI, duration of infertility and hormonal levels including AMH, TSH, prolactin were comparable between TTG and DHEA group.

Table 1: Cycle characteristics in TTG and DHEA group

Parameters	TTG Group (n=25)	Control group (n=25)	P value
Total gonadotrophin	3345.11±1223.9	3626.22±935.9	0.36
Days of stimulation	9.8±1.42	10.1±0.97	0.38
Terminal E_2	1041.37±147.2	864.86±110.7	<0.05*
No. of follicles	4.65±1.84	3.21±1.51	<0.05*
Total oocytes	5.1±1.4	3.3±1.7	<0.05*
No. of Grade A embryos	4.28±0.88	2.85±0.63	<0.05*
No. of Grade B+C embryos	1.91±1.28	1.54±1.02	0.13

CONCLUSIONS

Pre-treatment with testosterone gel in DOR patients improves ovarian response to stimulation and results in higher number of oocytes retrieved and good quality embryos as compared to oral DHEA. It is advantageous because of better bioavailability and sustained serum levels after once daily application. Clinical outcomes, however, are not improved significantly. This can further be investigated with more studies of larger sample size.

REFERENCES

- Schwarze JE, et al.(2018)DHEA use to improve likelihood of IVF/ICSI success in patients with diminished ovarian reserve: A systematic review and meta-analysis. JBRA Assist Reprod 22(4): 369-374.
- Noventa M, et al. Testosterone therapy for women with poor ovarian response undergoing IVF: a meta-analysis of randomized controlled trials. Journal of assisted reproduction and genetics. 2019; 36(4):673-683.

FIGURE 1: COMPARISON OF CLINICAL OUTCOMES BETWEEN TTG AND DHEA GROUPS

ESHRE Poster 4

AKANKSHA IVF CENTRE

Comparison of Letrozole versus Clomiphene Citrate (CC) for ovulation induction in infertile women with Polycystic ovary syndrome (PCOS) in Indian population: A prospective clinical trial

E. Gupta[1], K.D. Nayar[1], S. Gupta[1], M. Singh[1], R. Bhattacharya[1] , R. Gahlot[1], G. Kant[1], K.D. Nayar[1]
[1]Akanksha IVF Centre - Mata Chanan Devi Hospital, Reproductive Medicine, New Delhi, India

INTRODUCTION

Clomiphene citrate is a standard drug for inducing or augmenting ovulation in PCOS patients. It is not, however, equally successful in all the cases. Clomiphene resistance occurs in around 15-20% of the patients. In addition, CC may have a negative effect on the cervical mucus and endometrium.

Letrozole is an aromatase inhibitor used for ovulation induction in PCOS patients and may present as a real alternative to CC. It has a short half life (45 hours); hence, it is rapidly eliminated from the body without producing long-lasting adverse effects on cervical mucus and endometrial thickness (ET). Furthermore, it does not down regulate the estrogen receptors as compared to CC.

It has been shown to have good ovulation rate in CC-resistant PCOS women. Indian PCOS women have high prevalence of insulin resistance (~75%) and thus are likely to have high CC resistance. Letrozole could prove to be a good alternative for ovulation induction in such women.

OBJECTIVES

To compare the efficacy of Letrozole and Clomiphene Citrate for ovulation induction in infertile women with PCOS for intra-uterine insemination (IUI) cycles in Indian population.

MATERIALS AND METHODS

A prospective clinical trial on 120 infertile patients with PCOS diagnosed according to Rotterdam criteria was carried out at a tertiary care infertility centre in India from January 2019 – October 2019. These infertile women with PCOS were divided into two groups-61 patients with Letrozole, 2.5 mg/day and 59 patients with CC, 100 mg/day from day 3-7 of the menstrual cycle. Follicular monitoring was done and 10,000 IU of HCG was administered when the largest follicle was ≥18 mm. IUI was done 36-40 hours after HCG administration. 400mg micronized Progesterone was given intra-vaginally for 15 days as luteal phase support.

All the patients had atleast one patent fallopian tube diagnosed either by HSG or laparoscopy and a normal uterine cavity. Severe endometriosis, male factor infertility and patients with any other endocrinological diseases were excluded from the study.

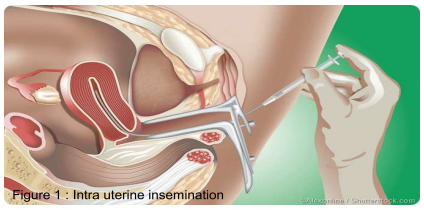


Figure 1 : Intra uterine insemination

RESULTS

Baseline characteristics in both Letrozole and CC group were comparable.

PARAMETER	LETROZOLE GROUP	CLOMIPHENE GROUP	P VALUE
Follicles ≥ 18mm on the day of HCG	1.13±0.53	2.6±1.15	**<0.0001**
ET on the day of HCG (mm)	8.21±0.86	7.35±0.99	**<0.0001**
Ovulation rate	77.04%	59.32%	0.05
Clinical pregnancy rate	14.75%	13.56%	>0.05
Multiple pregnancy rate	1.11%	2.5%	0.57

Table 1: Comparison of characteristics after ovulation induction between Letrozole and Clomiphene group

CONCLUSIONS

PCOS is among the most common endocrine disorders in women of reproductive age, with an estimated prevalence of 5%-10% of the general population, and by far the most common cause of an-ovulatory infertility. Letrozole leads to more monofollicular development and better endometrial response compared to CC. Hyperinsulinemia, which is frequently associated with PCOS, is one of the causes for CC resistance. Thus, Letrozole has an important role as first line treatment for PCOS patients.

The study was done at a single centre with small sample size. Replication with more subjects and multiple centres is needed.

REFERENCES

•Aromatase inhibitors for subfertility treatment in women with polycystic ovary syndrome
Franik S, Cochrane Database, 24 May 2018

•Systematic review and meta-analysis of letrozole and clomiphene citrate in polycystic ovary syndrome
Abdul Qadr,Middle East Fertility Society Journal, Sep 2018

•Letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome
Airao BB et al, International Journal of Current Research, 2019

INTERNATIONAL PRESENTATION FROM IFS MEMBERS

ESHRE Poster 5

AKANKSHA IVF CENTRE

Live birth rate of patients where sperm selected using microfluidic technique in high DNA fragmentation index sperm samples.

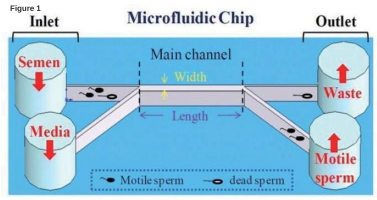
F. khan[1], K.D. Nayar[1], G. Kant[1], M. Singh[1], S. Mishra[1], S. Gupta[1], K.D. Nayar[1].
[1]Akanksha IVF Centre- Mata Chanan Devi Hospital, Reproductive Medicine, New Delhi, India.

QUESTION: Does microfluidic sorting technique help in increasing live birth rate in patient with high DNA fragmentation index (DFI) sperm samples?

STUDY ANSWER: Sperm selected by Microfluidic sorting are associated with significant increase in live birth rate, clinical pregnancy rate and reduced miscarriage rate.

WHAT IS KNOWN ALREADY: DNA damage is unrecognizable in living sperm prior to insemination and an increased sperm DNA fragmentation index has been associated with lower fertilization rates, impaired embryo development and reduced pregnancy rates. Standard semen processing techniques are associated with centrifugation, which may induce reactive oxygen species and DNA damage. Microfluidic systems are capable of working with small volume samples and have high sensitivity and low response time. This technique helps to improve the efficiency of sample preparation, enable consistency in embryo culturing and reduce human error. It has been demonstrated that Microfluidic technique could provide sperm with significantly reduced DNA damage. **Figure 1.**

Figure 1



MATERIALS AND METHODS: The study period included all normozoospermia patients with high DNA fragmentation index (>25%) while oligospermic, asthenozoospermic samples, patients with poor ovarian reserve and advanced age were excluded from the study. All A grade embryos were vitrified and transferred in frozen embryo replacement cycle. Both groups were compared on the basis of fertilization rate, day 3 grade A embryo development rate, clinical pregnancy rate, miscarriage rate and live birth rate.

RESULTS: Cycle characteristics (female age, length of stimulation, gonadotrophin dose, number of oocytes and number of transferred embryos) were similar in both groups.

Between the 2 groups, there was a significant increase observed in day 3 grade A embryo development rate (60% vs. 38%, p-0.003), clinical pregnancy rate (62% vs. 41%, p-0.004) and live birth rate (46% vs. 29%, p-0.011), while a significant decrease in miscarriage rate (12% vs. 25%, p-0.028). On the other hand, there was no statistical difference observed in fertilization rate (82% vs. 78%, p-0.80). As shown below in Chart 1.1 ,1.2 and 1.3 respectively.

LIMITATIONS: Larger randomized control studies are needed to strengthen these results.

WIDER

IMPLICATION:

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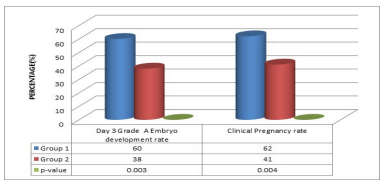
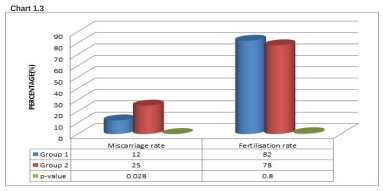
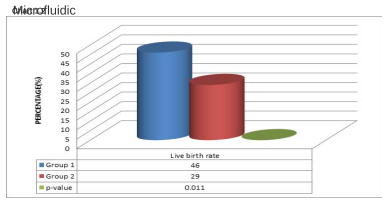


Chart 1.3



Microfluidic



REFERENCES:1. Whitesides GM. The origins and the future of microfluidics. Nature 2006; 442:368-73. 10.1038/nature05058 [PubMed] [CrossRef] [Google Scholar].

2. Nosrati R, Graham PJ, Zhang B, et al. Microfluidics for sperm analysis and selection. Nat Rev Urol 2017;14:707-30. 10.1038/nrurol.2017.175 [PubMed] [CrossRef] [Google Scholar]

DNA

but

also

ESHRE Poster 6

AKANKSHA IVF CENTRE

Empty follicle syndrome(EFS) in PCOS patients after GnRH agonist trigger at a tertiary level infertility centre in India: A prospective cohort study

K.D. Nayar[1], S. Gupta[1], M. Singh[1], R Bhattacharya[1], G. Kant[1], R. Gahlot[1], N. Sharma[1], D. Nayar[1].
[1]Akanksha IVF Centre - Mata Chanan Devi Hospital, Reproductive Medicine, New Delhi, India

INTRODUCTION

EFS is failure to retrieve oocytes after ovarian stimulation, despite normal follicular development, incidence being 0.045%–7% . EFS is diagnosed retrospectively, since it cannot be predicted by USG or hormonal levels. GnRH agonist trigger acts on the pituitary and causes gonadotropin release leading to LH surge lasting for 24-36hours in comparison to HCG trigger where it lasts for 8-9days. False EFS is mainly due to human error in timing, administration of trigger or manufacturing and cold chain problem. For genuine EFS, receptor polymorphisms, inability of the pituitary to release gonadotropins and dysfunctional folliculogenesis due to PCOS are implicated.

OBJECTIVES

To analyze the incidence and underlying physiology of EFS following GnRH agonist trigger in PCOS patients at a tertiary level infertility centre in India.

MATERIALS AND METHODS

A prospective cohort study including 225 patients diagnosed with PCOS according to Rotterdam`s criteria was carried out between January 1, 2017 through 31 December 2019. All patients underwent Controlled ovarian hyperstimulation using fixed GnRH antagonist protocol and GnRH agonist trigger. If no oocytes were retrieved from one ovary, serum progesterone levels were done to classify as genuine EFS (S. progesterone levels >3.5ng/ml) or false EFS(S. progesterone < 3.5ng/ml). In cases of False EFS, rescue hcg trigger was given and ovum pick up scheduled 35 hours after the trigger. Freeze all strategy was employed and embryo transfer done in a subsequent cycle.

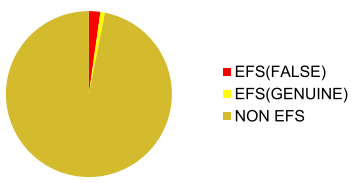


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Diagram 1. Incidence of EFS

RESULTS

Incidence of EFS in PCOS patients following GnRH agonist trigger was 3.11%(7/225). The age, BMI , parity, cause and duration of infertility were similar in EFS and non EFS group. There was no significant difference in AMH and AFC levels between the two groups. However, significantly higher doses of gonadotropins (2500±743 vs. 1850±690; p=0.02) and prolonged duration of stimulation(11.6±1.79 vs. 9.5±1.2; p=0.001) was noted in the EFS group as compared to the Non EFS group. Out of 7 EFS cases, False EFS was identified in 5 cases (71.43%) and 2 cases (28.57%) were attributed to Genuine EFS, wherein no cause was identified. Out of 5 False EFS cases, eggs were retrieved in 4 patients following rescue hcg trigger and 2 patients achieved a clinical pregnancy (40%). For Genuine EFS cases, GnRH antagonist protocol with Dual trigger was planned in the subsequent cycle. Eggs were retrieved in one patient while Genuine EFS recurred in second patient.

Although it is a prospective study, it has limitation of small sample size.

CONCLUSIONS

Our experience at a tertiary infertility care centre in India suggests that EFS is a rare occurrence in PCOS patients following GnRH agonist trigger. False EFS can have favourable outcomes following the rescue trigger and Genuine EFS is most likely attributed to intrinsic ovarian dysfunction.

	EFS 7/225 = 3.11%	Non EFS	P value
Doses of gonadotropins (IU)	2500±743	1850±690	0.02
Duration of stimulation (days)	11.6±1.79	9.5±1.2	0.001

Table 1. Comparison between EFS and Non EFS cases

REFERENCES

• Deepika K et al. Empty Follicle Syndrome Following GnRHa Trigger in PCOS Patients Undergoing IVF Cycles. J Reprod Infertil. 2018;19(1):16-25.

• Neeta Singh et al. Empty Follicle Syndrome: A Challenge to Physician. J Hum Reprod Sci. 2018 Jul-Sep; 11(3): 274–278.

INTERNATIONAL PRESENTATION FROM IFS MEMBERS

ESHRE Poster 7

Southend Fertility & IVF

eshre European Society of Human Reproduction and Embryology

Ovarian Sensitivity Index
A novel marker of ovarian responsiveness in IVF cycles

Authored by: Charu Jandial, Sonia Malik, Ved Prakash, Vandana Bhatia, Sandeep Talwar

STUDY QUESTION

To validate the use of OSI as a measure of ovarian response during IVF cycles by correlating it with other measures of ovarian response which include age, AMH, AFC, total dose of gonadotropins and quality of embryos.

SUMMARY ANSWER

OSI can be used as a dynamic marker for ovarian reserve, a guide for gonadotropin dose in future IVF cycles and a predictor of good quality embryos.

WHAT IS KNOWN ALREADY

Ovarian stimulation is an integral part of IVF and aims at producing adequate no of oocytes without increasing the risk of ovarian hyperstimulation syndrome.
In Controlled Ovarian Stimulation, different women respond differently to similar doses of exogenous gonadotropins. Preliminary studies suggested that a threshold level of gonadotropins may exist and no more competent oocytes can be obtained if exceeded. Recent studies, on the contrary, indicate that a high ovarian response to gonadotropins is not so detrimental. The key point is , not the gonadotropin dose or ovarian response alone, but a combination of these two , is important .This is the concept addressed in the ovarian sensitivity index. High OSI means, more oocytes are retrieved with fewer gonadotropin doses and offers the best pregnancy outcomes.

STUDY DESIGN, SIZE, DURATION

This is a retrospective, single centre study which included 256 women over a period of one year.

PARTICIPANTS, MATERIALS , SETTINGS , METHODS

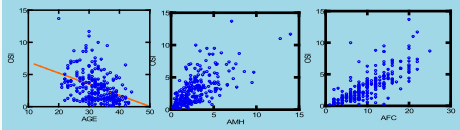
A Retrospective analysis conducted at Southend Fertility and IVF centre at New Delhi , India which included 256 women with age < 42 years , no previous history of ovarian surgery, chemotherapy/ radiation and had no evidence of endocrine disorders. A baseline scan was done in all the subjects to determine the antral follicle count. Subjects were treated with either long agonist or antagonist protocol as per the clinical and biochemical markers. Trigger injection was given when 3 or more follicles reached 18mm diameter. TVS guided OPU was done 36 hours later.

DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS IN STUDY

PARAMETERS	VALUES
AGE (years)	32 (30-37)
Type of sub fertility	
Primary	175 (68.36%)
Secondary	81(31.64%)
Duration of sub fertility (years)	4 (3-6)
Cause of sub fertility	
Male	48 (18.75 %)
Tubal	36 (14.06 %)
Endometriosis	14 (5.46 %)
Unexplained	54 (21.09 %)
Others	104 (40.62 %)

OSI	GROUP A (0.2 – 1.3)	GROUP B (1.4 – 2.6)	GROUP C (2.7–6.3)	GROUP D (6.4–18.7)
NO. OF CASES	63	65	65	63
MEAN TQE	2.73	4.04	6.27	9.50

TOP QUALITY EMBRYOS ACCORDING TO OSI



CORRELATION OF OSI & OR WITH AGE, AMH & AFC

CALCULATION OF OSI = $\frac{\text{No. of oocytes retrieved}}{\text{Total dose of FSH}} \times 1000$

MAIN RESULTS AND THE ROLE OF CHANCE

Out of 256 women enrolled in the study with a mean age of 32 years,175(68.36%) were a case of primary subfertility with an average duration of 4 years.208 women received antagonist protocol .Mean number of oocytes retrieved were 8.Statistical analysis as per Pearson's Correlation Coefficient showed a negative correlation of OSI with age and positive correlation with AMH and AFC (p value-0.0000). Further analysis of data revealed that as OSI increases the mean number of top quality embryos increases

LIMITATIONS, REASONS FOR CAUTION

A retrospective analysis, single centre, smaller group and includes patients with different protocols.

WIDER IMPLICATIONS OF THE FINDINGS

In failed IVF/ ICSI cycles, the management of future cycle can be guided by OSI. Patients with Higher values should receive same dose of FSH in future cycles while those with low OSI should receive higher dose of FSH, along with possibly considering other strategies to boost the ovarian response like change of protocol, addition of LH and use of DHEA. OSI can be used as a predictor of good quality embryos.

TRIAL REGISTRATION NUMBER

Not applicable.

designed at: www.ima-appweb.com

ESHRE Poster 8

Anti-Müllerian Hormone (AMH) Lower Reference Values Observed in a Population of Indian Women Compared to French Women, Using the Automated VIDAS® AMH Assay

Mougin Bruno. (1 *), **Kaur Jasneet.** (2), **Bourron P.** (1) **and Mahajan Nalini** (3)
(1) bioMérieux SA, 376 Chemin de l'Orme, 69280 Marcy l'Etoile - France, (2) Department of Reproductive Medicine, Mother and Child Hospital, New Delhi, India, (3) Mother and Child Hospital, New Delhi, India
* Corresponding author: bruno.mougin@biomerieux.com

BACKGROUND & OBJECTIVE

Serum AMH testing is routinely performed in female patients for the assessment of the ovarian reserve, especially in the context of controlled ovarian stimulation (COS) for assisted reproductive technology (ART), for the diagnosis of polycystic ovary syndrome (PCOS) and for other indications to assess the ovarian activity such as menopause, after laparoscopic surgery or gonadotoxic treatment. Several published studies have reported differences in age-specific AMH reference values in various countries (1-4). Reference intervals have been previously defined for VIDAS® AMH, in populations living in France and in India (5).

The objective of this study was to compare AMH reference values between two populations of women in France and in India.

METHODS

Studied populations: ***French cohort***: 435 women, age 12 to 44 years, without known pathologies, with regular menstrual cycles, not taking hormonal contraception, enrolled in 30 sites throughout France (Clinical Trial for VIDAS® AMH assay, 2016). ***Indian cohort***: 975 women aged 19-50 years with a fertility criteria (at least one natural pregnancy with a living child), presence of both ovaries, not currently using oral contraceptives and body mass index <30; exclusion criteria were PCOS (Rotterdam criteria), other endocrine disorders, endometriosis stage III-IV, who underwent adnexal surgery, tubal ligation; enrolled in New Delhi (5). For the comparison of AMH reference values, women aged 20 to 44 years were selected: 356 and 748 for the French and Indian cohorts, respectively.

AMH measurement: Serum AMH concentrations were measured on a single sample using the automated VIDAS® AMH assay (bioMérieux, Marcy L'Etoile, France). Values under the limit of detection (LoD = 0.01 ng/mL) were arbitrarily assigned to 0.005 ng/mL. Values above the range of measurement (9 ng/mL) were excluded. Statistics and linear regression modelling were done after log transformation (Analyse-It).

RESULTS

REFERENCE AMH VALUES

Table 1: Reference AMH values (ng/mL) determined in the two cohorts from India (n = 748) and from France (n = 356).

Age (years)	N	5th percentile [CI 90%]	10th percentile [CI 90%]	Median [CI 90%]	90th percentile [CI 90%]	95th percentile [CI 90%]	IQR
20 – 24	138	0.60 [0.19 ; 0.88]	0.95 [0.61 ; 1.18]	2.78 [2.52 ; 3.16]	6.33 [5.68 ; 7.27]	7.27 [6.66 ; 8.79]	2.36
	45	1.49 *	2.37 [1.28 ; 2.92]	4.29 [3.50 ; 5.01]	6.84 [6.42 ; 8.76]	7.42 *	3.25
25 – 29	163	0.65 [0.49 ; 0.83]	1.04 [0.71 ; 1.24]	2.68 [2.42 ; 3.13]	6.26 [5.45 ; 7.23]	7.33 [6.48 ; 7.88]	2.82
	81	1.34 [0.56 ; 1.55]	1.56 [1.08 ; 1.74]	3.18 [2.69 ; 3.55]	7.15 [6.15 ; 8.50]	8.41 [7.56 ; 8.83]	2.77
30 – 34	151	0.19 [0.07 ; 0.24]	0.37 [0.19 ; 0.54]	1.94 [1.60 ; 2.46]	5.52 [4.95 ; 6.68]	6.85 [5.73 ; 7.91]	2.97
	100	0.86 [0.57 ; 1.19]	1.19 [0.79 ; 1.37]	3.53 [3.01 ; 3.87]	6.58 [6.19 ; 7.26]	7.21 [6.70 ; 8.28]	3.11
35 – 39	154	0.14 [0.01 ; 0.19]	0.21 [0.14 ; 0.34]	1.30 [1.01 ; 1.46]	3.93 [3.46 ; 4.50]	4.68 [4.31 ; 6.79]	1.90
	64	0.15 [0.06 ; 0.38]	1.84 [0.10 ; 0.70]	4.17 [3.35 ; 2.35]	4.17 [3.43 ; 6.52]	5.4 [4.20 ; 8.59]	2.31
40 – 44	142	0.01 [0.005 ; 0.03]	0.03 [0.01 ; 0.07]	0.79 [0.59 ; 0.89]	1.71 [1.48 ; 1.90]	1.90 [1.75 ; 2.66]	0.94
	66	0.13 [0.005 ; 0.18]	0.18 [0.09 ; 0.20]	0.98 [0.76 ; 1.40]	3.63 [2.41 ; 5.96]	5.30 [3.64 ; 8.73]	1.55

CI = confidence intervals ; IQR= inter-quartiles range
*Due to the small number of patients, the extreme percentiles for this age group were not estimated.

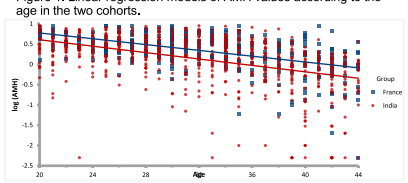
Table 2: Comparison of the Median AMH values between the Indian (n=748) and the French (n=356) cohorts.

Age (years)	Median AMH France cohort [CI 90%]	Median AMH India cohort [CI 90%]	Difference (%)	P-value*
20 – 24	4.29 [3.50 ; 5.01]	2.78 [2.52 ; 3.16]	35.3	0.0003
25 – 29	3.18 [2.69 ; 3.55]	2.68 [2.42 ; 3.13]	15.7	0.0736
30 – 34	3.53 [3.01 ; 3.87]	1.94 [1.60 ; 2.46]	45.0	<0.0001
35 – 39	1.84 [1.35 ; 2.35]	1.30 [1.01 ; 1.46]	29.3	0.0394
40 – 44	0.98 [0.76 ; 1.40]	0.79 [0.59 ; 0.89]	19.0	0.0038

* P-values estimated with the Wilcoxon-Mann-Whitney method

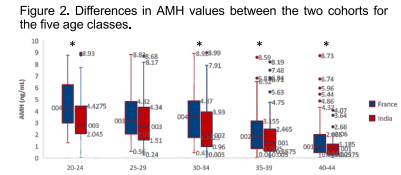
COMPARISON BETWEEN FRENCH AND INDIAN COHORTS

Figure 1. Linear regression models of AMH values according to the age in the two cohorts.



The equations for the linear regression models were the following:
log(AMH)=-0.0358*(age)+1.4916 for France and
log(AMH)=-0.0396*(age)+1.4006 for India.

Figure 2. Differences in AMH values between the two cohorts for the five age classes.



* Statistically significant difference

DISCUSSION

These results confirm previous data reporting lower serum AMH values in women living in India compared to women living in Europe. This difference in AMH values is found to be statistically significant for all age classes within the 20-44 range (except for the 25-29 age range). Apart from the observed shift between the French and Indian observations, the pace of decline in AMH values appears to be similar. These results call for caution in clinical practice, as misuse of AMH results could have direct consequences on medical care. This is also aligned with the Clinical and Laboratory Standards Institute (CLSI) recommendations (EP28-A3c) that laboratories should locally verify reference values provided by the manufacturer. This is particularly important for AMH, which is influenced by genetics and environmental factors. These results emphasize the need to perform such local studies in order to optimize routine use of this biomarker.

Limitations: 1) age range is limited to 20-44 years, 2) inclusion criteria were not perfectly similar between the two cohorts, 3) unbalanced numbers of patients for the two cohorts, 4) linear regression does not represent the exact course of the age-dependent AMH decline, and 5) only the New Delhi region is documented for India.

CONCLUSION

For this first comparison study, VIDAS® AMH reference values are observed to be lower in the Indian cohort, compared to the French cohort. This study emphasizes the importance of locally verifying or establishing the AMH reference values , to adequately interpret AMH values.

Funding: The research was partially funded by bioMérieux (Marcy l'Etoile, France) who also provided VIDAS® AMH assays.
Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

[1] Seifer DB, Golub ET, Lambert-Messerlian G, et al. Variations in serum müllerian inhibiting substance between white, black, and Hispanic women. Fertil Steril. 2009;92(5):1674–1678. doi:10.1016/j.fertnstert.2008.08.110
[2] Iglesias C, Banker M, Mahajan N, Herrero L, Meseguer M, Garcia-Velasco JA. Ethnicity as a determinant of ovarian reserve: differences in ovarian aging between Spanish and Indian women. Fertil Steril. 2014;102(1):244–249. doi:10.1016/j.fertnstert.2014.03.050
[3] Scott M Nelson et al. Ethnic discordance in serum mullerian hormone (AMH) in healthy women; population study from China and Europe, Reproductive BioMedicine Online (2019), https://doi.org/10.1016/j.rbmo.2019.11.013
[4] HAS. Argumentaire – Evaluation du dosage sérique de l'hormone anti-müllérienne. Juillet 2017
[5] Kaur, J., et al. (2019). "Age-dependent decline of anti-Müllerian hormone (AMH) in a large population of Indian fertile women as measured using the automated VIDAS® AMH assay." Fertility Science and Research 6: 120
[6] Ovarian stimulation for IVF/ICSI, ESHRE Reproductive Endocrinology Guideline Group, October 2019

INTERNATIONAL PRESENTATION FROM IFS MEMBERS

ESHRE Poster 9

P 786

Comparison of physical growth parameters of children conceived by donor oocytes with fresh versus frozen embryo transfer upto 5 years of age *: a prospective study*

M. Varma[1], S. Singh[2], S.Verma[3], H. Tuli[1], R. Kumar[1], T. Kaur[1]
[1] Sadbhavna Medical and Heart Institute, Patiala, India. [2] Artemis Health Institute, Gurugram, India
[3]University of California, Life Sciences, San Diego , USA

CONCLUSION
Weight of children at 2-5 years was significantly more in frozen than in the fresh embryo transfer group with donor oocytes after adjusting for maternal age and BMI

STUDY QUESTION
Are the weight/length/height/head circumference (mean Z-scores) different in children conceived by frozen embryo transfer (FET) or fresh ET in a donor oocyte (DO) model, during the first 5 years.

WHAT IS KNOWN ALREADY
Prospective studies regarding the potential effect of freezing protocols on childhood growth are limited with comparable / trends of increased weight. Fresh ET has been compared to FET where ovarian stimulation remains an important variable affecting early events in pregnancy [1].

In this study, comparing the growth of children conceived by fresh ET versus FET, in a DO model, with similar laboratory procedures and vitrification protocols, a better insight into the effects of vitrification is observed, as several important confounders are eliminated.

STUDY DESIGN
In this prospective cohort study, conducted from 2014-2019 at a tertiary centre,209 children conceived by DO(delivered after 32 weeks) were followed-up at birth and at one point of time (age 1 month- 5 yrs).

Data was available for mothers(n=161), children(n=189); conceived by fresh ET (n=109),FET(n=80). Both groups had similar ICSI, ET (2/3 cleavage stage) protocols. Vitrification/ thawing protocols were similar in all FETs. The IVF program, deliveries, follow-up was conducted at the same institution. Some children were followed-up by post.

PARTICIPANTS / MATERIALS, SETTING, METHODS
Weight/length/height/head circumference (HC) were recorded at birth and later at one point of time as Z-scores (WHO child growth standards) [2] to adjust for age at measurement. This was further adjusted for maternal age and BMI. Children were divided into two groups < 2 years and 2-5 years. Singletons were analyzed as a sub-set. Two-sample t- test was used to compare means. Multiple regression analysis was used to adjust for potential confounders. Statistical

RESULTS

Weight- for- age Z –scores for all children

	Fresh ET (n=109)	FET (n=80)	*P* value	*P* value (adjusted for maternal age and BMI)
Children < 2 years (n=75)	-0.39±1.23 (n=34)	-0.26±1.23 (n=41)	.65	.51
Children 2-5 years (n=114)	-0.09± 1.15 (n=75)	0.45±1.18 (n=39)	.02	<.001

Weight- for- age Z –scores for all singletons

	Fresh ET (n=68)	FET (n=65)	*P* value	*P* value (adjusted for maternal age and BMI)
Singletons < 2 years (n=50)	-0.32±1.30 (n=19)	-0.09±1.25 (n=31)	.54	.82
Singletons 2-5 years (n=83)	-0.10± 1.09 (n=49)	0.53±1.18 (n=34)	.01	.02

In the 2-5 years cohort, mean Z -scores for weight-for-age was significantly more for the FET group of all children & for the singleton subset compared to the respective fresh ET groups. This difference remained significant in both groups after adjusting for maternal age and BMI.
Mean Z -scores for weight-for-age in the <2year groups, as well as, length/height-for-age in all the groups were comparable. HC did not follow any definite statistically significant trend.

LIMITATIONS
This was a single centre study with a limited sample size. After birth, the growth parameters of children were recorded at a single point in time only (requiring the need for Z -scores for comparison).

WIDER IMPLICATIONS
Our study, using the DO model, shows significant greater weight of children at 2-5 years conceived by frozen compared to fresh ET. This needs to be confirmed in larger studies with longer follow-ups. The mechanism and clinical relevance of this, also needs to be scientifically explored.

REFERENCES
1 Alessandra J Ainsworth , Michelle A Wyatt et al Fresh Versus Frozen Embryo Transfer Has No Effect on Childhood Weight Fertil Steril.. 2019 112(4):684-690. https://doi.org/10.1016/j.fertnstert.2019.05.020
2 The WHO Child Growth Standards; https://www.who.int/childgrowth/standards/weight_for_age/en/

ESHRE Poster 10

P-709

"A COMPARATIVE STUDY OF ORAL DYDROGESTERONE WITH MICRONISED VAGINAL PROGESTERONE FOR SUPPORTING THE LUTEAL PHASE IN IVF-ICSI CYCLES

P.C. JINDAL, M. SINGH, R. SINGH,
Bhopal Test-Tube-Baby Centre & International Infertility Institute, Bhopal, India.
Web : www.ivfgo.com, Email :bttbcentre@gmail.com Mobile : +91 9200002833

BACKGROUND
- Oral dydrogesterone has been used for luteal phase support on an empirical basis since the early days of IVF treatment, but systematic comparisons of oral dydrogesterone with vaginal progesterone started to appear in the middle 2000s.
- Recently, a large, randomized, double-blind, double-dummy phase III trial on the use of daily 30 mg oral dydrogesterone versus daily 600 mg micronized vaginal progesterone for LPS in IVF was published. This trial confirmed the efficacy and established the noninferiority of daily 30 mg oral dydrogesterone for luteal phase support. Despite oral administration and first pass through the liver, dydrogesterone was as well tolerated as vaginal progesterone in safety analyses with no new fetal safety concerns.
- Given the widespread preference of women for an oral compound, dydrogesterone may well become the new standard for luteal phase support in fresh embryo transfer IVF cycles.

STUDY QUESTION:
Is oral dydrogesterone administration as effective as micronised vaginal progesterone for luteal-phase support in IVF-ICSI cycles ?

SUMMARY ANSWER:
Yes, oral dydrogestrone is as effective as micronised vaginal progesterone for luteal-phase support in women undergoing IVF-ICSI cycles.

WHAT IS KNOWN ALREADY:
- In ART cycles, there is a significant reduction in pregnancy rates without luteal-phase support, because of suboptimal progesterone levels accompanied by premature luteolysis, short luteal phase and early bleeding. Progesterone is necessary for implantation and early pregnancy maintenance.
- Luteal phase support in ART cycles is provided by using progesterone, addition of estradiol to progesterone, hCG or gonadotropin releasing hormone (GnRH) agonists.

STUDY DESIGN, SIZE, DURATION:
- This is a prospective trial carried out in Bhopal from Dec-2018 to Dec-2019.
- Explained and informed written consent concerning the study protocol was obtained from all participants.
- 60 infertile women undergoing controlled ovarian stimulation for IVF-ICSI treatment (fresh cycle) were included in this study.
- Patients were divided into group A (oral dydrogesterone group) and group B (micronised vaginal progesterone group) and outcome evaluated in terms of clinical pregnancy and miscarriage rates.

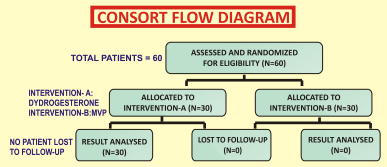
MATERIAL AND METHOD
Group A (n=30) received 10 mg dydrogesterone thrice a day (Duphaston; Abbott) and group B (n=30) received 400 mg micronised vaginal progesterone (Cap Utreva, Intas) twice per day.

BASELINE CHARACTERISTICS OF PATIENTS

GROUPS	DYDROGESTERONE (n=30)	MVP (n=30)	P-value
MEAN AGE (years)	29.5 +/- 5.5	30.4 +/- 4.9	NS
MEAN BMI (kg/m2)	23 +/- 3.1	23.5 +/- 3.5	NS
AMH	2.2 +/- 0.50	2.4 +/- 0.72	NS
BASAL FSH (D-2)	6.2 +/- 2.43	6.4 +/- 2.42	NS
AFC	7 +/- 3.3	7 +/- 3.5	NS
ENDOMETRIAL THICKNESS	9.08 +/- 1.99 mm	8.52 +/- 1.15 mm	NS

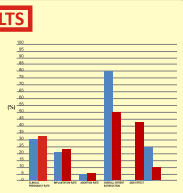
MAIN RESULTS AND THE ROLE OF CHANCE
- Clinical pregnancy rate in the micronised vaginal progesterone (group B) was higher than the oral dydrogesterone (group A), but the difference was not significant. Furthermore, the miscarriage rate in the two groups was the same.
- The difference between the two groups in the endometrial thickness and number of embryos transferred was not significant.
- The clinical pregnancy rate and implantation rate were also similar in the two groups. Moreover, most of the patients tolerated oral dydrogesterone well.

CONSORT FLOW DIAGRAM



RESULTS

PARAMETER	DYDROGESTERONE GROUP (GROUP-A)	MVP GROUP (GROUP-B)	VALUE	P-VALUE
NUMBER OF PATIENTS	30	30		NS
CLINICAL PREGNANCY RATE	31%	33%		NS
IMPLANTATION RATE	22%	24%		NS
ABORTION RATE	5%	6%		NS
OVERALL PATIENT SATISFACTION	80%	50%		SIG
SIDE EFFECTS: 1) Vaginal Irritation & Discharge 2) Nausea	0% 25%	43% 10%		SIG SIG



CONCLUSION
- **In summary, the use of oral dydrogesterone avoids the frequently reported and negatively perceived side effects of vaginal preparations, whereas no systemic tolerability difference from micronized vaginal progesterone has been identified.**
- **Given the widespread preference of women for an oral compound, dydrogesterone may well become the new standard for LPS in fresh embryo transfer IVF cycles.**

LIMITATIONS OF THE STUDY AND REASON FOR CAUTION:
- Very few studies have compared the advantages of oral dydrogestrone with vaginal progesterone for luteal support in ART cycles.
- The main limitation of our study was the relatively small sample size. More studies are recommended with larger number of patients and longer duration in order to validate our results.

INTERNATIONAL PRESENTATION FROM IFS MEMBERS

ESHRE Poster 11

Make hey while sun shines! Hormone 25 OH D (Vitamin D3) in follicular-fluid: a determinant factor for top grade blastocyst formation?

P-254

Natchandra M. Chimote; Bindu N. Chimote
Vaunshdhara Fertility Centre, Nagpur-Maharashtra (India)

Aim

To investigate relationship of 25(OH) D (vitamin D3) in follicular fluid (FF) with oocyte competence to fertilize, cleave and for top quality blastocysts.

Introduction

There is growing evidence that [25(OH)]D has very important role in human reproduction. Vitamin D3 contributes to restoration of the menstrual cycle and endometrial proliferation, growth of follicles, improves primary dysmenorrhea, and reduce occurrence of uterine fibroids. However, owing to conflicting results, the relationship of serum levels of Vitamin D3 with ovarian stimulation characteristics or with embryo quality has been rather obscure. IVF provides a unique opportunity to explore such a relationship as measurement of vitamin D3 in follicular-fluid can help trace the fate of individual oocytes, their fertilization and embryonic development.

Materials and Methods

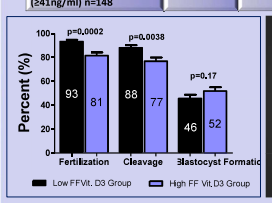
Non-randomized prospective study of women (n=300, 22-42 years) undergoing IVF during January2017- December2019. None of the patients received vitamin D3 supplementation before Controlled Ovarian Hyperstimulation (COH). Follicular-fluid collected from first aspirate of individual follicle was pooled, for each patient, to measure Vitamin D3 levels using RIA kits. Embryonic development from fertilization to blastocyst formation was recorded. Embryo gradation was done as per conventional criteria. All blastocysts were vitrified for next natural cycle embryo transfer. Women with endometriosis, tuberculosis and hydrosalpynx and their male partners with severe or moderate male factor were excluded from this study. Women with Poor ovarian response (≤ 3 retrieved oocytes) to recombinat FSH / gonadotropin stimulation were also excluded. FF Vitamin D3 levels were divided into Low and High groups as per their median value. Fertilization, cleavage and blastocyst formation rates were recorded in low and high FF vitamin D3 groups.

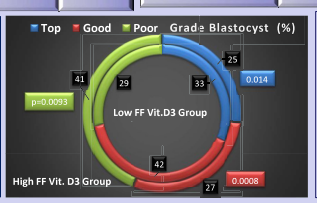
Results

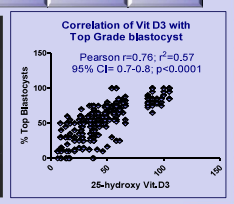
Fertilization and cleavage rates were significantly higher in the low FF Vit.D3 group
However, the blastocyst formation rate was higher, although not significantly, in the High FF Vit. D3 group.
Top and good grade blastocysts were significantly higher in High FF Vit.D3 group whereas the Low FF Vit. D3 group had significantly higher percent of poor grade blastocysts.
Follicular fluid levels of Vit. D3 correlated with top grade blastocysts. The ROC cut-off of Vit.D3 levels in FF to increase the chances of top grade blastocysts was >50 ng/ml

Parameter	Age	Mean Eggs Retrieved	Mean MII oocytes
Low FF Vit. D3 Group (<41 ng/ml) n=152	32.76 ±4.4	9.61±5.1	6.1±1.1
High FF Vit.D3 Group (≥41ng/ml) n=148	34.06±4.5	8.56±7.2	5.9±1.5

ROC Threshold of FF Vit.D3 for top grade blastocysts	AUC	Sensitivity	Specificity
>50 ng/ml	73%	78%	75%







Conclusion

Measurement of vit. D3 in follicular fluid has tremendous potential to identify the embryonic development to blastocyst stage with top or good quality so as to select the best embryo for transfer. It also helps enhance the chances of getting a viable pregnancy resulting in live birth.
Follicular-fluid level of 25(OH)D (Vitamin D3) is a potentially predictive marker for oocyte competence to fertilize, cleave and form top-grade blastocysts in women undergoing IVF.

Wider implications of the findings

Drastic alteration in climate and weather conditions affecting the ozone layer and carbon emissions all over the world; has seemingly also disturbed the natural synthesis of Vit. D3. Hence, proper evaluation of this hormone should be judiciously done to improve excellent embryo development leading to a live-birth.

References
1. Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal. Lagana AS et al Eur Rev Med Pharmaco Sci 2017; 21:4243-51
2. Vitamin D as a follicular marker of human oocyte quality and a serum marker of in vitro fertilization outcome. Ciepiela P et al JARG 2018;35:1265-76
3. Characterizing the influence of vitamin D levels on IVF outcomes. Rudick B et al Human Reproduction 2012; 27 (11): 3321-27

 nmchimote@yahoo.co.in Mobile +919923445243

ESHRE - ORAL PRESENTATION

Abstract Details

Session title: Session 50: Androgen treatment in fertility management
Session type: Selected oral communications
Presentation number: O-198

Abstract title:

A prospective study of testosterone gel treatment in poor ovarian reserve in IVF-ICSI cycles

Biography

Dr. Randhir Singh, Associate Prof. in LN Medical CIlege and JK Hospital, Bhopal, India
ESHRE Certified Clinical Embryologist (2014),
Special interest in EMBRYOLOGY and Legal ART in developing countries

R. Singh[1], M. Singh[2].
[1]BHOPAL TEST TUBE BABY CENTRE, INFERTILITY, BHOPAL, India.
[2]BTTB Centre, Infertility, Bhopal, India.

Study question:

Does transdermal testosterone gel pretreatment improve the outcome in women with poor ovarian reserve undergoing IVF-ICSI Cycles ?

Summary answer:
The testosterone gel has a significant impact on the fertility rate in women with a poor response in the IVF cycles.

What is known already:
Poor ovarian reserve to external gonadotropin drugs is one of the problems with IVF-ICSI cycles which can lead to cycle stop, access to fewer oocytes and embryos, and finally reduced pregnancy rates.

No effective approach has been found yet to treat poor response to ovarian stimulation.

**However, there are possible methods affecting the performance of gonadotropins on the ovaries such as high-dose gonadotropins, growth hormone, glucocorticoids, and low-dose aspirin.
Another treatment is the use of low-dose androgens to improve ovarian response to gonadotropins which acts by increasing the intrafollicular androgen and the number of follicle-stimulating hormone (FSH) receptors on granulosa cells.**

Study design, size, duration:
52 patients from July 2017 to July 2019 , were randomly divided into two groups , 26 patients treated with a placebo (lubricant gel, control group) and 26 patients treated with testosterone gel (Study group).

Inclusion criteria were :
patients for IVF cycles,
patients older than 40 years,
a cycle with previous poor response, i.e., to obtain 3 or <3 oocytes of the cycles by normal stimulation ,
AFC <5-7,
AMH <0.5-1.1 ng/ml,

Fertility outcomes were compared .

Participants/materials, setting, methods:

**52 patients were randomly divided into two groups. 26 patients treated with a placebo gel and 26 patients treated with testosterone gel .
Patients who met inclusion (Bologna) criteria were placed in the antagonist cycle group. The patients were randomly divided into two groups each included 26 participants treated with a placebo and testosterone gel . Fertility outcomes were compared between two groups.
The two groups were not statistically different in terms of FSH , AFC, AMH,**

Main results and the role of chance:

The number of oocytes and embryos in the study (testosterone gel) group were significantly higher than in the control group

The mean number of oocytes obtained was 3.12 ± 1.14 versus 1.27 ± 1.03 and embryos was 2.10 ± 1.08 versus 0.39 ± 0.48 .

The clinical pregnancy rate was 15% (4/26) in the study (testosterone gel) group ,were significantly higher versus than in the control group 04 % (1/26) .

In conclusion, there is evidence from this study that the use of transdermal testosterone prior to ovarian stimulation in women who are considered poor responders, and this treatment has shown to significantly improve live birth rates and reduce the doses of FSH required for ovarian stimulation.

Androgen receptors are expressed in granulosa cells at early stages of follicle maturation, it is surprising that such a short treatment up to 20 days of testosterone supplementation could achieve significantly higher live birth rates. Hence, extending testosterone supplementation for a longer period could enhance the pool of follicles sensitive to gonadotrophins and therefore increase the number of oocytes available for retrieval.

Limitations, reasons for caution:
Transdermal-testosterone may improve the clinical outcomes for poor-ovarian-reserve.

One limitation is the low number of participants and exact subgroup of poor-ovarian-reserve who would benefit from this treatment still needs to be identified.

Although trends in all parameters appear to favour testosterone supplementation, further investigations are needed to confirm these findings.

Wider implications of the findings:

According to the results of our study, the testosterone gel has a positive impact on fertility rate in patients with poor-ovarian-reserve.

**The identification of poor responders that could especially benefit from testosterone treatment should be addressed in further studies.
Large studies on larger populations are recommended to be conducted.**

Keywords:
Androgens
Poor-Ovarian-Reserve
IVF-ICSI
Testosterone-transdermal-gel
AMH

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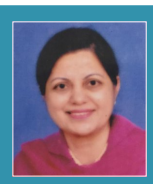

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