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ART LEARNING INITIATIVES FOR EXPERTS

Time to pregnancy

Issue 1

March 2018

MERCK

EXPERT INSIGHTS

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Currently, *in vitro* fertilization (IVF) success rate is dependent on several factors such as stimulation protocol, type of gonadotropin, numbers of retrieved oocytes, mature oocytes, fertilized eggs, good quality and quantity of embryos, live birth rate, and embryo transfer techniques.

The probability of having a baby after assisted reproductive technologies (ART) can be increased by optimizing the time to pregnancy (TTP). TTP can be optimized using preimplantation genetic diagnosis (PGD) combined with elective single embryo transfer (SET). The use of a gonadotropin-releasing hormone (GnRH) antagonist may shorten the treatment period with lower follicle-stimulating hormone (FSH) consumption and a reduced number of injections.

The use of optimized approaches by the *IVF* success specialists to reduce TTP in the field of Reproductive Medicine is inching ever closer towards the successful pregnancies with lesser complications. The IVF providers can implement the empirical strategies that may reduce the stress and improve the patient's outcome.

Growing evidence supports the role of ethnicity in the field of reproductive medicine. Ethnicity strongly influences the prevalence of several gynecological diseases. For example, patients of South Asian Indian descent have higher rates of insulin resistance and polycystic ovary syndrome. Ethnicity has been demonstrated to affect ART outcome.

Several ethnic groups (Asian, African American, and Hispanic) have significantly lower clinical pregnancy and live birth rates and higher miscarriage rates after ART than whites. Indian American women, despite of younger age and similar embryo quality have significantly lower live birth rate than white American women.

Ethnicity should be considered to be a risk factor for diminished ovarian reserve, and observed ART outcomes were less optimal in a population of infertile Indian women compared with white Spanish women. According to the age and ethnic characteristics, clinicians may counsel infertile women about the current approaches to reduce TTP. In ART, it is imperative to shorten the TTP or time to birth for better IVF outcome.

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CLINICAL CORNER

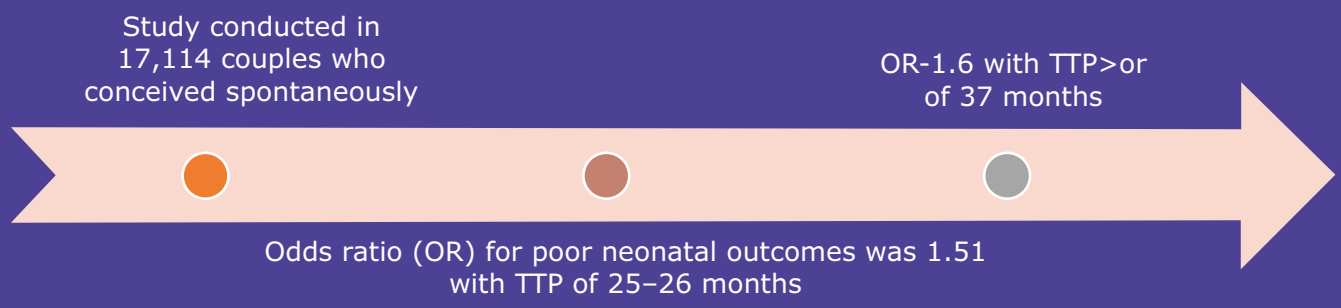
THE RELATION BETWEEN A LONG TTP AND PREGNANCY OUTCOME

Tehrani HG, Allameh ZS, Mehrabi AK. Relation between time to pregnancy and pregnancy outcome. Advanced Biomedical Research. 2014;3:175.

Time to pregnancy (TTP) is defined as the time which is needed for achieving a wanted pregnancy. TTP has been found to be a useful tool for an assessment of reproductive effects. TTP is affected by several biological, psychological and environmental factors.

The authors investigated relationship between TTP and outcomes

Neonatal Outcomes: Poor neonatal outcomes associated with increased TTP are poor neonatal health, including low Apgar score, low umbilical vein pH, and the need for neonatal intensive care.



Pregnancy Outcomes

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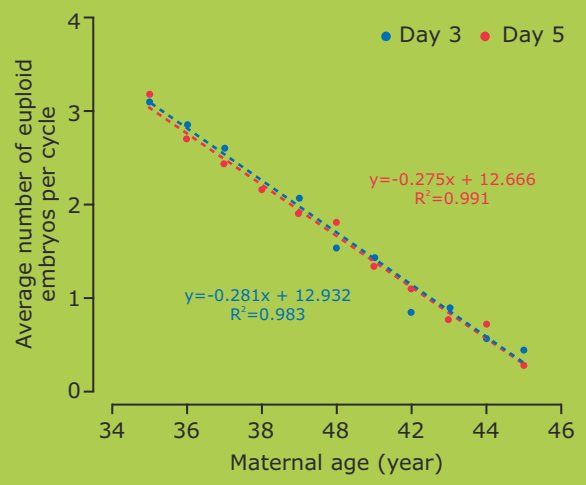
IMPACT OF MATERNAL AGE ON EUPLOIDY RATES: THE LARGEST STUDY

Zachary D, Simon AL, McCoy RC, et al. Effects of maternal age on euploidy rates in a large cohort of embryos analyzed with 24-chromosome single-nucleotide polymorphism–based preimplantation genetic screening. Fertility and Sterility. 2016;105 (5):1307–1313.

Abnormal chromosome number, or aneuploidy, is common in human embryos. It is responsible for more than 50% of all missed abortions and miscarriages, and it is the leading cause of congenital birth defects.

- Zachary, *et al.*, analyzed 22,599 day-3 embryos and 15,112 day-5. In women aged 27 to 35 years, the median proportion of euploid embryos in each cycle remained constant at 35% in day-3 biopsies and 55% in day-5 biopsies, but it decreased rapidly after age 35 (Figure 1).
- On an average, women in their late 20s had four euploid embryos (day 3 or day 5) per cycle, but this number decreased linearly after 35 years of age. The effect of maternal age on the probability of retrieving at least one euploid embryo in a cohort (PrE) was similar, with a rapid exponential decline (R^2=0.986).
- Across all maternal ages, the euploid proportion and number of embryos per cycle were counterbalanced, so the number of euploid embryos per cycle was the same for day-3 and day-5 biopsies. This study report suggests that the loss of embryos from day 3 to day 5 was primarily due to aneuploidy.

Figure 1. Distribution of the number of euploid embryos per IVF cycle after the age of 35 years



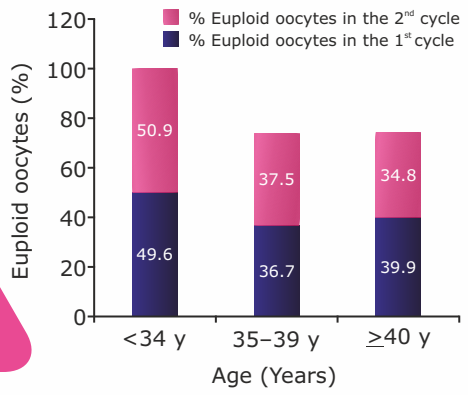
An inverse relationship exists between the advanced maternal age (>35 years) and embryo euploidy, demonstrating that equal numbers of euploid embryos are available at day 3 and day 5.

INTRA-AGE, INTERCENTER, AND INTERCYCLE DIFFERENCES IN CHROMOSOME ABNORMALITIES IN OOCYTES

Munne S, Held KR, Magli CM, et al. Intra-age, intercenter, and intercycle differences in chromosome abnormalities in oocytes. Fertil Steril. 2012;97(4):935–942.

- Fertility decreases with advancing maternal age, with implantation rates declining from 30% in women younger than 35 years to 6% in women 41–42 years (Figure 2). This is primarily due to an increase in chromosome abnormalities in the oocytes as a result of aging.
- Preimplantation genetic diagnosis (PGD), with full chromosome analysis using microarrays coupled with blastocyst biopsy, ameliorates the decrease in implantation rates with advancing maternal age when euploid embryos were identified and replaced.
- Euploidy rates between centers were significantly different (48% *vs.* 25%), and 68.5% of patients were having less than ±2 euploid eggs of difference between cycles.

Figure 2. Euploidy frequency in the two cycles of the same patient, by age group and center



Euploidy rate decreased on an average with advancing maternal age. The high intra-age and intercenter variation in oocyte chromosome abnormalities emphasize the difficulty in estimating how many euploid oocytes a specific woman will have.

Overall, the majority of patients (68.5%) had less than ±2 euploid eggs of difference between cycles.

BIRTH DEFECTS AND CONGENITAL HEALTH RISKS IN CHILDREN CONCEIVED THROUGH ART: A MEETING REPORT

ESHRE Capri Workshop Group. Birth defects and congenital health risks in children conceived through assisted reproduction technology (ART): A meeting report. J Assist Reprod Genet. 2014;31:947–958.

Table 1. Hazard ratios (95 % C.I.) of congenital malformations in singletons conceived either spontaneously or after subfertility treatment according to the TTP

TTP (months)	Conceived spontaneously (No. 56.661)	Conceived after treatment for subfertility (No. 4.588)
0-2	1.00	-
3-5	1.16 (1.06 to 1.27)	-
6-2	1.17 (1.06 to 1.30)	1.00
>12	1.29 (1.14 to 1.45)	1.34 (0.94 to 1.92)
Test for trend*	p<0.0001	p=0.10

In light of increasing complications associated with long pregnancy time in ART, it is critical to shorten the TTP/B. It is important to achieve early pregnancy to avoid aneuploidies and other complications.

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THE IMPACT OF THE TIME INTERVAL ON IVF SUCCESS AFTER THE FAILURE OF THE FIRST ATTEMPT

Bayoglu Tekin Y, Ceyhan ST, Kilic S, Korkmaz C. The impact of the time interval on in-vitro fertilization success after the failure of the first attempt. J Obstet Gynaecol. 2015;35(4):403–406.

This study demonstrated that clinical pregnancy rates achieved during the second attempt in women who failed their first try declined as the time interval increased: 45.5% (at 1-month); 41.2% (at 2 months); 37.5% (at 3 months); 30.4% (at 4 months); 28.2% (at 5 months) and 30.2% (at 6 months). The time interval between IVF cycles should not be prolonged for several months. Women who are counselled about the optimal time for the next attempt should be informed about reproductive ageing and the positive effect of performing the consecutive attempt early.

OPTIMUM STRATEGIES TO REDUCE TTP IN ART

Merck Symposium at ESHRE 2016. Available at https://www.professionalsinfertility.com/en/news/eshre2016_symposium.html. Accessed on February 28, 2018.

Clinical strategies

- Use GnRH antagonist
- Use the right gonadotropin type and dose to obtain a sufficiently high number of eggs
- Prevent cycle cancellation

Laboratory techniques

- Assess and transfer embryo with highest implantation potential (PGD-A, time lapse technology studies promising)
- Embryo cryopreservation by vitrification in a standardized way (semi-automated systems are promising)

Patient outcomes

- Highest probability of a safe singleton live birth/pregnancy
- Start of ART treatment within the shortest time period by
  - Increasing treatment efficacy
  - Reducing treatment discontinuation
  - Preventing cycle cancellation

PGD-A: Preimplantation genetic diagnosis for aneuploidies

The time interval has a positive impact on the pregnancy rates of a subsequent try after failure of the first IVF attempt. An interval between 2 to 4 months seems to be the appropriate time to initiate the second attempt, without any difference in the stimulation outcomes.

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DELPHI RECOMMENDATIONS TO SHORTEN THE TTP

Poster no P-352 presented at ESHRE 2017.

A Delphi consensus poster was presented during the European Society of Human Reproduction and Embryology (ESHRE) conference in 2017 to evaluate expert opinion on how TTP/B might impact the individualization of the ART treatment. A consensus of 12 experts was analyzed and presented at ESHRE. The discussion approaches mainly focused on reduced TTP.

Statements that were developed on how TTP/B might impact individualization of ART treatment are:

Oocyte retrieval and time to healthy singleton delivery

- The cumulative live-birth rate (including live births from fresh and frozen–thawed embryos) significantly increases with the number of oocytes retrieved.

Age and time to healthy singleton delivery

- It is crucial that fertility treatment is managed in a timely manner that avoids over/under treatment.
- In all subfertile women <40 years old, an optimal cumulative IVF outcome could be obtained by performing up to six single-embryo transfers.
- Patient age does not affect the cumulative live-birth rate in oocyte donation cycles if oocyte donors are aged 18–34 years old.

Procedures that could optimize TTP/B

- PGD for aneuploidies can decrease the aneuploidy rate and shorten TTP and time to healthy singleton delivery.
- PGD for aneuploidies combined with comprehensive chromosomal screening can increase both clinical and sustained implantation rates.
- In women >35 years old, elective SET combined with enhanced embryo selection using PGD for aneuploidies can reduce the multiple pregnancy rate while maintaining the cumulative success rate of an IVF programme.
- A frozen-thawed replacement transfer cycle could be considered immediately after a failed fresh transfer cycle, because they result in a similar clinical pregnancy rate to that for a frozen-thawed transfer cycle postponed to a later time.

GnRH antagonist use and time to healthy singleton delivery

- The use of a GnRH antagonist may shorten the treatment period (i.e., fewer stimulation days) with lower FSH consumption and a reduced number of injections.
- In normal responder patients, GnRH antagonists have similar efficacy to GnRH agonists.
- A GnRH agonist can be used to trigger ovulation in a GnRH antagonist cycle, significantly decreasing the risk of cycle cancellation and ovarian hyperstimulation syndrome in normal responders.

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OPTIMAL NUMBER OF OOCYTES

Ovarian Response on Cumulative Live Birth Rates In Women Undergoing Their First Ovarian Stimulation Cycle Planned to Undergo Single Embryo Transfer (SET)

Drakopoulos P, Blockeel C, Stoop D, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos. Hum Reprod. 2016;31(2):370–376.

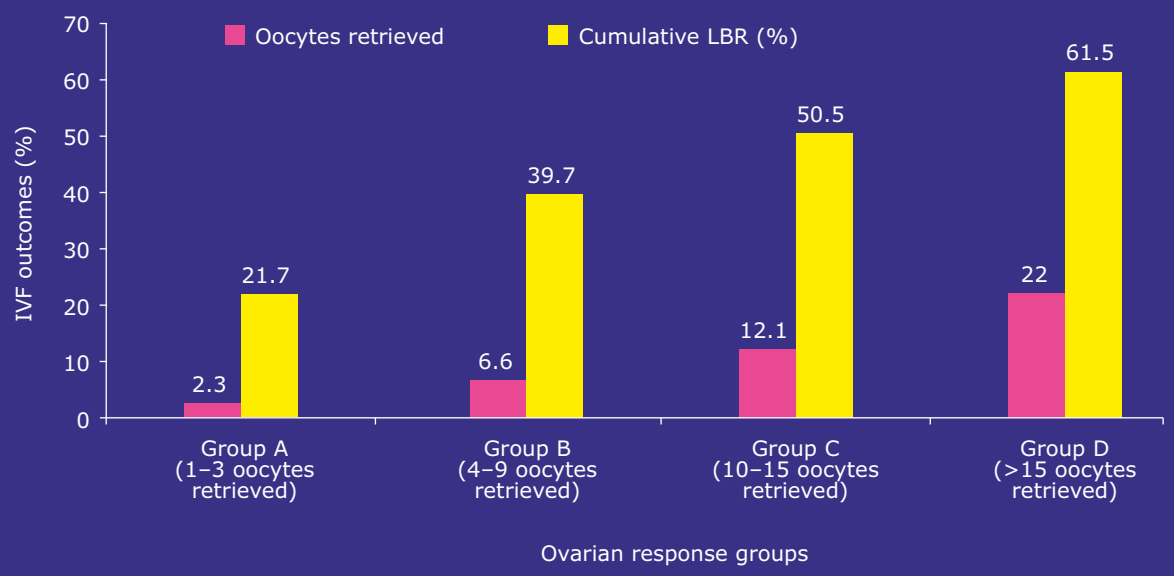
The increased number of follicles, and consequently the number of oocytes retrieved, improved pregnancy rates in women undergoing IVF/Intracytoplasmic Sperm Injection (ICSI), not only by increasing the number of available embryos but also by allowing extended embryo culture and enabling the selection of the best quality embryo for transfer.

This study included 1099 eligible consecutive women 18–40 years old undergoing their first IVF cycle and planned to undergo SET in their fresh cycle. To evaluate the impact of oocyte yield on fresh live birth rates (LBR) and on cumulative LBR after utilization of all cryopreserved embryos, patients were categorized into four groups according to the number of oocytes retrieved: 1–3 (Group A), 4–9 (Group B), 10–15 (Group C) or .15 oocytes (Group D).

The cumulative LBR significantly increased the number of oocytes retrieved. High responders (>15 oocytes) demonstrated a significantly higher LBR not only *vs.* poor (0–3 oocytes) ($p<0.001$) and suboptimal (4–9) responders ($p<0.001$), but also *vs.* women with normal (10–15) ovarian response ($p=0.014$) (Figure 3).

Figure 3. The relationship between oocytes retrieved and cumulative LBR

Women undergoing controlled ovarian stimulation for their first IVF/ICSI cycle and planned SET should be informed that, although the number of oocytes retrieved does not affect LBR in the fresh cycle, the higher the oocyte yield, the higher the probability to achieve a live birth after utilization of all cryopreserved embryos.

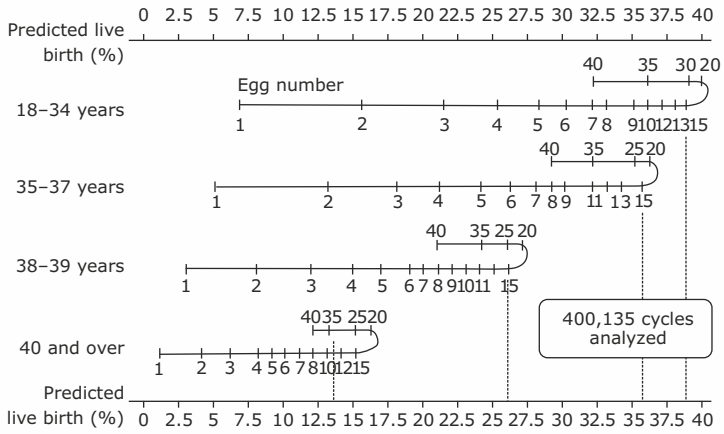


ASSOCIATION BETWEEN THE NUMBER OF EGGS AND LIVE BIRTH IN IVF TREATMENT: AN ANALYSIS OF 4,00,135 TREATMENT CYCLES

Sunkara SK, Rittenberg V, Raine-Fenning N, et al. Association between the number of eggs and live birth in IVF treatment: An analysis of 400 135 treatment cycles. Hum Reprod. 2011;26(7):1768–1774.

- Sunkara, *et al.,* reported that the LBR was the principal clinical outcome following IVF treatment, the number of eggs retrieved following ovarian stimulation was used as a surrogate outcome in clinical practice and research.
- The overall LBR was 21.3% per fresh IVF cycle. There was a strong association between the number of eggs and LBR. The predicted LBR for women with 15 eggs retrieved in age groups 18–34, 35–37, 38–39 and 40 years and over was 40, 36, 27 and 16%, respectively (Figure 4).
- More oocytes allow for more frozen embryo transfers, thereby increasing cumulative pregnancy and LBR. One more oocyte makes a difference in LBR for all age categories.

Figure 4. Predicted live birth probability with given egg number and age



It is crucial that fertility treatment is managed in a timely manner that avoids over/under treatment. In all sub-fertile women with <40 years age, an optimal cumulative IVF outcome could be obtained by performing up to six single embryo transfers. Patient age does not affect the cumulative LBR in oocyte donation cycles if oocyte donors are aged between 18–34 years old. The relationship between the number of eggs and live birth, across all female age groups, suggests that the number of eggs in IVF is a robust surrogate outcome for clinical success.

HUMAN RECOMBINANT FSH (rFSH) COMPARED TO URINARY HUMAN MENOPAUSAL GONADOTROPIN (HMG) FOR OVARIAN STIMULATION IN ART

Levi Setti PE, Alviggi C, Colombo GL, et al. Human recombinant follicle stimulating hormone (rFSH) compared to urinary human menopausal gonadotropin (HMG) for ovarian stimulation in assisted reproduction: A literature review and cost evaluation. J Endocrinol Invest. 2015;38(5):497–503.

Number of oocytes retrieved

The number of oocytes retrieved appeared to be higher for r-hFSH (11-14.4) than HMG (5-11.3).

The review was conducted selecting prospective, randomized, controlled trials comparing the two gonadotropin medications from a literature search of several databases. The outcome measure used to evaluate efficacy was the number of oocytes retrieved per cycle.

Treatment with HMG resulted in fewer oocytes ($p<0.0001$) compared to rFSH.

Meta-analysis

Cochrane review

rFSH to other gonadotropins, presented evidence of a major oocyte production for rFSH in comparison with HMG in most of the studies.

In several studies, the superiority of r-FSH over HMG is well proven regarding oocytes retrieval, follicular development, oocyte/embryo quality.

Considering the number of oocytes retrieved as the best direct measure of efficient ovarian stimulation and considering the strong correlation between egg number and live birth, rFSH resulted to be more effective in comparison with HMG.

Embryo Developmental Kinetics

P-504. The type of gonadotropins used for controlled ovarian stimulation affects embryo developmental kinetics.
Munoz, M. Cruz, P. Humaidan, N. Garrido, I. Perez-Cano, M. Meseguer. IVI Alicante, Alicante, Spain; The Fertility Clinic, Odense, Denmark.

Munoz *et al.*, examined 751 embryos developed using either HMG or rFSH in the stimulation protocols for calculating embryo developmental kinetics. It was observed that embryos obtained after stimulation with rFSH divided significantly earlier T2 (2-cell embryos), T3 (3-cell embryos) as compared to those after HMG stimulation.

	rFSH (n=43)	CI 95%	HMG (n=58)	CI 95%	p value
T2 (h)	27.0	26.5–27.5	28.3	27.9–28.7	<0.05
T3 (h)	38.8	38.1–39.5	40.1	39.6–40.6	<0.05

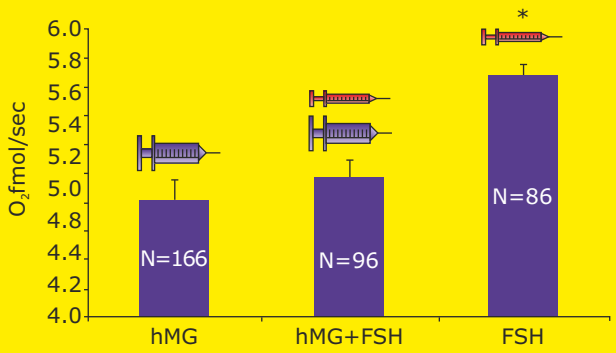
Munoz *et al.*, also noticed a significant increase in embryo quality in cycles stimulated with rFSH.

Oxygen Consumption as a Marker of Oocyte Quality

Tejera A, Herrero J, Santos MJ, et al. Oxygen consumption is a quality marker for human oocyte competence conditioned by ovarian stimulation regimens. Fertil Steril 2011;96:618–623.

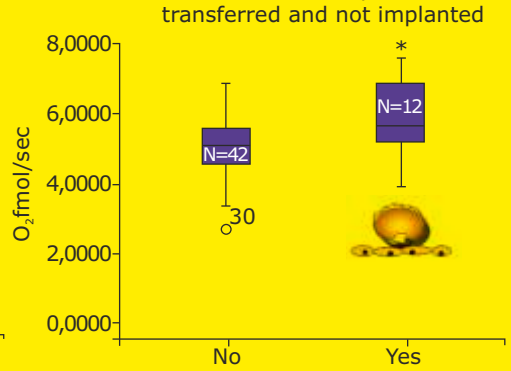
- Measurement of oxygen consumption rates for individual oocytes before fertilization provides a non-invasive marker of oocyte quality and hence a quantitative assessment of the reproductive potential for the oocyte.
- Tejera *et al.*, evaluated 349 oocytes from 56 IVF treatment cycles in the oocyte donation program.
- These oocytes were retrieved using rFSH, hMG or the combination of hMG and FSH.
- It was observed that the oxygen consumption for oocytes retrieved using rFSH was higher.
- Also, higher oxygen consumption was observed for those oocytes which generated embryos that implanted compared with those that did not implant.

Figure 5. Oocyte oxygen consumption rate and ovarian stimulation protocols



A) Oxygen consumption and gonadotropin use, *p<0.05

Figure 6. Oocyte consumption levels in oocytes before ICSI that produced embryos that were transferred and implanted *vs.* those transferred and not implanted



B) Higher implantation rates and oxygen consumption, *p<0.05

PROCEDURES THAT MAY SHORTEN TTP/TIME TO HEALTHY SINGLETON DELIVERY

PGD-A may shorten TTP/Time to healthy singleton delivery

Ubaldi FM, Capalbo A, Colamaria S, et al. Reduction of multiple pregnancies in the advanced maternal age population after implementation of an elective single embryo transfer policy coupled with enhanced embryo selection: pre- and postintervention study Hum. Reprod 2015;30:2097–2106.

- A SET policy is usually recommended in cases of good prognosis patients but no consensus has been reached for SET application in the advanced maternal age (AMA) population. Thus, Ubaldi *et al.*, evaluated the results in terms of efficacy, efficiency and safety of an elective SET policy coupled with increased application of blastocyst culture and PGD.
- This retrospective analysis is based on a total of 2183 oocyte retrieval cycles and 1452 subsequent warming cycles performed in a 4-year period in a population with maternal age over 35 years.

Thus, it was concluded that PGD-A can decrease the aneuploidy rate and shorten TTP and time to healthy singleton delivery.

Figure 7. Clinical outcomes of IVF cycles with and without PGD during the study period

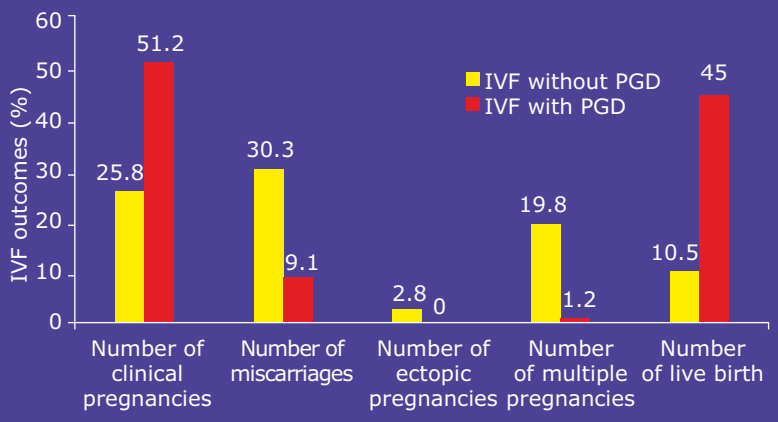
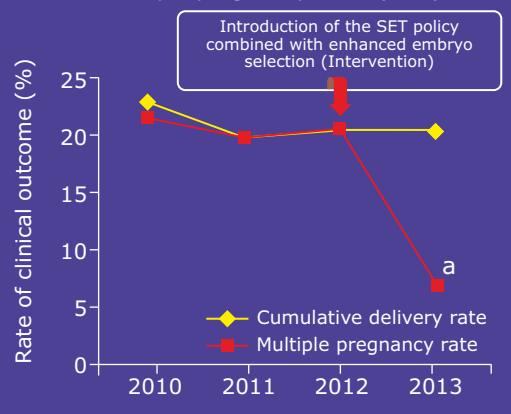


Figure 8. Impact of the SET policy on the cumulative delivery rate and multiple pregnancy rates (MPR) over 4 years



FROZEN EMBRYO TRANSFER (FET) RECOMMENDATIONS

Santos-Ribeiro S, Siffain J, Nikolaos P, et al. To delay or not to delay a frozen embryo transfer after a failed fresh embryo transfer attempt? Fertil Steril. 2016;105:1202–1207.

- Santos-Ribeiro S *et al.*, carried out a study to evaluate if increasing the interval between a failed fresh embryo transfer and a subsequent FET cycle has any effect on clinical pregnancy rates (CPRs).
- Women who underwent at least one FET after ovarian stimulation for IVF and a failed FET attempt were included in the study.
- The start of the FET was classified as either immediate (≤22 days after oocyte retrieval) or delayed (>22 days after oocyte retrieval).
- Authors found no significant differences between the outcomes of immediate and delayed FET. The CPRs of the first FET did not differ significantly according to the timing of FET that is 32.5% after immediate FET *vs.* 31.7% after delayed FET.
- Thus, a frozen-thawed replacement transfer cycle could be considered immediately after a failed fresh transfer cycle, because they result in a similar CPR to that for a frozen-thawed transfer cycle postponed to a later time.

The use of GnRH antagonist and TTP

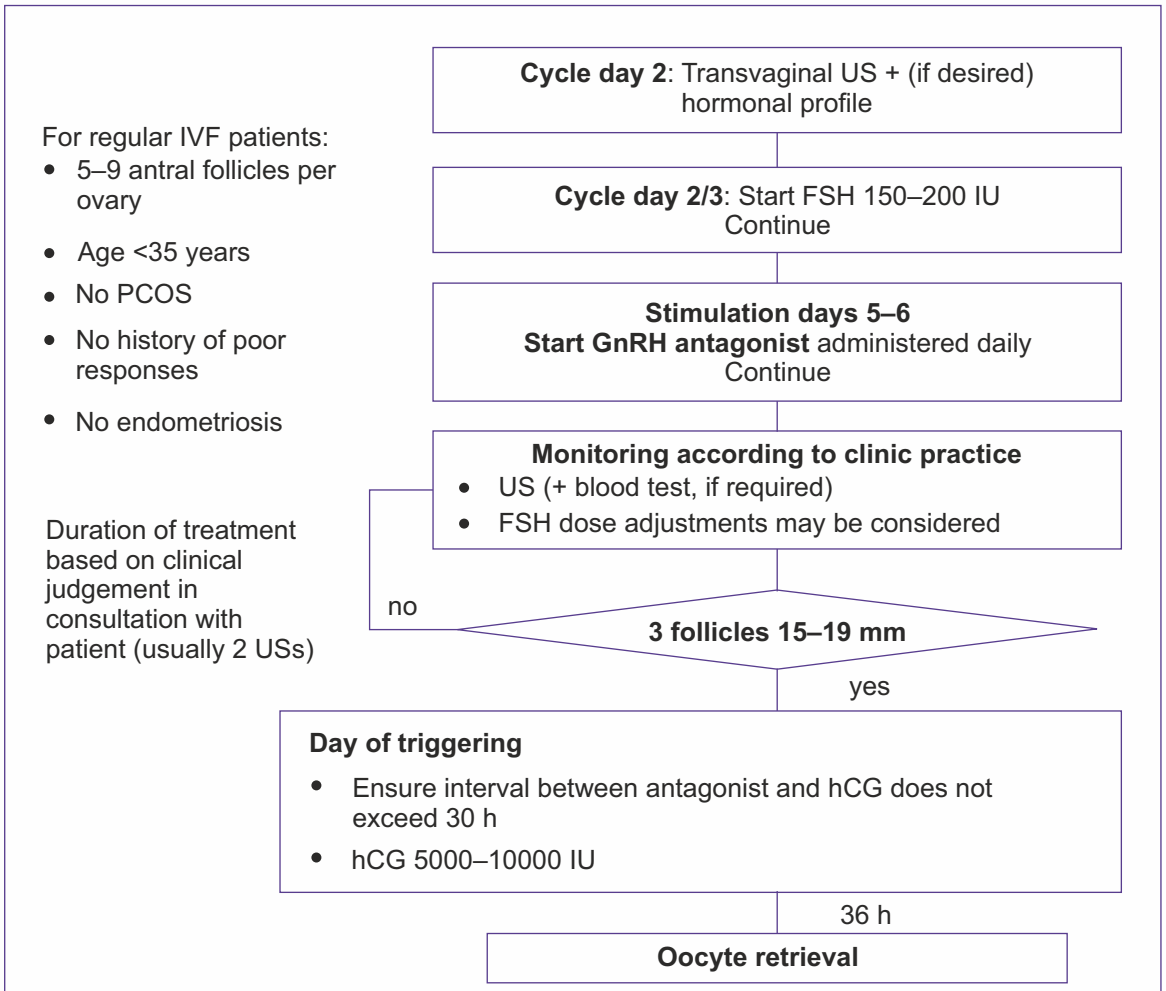
Devroey P, Aboulghar M, Garcia-Velasco J, et al. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Hum Reprod 2009;24:764–774.

Improving patient experience and suggested protocols

- Compared with GnRH agonists, GnRH antagonists are associated with reduced treatment duration and reduced risk of ovarian hyperstimulation.
- Use of GnRH antagonists avoids pituitary down-regulation, which is associated with hypo-estrogenic adverse events.
- Meta-analysis comparing GnRH agonists and antagonists have calculated almost identical OR (0.82–0.86) for the probability of live birth.
- A GnRH antagonist protocol for predicted normal responders is suggested.
- Use of GnRH agonists for triggering of final oocyte maturation.

RECOMMENDED GNRH ANTAGONIST TREATMENT PROTOCOL FOR NORMAL RESPONDERS

- The use of a GnRH antagonist may shorten the treatment period (i.e., fewer stimulation days) with lower FSH consumption and a reduced number of injections.
- In normal responders, GnRH antagonists have similar efficacy to GnRH agonists.
- GnRH agonist used to trigger ovulation in a GnRH antagonist cycle and it significantly decreases the risk of cycle cancellation ovarian hyperstimulation syndrome (OHSS) in normal responder patient.



US: Ultrasound; hCG: Human chorionic gonadotrophin; FSH: Follicle stimulating hormone; PCOS: Polycystic ovary syndrome

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DISCUSSIONS FROM A SYSTEMATIC REVIEW AND META-ANALYSIS

Kolibianakis EM, Collins J, Tarlatzis BC, et al. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Hum Reprod Update 2006;12(6):651–671.

Compared with GnRH agonists, GnRH antagonist protocols may drive a reduction in TTP by reducing the duration of treatment, the time between cycles and OHSS stimulation.

Duration of treatment

Weighted mean difference –19.48 days CI 95%

Time between cycles

OHSS

Was significantly lower in antagonist *vs.* agonist group, OR 0.46

DISCUSSIONS FROM COCHRANE REVIEW

Al-Inany HG, Youssef MA, Ayeleke RO, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database SystRev 2016;4. Art. No.:CD00175.

Reduction in

- Cycle cancellation due to high-risk of OHSS
- Adverse events
- Drop-out rates

As per the Cochrane review, there is no difference in LBR between GnRH antagonists and long-course agonist protocols (OR 1.02, 95% CI 0.85–1.23; n=2303)

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Patient-oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) stratification

Humaidan P, Alviggi C, Fischer R, et al. The novel POSEIDON stratification of 'Low prognosis patients in Assisted Reproductive Technology' and its proposed marker of successful outcome. F1000Research. 2016;5:2911.

Four groups of 'low prognosis patients' in ART according to the POSEIDON's stratification based on oocyte quantity and quality

POSEIDON GROUP 1

Young patient <35 years with adequate ovarian reverse parameter (AFC≥5; AMH≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response.

Subgroup 1a:4<oocytes*
Subgroup 1b:4-9<oocytes retrieved*
*after standard ovarian stimulation

POSEIDON GROUP 2

Older patient ≥35 years with adequate ovarian reserve parameters (AFC≥5; AMH≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian respose.

Subgroup 2a: <4 oocytes*
Subgroup 2b: 4–9 oocytes retrieved*
*after standard ovarian stimulation

POSEIDON GROUP 3

Young patient (<35 years) with poor ovarian reserve pre-stimulation parameters (AFC<5; AMH<1.2 ng/mL)

POSEIDON GROUP 4

Older patient (≥35 years) with poor ovarian reserve pre-stimulation parameters (AFC<5; AMH<1.2 ng/mL)

AFC: Antral follicle count; AMH: Anti-Müllerian hormone

- The POSEIDON group was recently established to focus specifically on the diagnosis and management of low prognosis patients.
- The POSEIDON group also introduced a new measure for successful ART treatment, namely, the ability to retrieve the number of oocytes needed for the specific patient to obtain at least one euploid embryo for transfer. This feature represents a pragmatic endpoint to clinicians and enables the development of prediction models to reduce the TTP, specially in the low prognosis patient group.

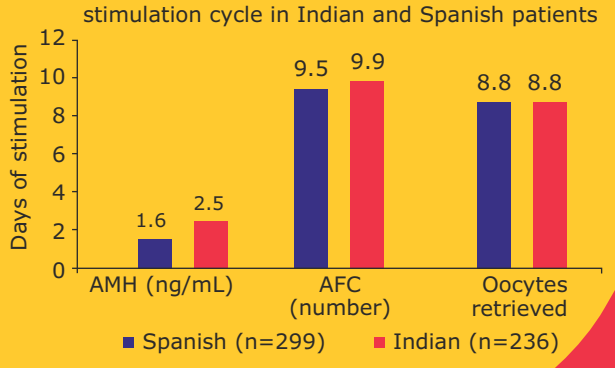
Clinical Significance in India

Iglesias C, Banker M, Mahajan N, et al. Ethnicity as a determinant of ovarian reserve: Differences in ovarian aging between Spanish and Indian women. Fertil Steril. 2014;102(1):244–249.

- Ethnicity has been consistently shown to affect ART outcomes.
- Iglesias *et al.,* thus investigated the differences in ovarian reserve markers anti mullerian hormone (AMH) and antral follicle count (AFC) in Indian and Spanish women (Figure 9).
- The mean age of women undergoing their first or second IVF cycle was significantly higher in Spanish than in Indian women (37.5 *vs.* 31.5).

Indian: Discrepancy AMH *vs.* AFC
Ovarian aging: Indian women age 6 years earlier than white Spanish women.

Figure 9. Correlation between ovarian markers and stimulation cycle in Indian and Spanish patients



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TECH CORNER

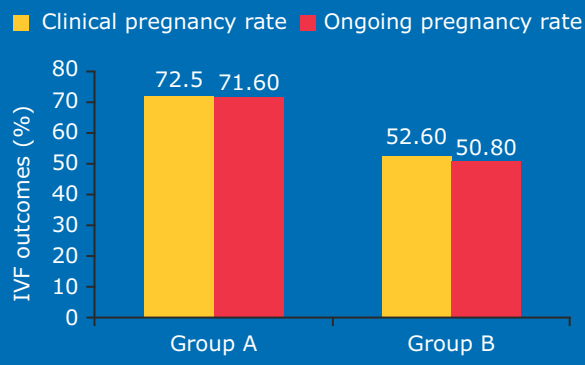
COGNITIVE AUTOMATION OF TIME-LAPSE IMAGES (CATI): ADVANCED FERTILITY TREATMENT

Fertility treatment revolutionizes embryo selection, boosting pregnancy success rates by 30-40%. Available at https://thhb.co.uk/2018/02/06/fertility-treatment/. Accessed on March 3, 2018.

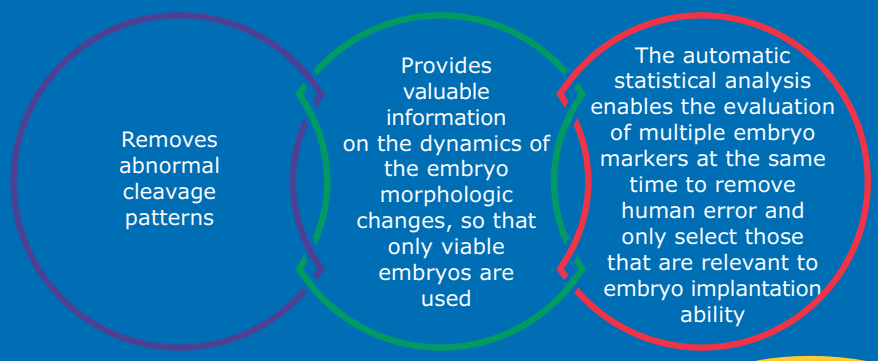
CATI, combined with PGD boosts success rates by 30–40%. For example, a woman aged 40, who has a 20% chance of pregnancy, will reach the rates of a younger woman, with 50–60% chance of success.

A recent study showed a significant difference in clinical pregnancy rates between 'Group A' patients that had embryos undergo time-lapse and PGD, and 'Group B' patients that had embryos cultured in time-lapse alone, (72.5% *vs.* 52.6%, respectively). For ongoing pregnancy rates, a significant difference was observed between the two groups (71.6% for Group A *vs.* 50.8% for Group B (Figure 10).

Figure 10. Clinical and on-going pregnancy rate with embryos cultured in time-lapse alone, or in combination with PGD



CLINICAL ADVANTAGES OF CATI



NEWS CORNER

FROZEN EMBRYOS RESULT IN MANY LIVE BIRTHS IN IVF

Frozen embryos result in just as many live births in IVF. Available at https://www.sciencedaily.com/releases/2018/01/180110223410.htm. Accessed on March 7, 2018.

The study investigated almost 800 women who had infertility not related to PCOS. Women were given one cycle of IVF, where either a transfer of fresh embryos occurred, or all embryos were frozen, and one cycle of thawed embryos occurred subsequently without the use of IVF drugs.

- After the first completed cycle of IVF, on-going pregnancy occurred in 36% of women in the frozen embryo group, and in 35% of the fresh embryo group.
- Rates of live birth after the first embryo transfer were 34% in the frozen embryo group, and 32% in the fresh embryo group.

The key finding is that freezing embryos for IVF is not harming a couple's chances of having a baby. After the first FET, it will be possible to freeze the remaining embryos and transfer them one by one, which is safe and effective.

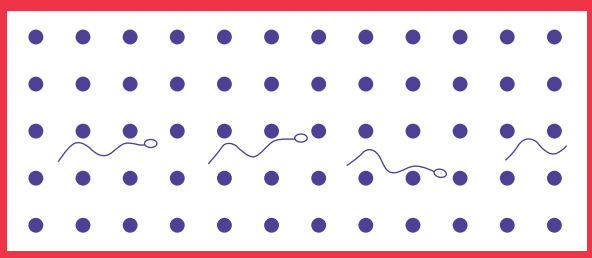
SPARTAN: A SPERM-SORTING DEVICE COULD IMPROVE IVF SUCCESS

Sperm-sorting device could improve IVF success. Available at https://www.sciencedaily.com/releases/2018/01/180103160159.htm. Accessed on March 7, 2018.

The microfluidic device, which can be used in clinics, is dubbed SPARTAN, short for Simple Periodic ARray for Trapping And IsolatioN. It uses a field of three-dimensional posts that create an obstacle course for the swimming sperm cells. The strongest and healthiest sperm get through this array the fastest and then are collected at the outlet to be used in the IVF process.

SPARTAN BENEFITS

- A sperm-sorting device to improve success in IVF has been developed.
- This device collects the fastest and the healthiest sperms.
- SPARTAN prevents damage to cells that can occur with traditional sorting methods, such as those using high-force centrifuges.
- SPARTAN, we get sperms with excellent motility, normal morphology and better DNA integrity. Worldwide, SPARTAN reduces the multiple pregnancy stress and increases pregnancy rate.



FERTILITY TOOLS

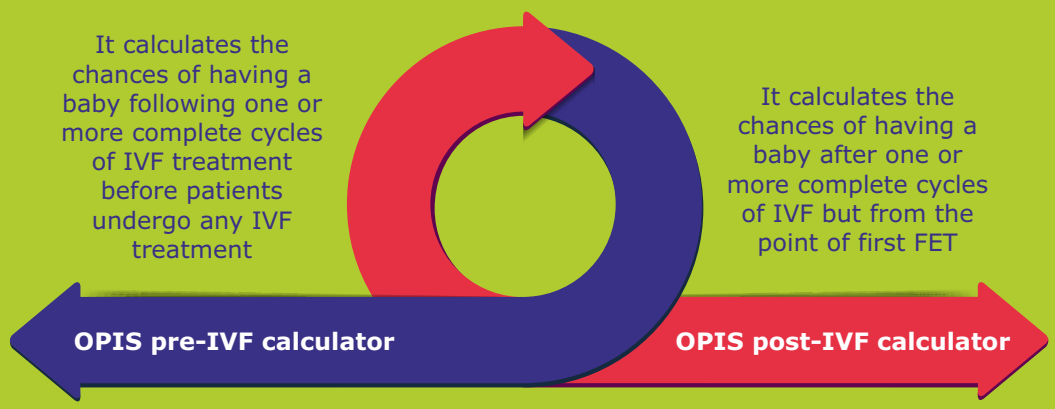
THE ART CALCULATOR: A NEW MARKER OF SUCCESS

The ART Calculator: Estimating a new marker of success in ART. Available at https://www.excemed.org/resources/art-calculator-estimating-new-marker-success-art. Accessed on March 12, 2018.

- **ART calculator is compatible with POSEIDON classification**
- **ART calculator will allow the clinicians to estimate the number of oocytes needed to achieve a new marker of successful outcome i.e., at least 1 euploid blastocyst transfer in each patient**
- **ART calculator identify low prognosis patients and stratify as per the POSEIDON groups**
- **It provide clinicians a goal to reduce TTP**

OUTCOME PREDICTION IN SUBFERTILITY (OPIS) TOOLS

OPIS. Available at https://w3.abdn.ac.uk/clsm/opis/. Accessed on March 12, 2018.



ALIVE

ART LEARNING INITIATIVES FOR EXPERTS

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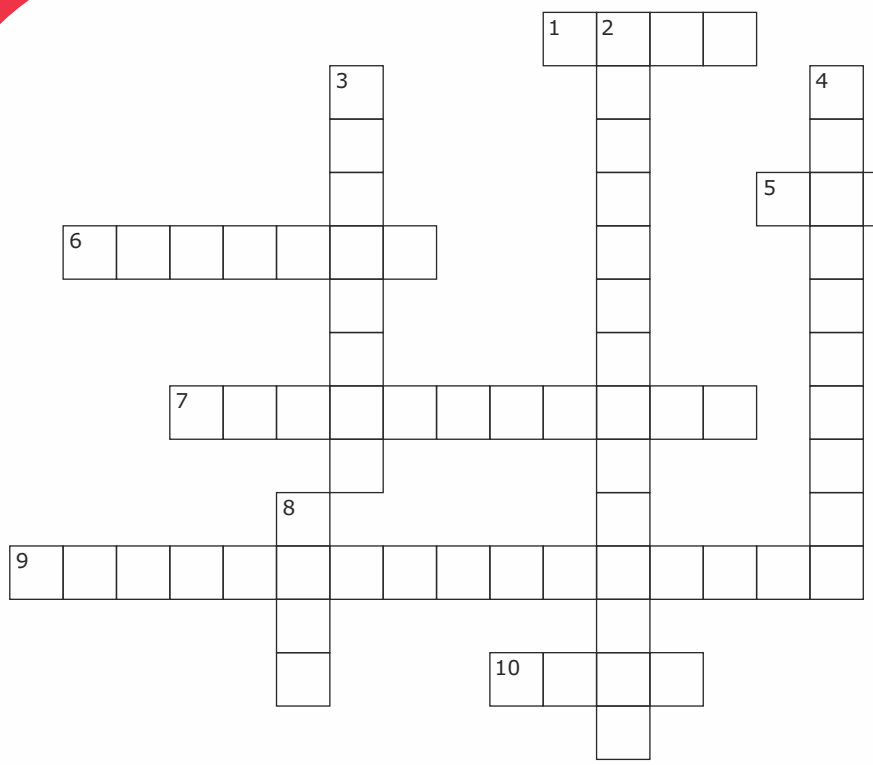
CROSSWORD



Across

1. Procedure that may help reduce the aneuploidy rates……
5. Consensus poster presented at ESHRE……..
6. Optimum number of oocytes needed for maximum chances of pregnancy……
7. Technology that improves the quality of gonadotrop ins……
9. Complication of long-time to pregnancy……
10. Clinical scenario after excessive stimulation during ART cycle……

Down

2. Drug which may reduce time to pregnancy ……..
3. New stratification of low prognosis women in ART……
4. Abnormality which increases with age……..
8. New measure for optimizing pregnancy outcomes……..

ACROSS
1 PGDA
5 DELPHI
6 FIFTEEN
7 RECOMBINANT
9 ECTOPIC PREGNANCY
10 OHSS

DOWN
2 GnRH ANTAGONIST
3 POSEIDON
4 ANEUPLOIDY
8 TIME

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ART LEARNING INITIATIVES FOR EXPERTS

FEEDBACK FORM

Issue 1
March 2018

Thank you for going through the contents of **ALIVE Newsletter.** To ensure that future issues will be of interest to you we would greatly appreciate your feedback on the format and content of this issue.

Name (Optional): _____

Satisfaction Score for ALIVE Newsletter:

Time to Pregnancy: Issue 1; March 2018

Rating Scale	**Poor ----------Excellent** (Please circle the appropriate rating)									
Scientific content	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Relevance of the topic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Impact on my daily practice	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Innovation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Overall level of satisfaction	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

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March 2018

ALIVE

What aspects of the Newsletter did you find particularly interesting and/or informative?

_____

_____

Please suggest topics/areas that you would like to be covered in future issues of the ALIVE Newsletter?

_____

_____

How can the Newsletter be improved?

_____

_____

Disclaimer: *This information is being collected for informational purpose only which will help us in evaluating the quality and content of the Newsletter and making improvements in future.*

MERCK

350 years of rich history and heritage

It all started with Friedrich Jacob Merck taking a chance. He decided not to remain in Schweinfurt, Germany. He wanted to get ahead, to succeed.

Following an apprenticeship in a pharmacy in Schweinfurt, the 20-year-old Friedrich Jacob Merck left his hometown in 1641.

He went on to manage the court pharmacy in Danzig as well as to own a pharmacy in Wesselburen, located in Schleswig-Holstein. He finally moved to Darmstadt in the 1660s.

In 1668, he acquired what later became the Angel Pharmacy in Darmstadt, the roots of Merck, the world's oldest Pharmaceutical-chemical company. The Pharmacy is still owned by members of the family today.

Angel Pharmacy

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