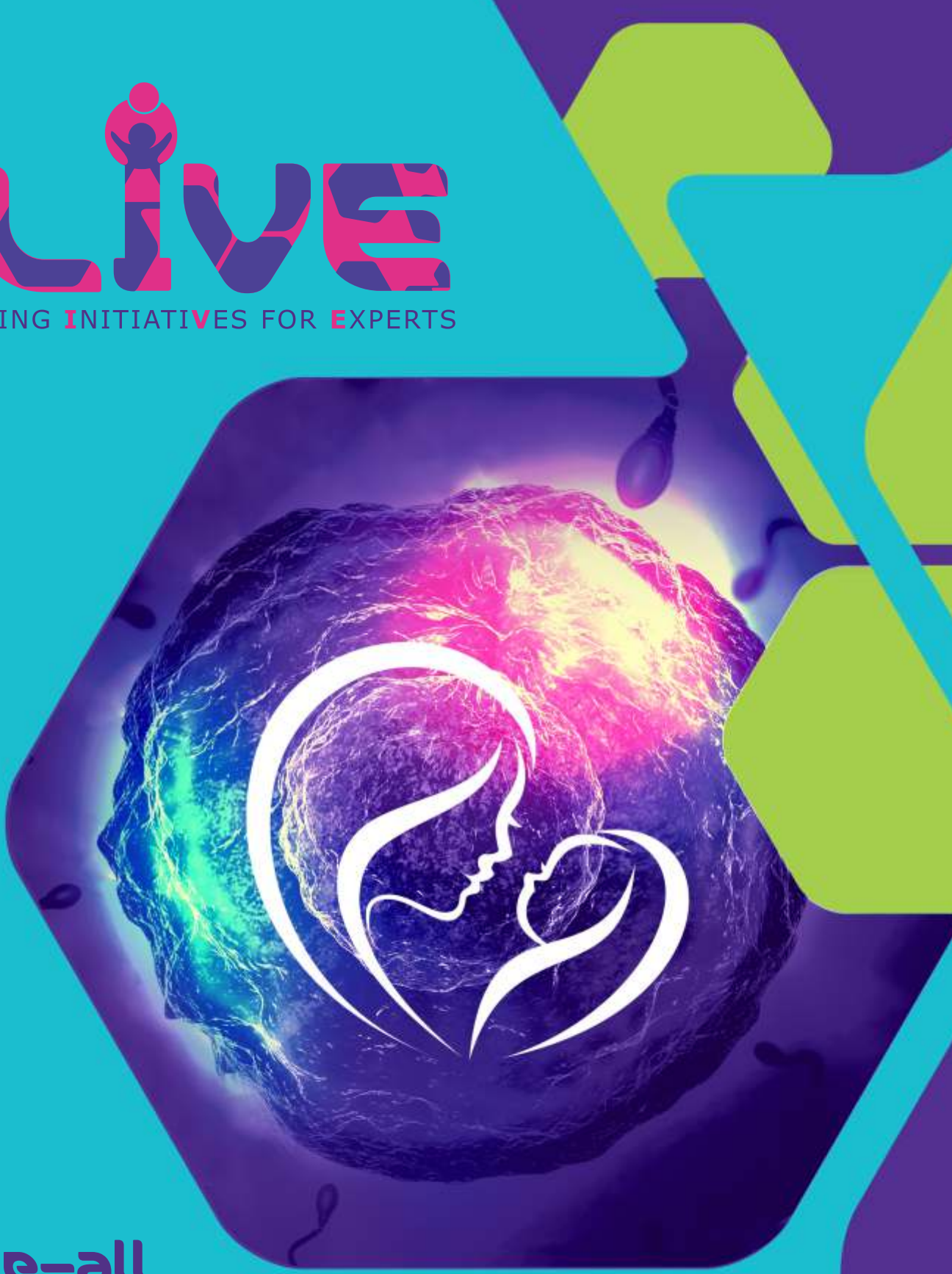
ALIVE

ART LEARNING INITIATIVES FOR EXPERTS

Issue 3



Freeze-all
A Novel Approach to Improve IVF Outcomes

January 2019

MERCK

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abbreviations

IVF	*In-Vitro* Fertilization
COS	Controlled Ovarian Stimulation
WOI	Window of Implantation
GnRH	Gonadotropin-Releasing Hormone
LH	Luteinizing Hormone
hCG	Human Chorionic Gonadotropin
SWOT	Strengths Weaknesses Opportunities and Threats
FET	Fresh Embryo Transfer
IR	Implantation Rate
RR	Relative Risk
OPR	On-going Pregnancy Rate
IR	Infertility Rate
PCOS	Polycystic Ovarian Syndrome
NNT	Number Needed to Treat
OHSS	Ovarian Hyperstimulation Syndrome
PGT	Preimplantation Genetic Testing
ASCO	American Society of Clinical Oncology
GnRHa	Gonadotrophin-Releasing Hormone agonist
ASRM	American Society for Reproductive Medicine
ART	Assisted Reproductive Treatment

expert insights

Dr. Matheus Roque
Scientific Director at Origen Center for Reproductive, Medicine, Brazil

Dr. G. A. Rama Raju
Founder & Director, Krishna IVF Clinic, Visakhapatnam, India.

Dr. Manish Banker
Director, Nova IVI Fertility, Ahmedabad, India.

In the era of precision (personalized) medicine, it appears that we should stop following a one size fits all approach. We should consider defining parameters to discriminate and choose the optimal strategy for each of our patients.

In this Newsletter issue, clinical rationale, efficacy and clinical implications of "Freeze-all strategy" are the driving issues. In recent years, infertility treatment specialists are increasingly recommending the freezing of all available good quality embryos and are scheduling patients for delayed embryo transfer during more controlled and endocrinologically more physiologic (natural or hormonally programmed) cycles.

However, in this issue, we have discussed the lingering questions of a freeze-all approach like "what is the evidence that this approach leads to improved live birth rates and better obstetrical/perinatal outcomes? Are there risks accompanying with frozen-human embryos? Is there experimental evidence indicating the biologic basis for such an approach? What is the impact of progesterone levels on a freeze-all approach?

At the end as per the strengths of evidence we are encouraged to recommend and adopt **"freeze-all"** approach to our patients with more clarity and vigor.

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clinical corner

The rationale of freeze-all strategy

Roque M, Valle M, Kostolias A, Sampaio M, Geber S. Freeze-all cycle in reproductive medicine: current perspectives. JBRA Assist Reprod. 2017;21(1):49–53.

Roque M, Nuto Nóbrega B, Valle M, et al. Freeze-all strategy in IVF/ICSI cycles: an update on clinical utility. Panminerva Med. 2018.

- It is well evident that *in-vitro* fertilization (IVF) success depends not only on embryo quality but also on endometrial receptivity and on the embryo-endometrium interaction.
- Labarta *et al.,* (2011) found differences in endometrial gene expression between patients with elevated progesterone (>1.5 ng/mL) on the day of final oocyte maturation when compared with patients with normal progesterone levels. This study suggested that hyperstimulation might be detrimental to implantation, by altering genes that are crucial for the embryo-endometrium interaction. Controlled ovarian stimulation (COS) associated endometrial modifications may have consequences not only on implantation rates during IVF treatments, but also be associated with obstetric and perinatal complications.
- Thus, a freeze-all strategy has emerged as an alternative to fresh-embryo transfer during IVF cycles. However, the freeze-all strategy is not designed for all IVF patients. There is a need to develop a non-invasive clinical tool to evaluate the endometrial receptivity during a fresh cycle, which enables the selection of patients that would benefit from this strategy.

Impact of COS on endometrium: concept of genomic delay

Horcajadas JA, Riesewijk A, Polman J, et al. Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles. Mol Hum Reprod. 2005; 11:195–205.

During the window of implantation (WOI) COS induces structural, biochemical, and functional genomic modifications of the human endometrium. In 2005, Horcajadas *et al.,* compared the gene expression profile of the human endometrium in natural *vs.* COS cycles throughout the early-mid secretory transition using microarray technology.

Furthermore, COS may lead to differences in the timing of endometrial maturation compared with natural cycles. This genomic delay may be of interest to define gene targets for the understanding of endometrial development under COS and search for the optimal stimulation treatments that better mimic the gene expression profile of the natural cycle.

Endometrial receptivity is affected in stimulation cycles

Papanikolaou EG, Bourgain C, Kolibianakis E, et al. 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(6):1541–7.

Roque M, Nuto Nóbrega B, Valle M, et al. Freeze-all strategy in IVF/ICSI cycles: an update on clinical utility. Panminerva Med. 2018.

Roque M, Valle M, Kostolias A, et al. Freeze-all cycle in reproductive medicine: current perspectives. JBRA Assist Reprod. 2017;21(1):49–53.

- Scientific studies suggested that COS might be detrimental to implantation, by altering genes that are crucial for the embryo-endometrium interaction.
- Several studies continued to show receptivity impairment in stimulated cycles, due to histologic advancement, glandular-stromal desynchrony, genomic dysregulation, and an increased an occurrence of uterine contractions.
- Indeed, it has been suggested that, when comparing the stimulated cycle to the natural cycle, more than 200 genes related to implantation are over or under expressed, suggesting that ovarian stimulation affects the endometrial receptivity.
- Moreover, cycles with supra-physiologic levels of progesterone (>1.5 ng/mL) on the trigger day show differences in around 140 implantation-related genes when compared to cycles with lower progesterone levels.
- Few studies demonstrated that the endometrial modifications related to COS may have consequences not only on implantation rates during IVF treatments, but also an association with obstetric and perinatal complications.

The window of implantation (WOI)

Roque M, Nuto Nóbrega B, Valle M, et al. Freeze-all strategy in IVF/ICSI cycles: an update on clinical utility. Panminerva Med. 2018.

- The idea of the **WOI** is driven by programmed progesterone exposure after enough estrogen exposure. In a natural 28-day cycle, the WOI is supposed to occur during days 22 to 24. However, it seems that compared to natural cycles WOI is different in stimulated cycles.
- Late 1990's research associated supra-physiologic hormone levels during COS with endometrial histologic advancement and poor implantation.
- These studies showed receptivity impairment in stimulated cycles, genomic dysregulations and increased frequency of endometrial waves. So it is necessary to define the situations before implementing the freeze-all policy.

Effect of COS on endometrial gene expression.

Horcajadas JA, Riesewijk A, Polman J, et al. Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles. Mol Hum Reprod. 2005;11:195–205.

Roque M, Nuto Nóbrega B, Valle M, et al. Freeze-all strategy in IVF/ICSI cycles: an update on clinical utility. Panminerva Med. 2018.

Recently, several clinical studies have demonstrated the fact that endometrial gene expression profiles are disturbing and deleterious to embryonic implantation. The endometrium suffers a morphological advancement in the early luteal phase, which is demonstrated by histological techniques and scanning electron microscopy, there is a down-regulation of endometrial estrogen receptor and progesterone receptor and biochemical changes in the endometrial fluid.

In 2005 Horcajadas *et al.,* published a study evaluating the endometrium gene expression profile. They performed endometrial biopsies in the same oocyte donors during a fresh cycle on the 7th day after luteinizing hormone (LH) surge and compared it to endometrial samples on the 7th day after human chorionic gonadotropin (hCG) trigger in a stimulated cycle. They found that there were over 200 genes related to implantation that were over or male it one word during COS when compared to a natural cycle. These changes may be associated with the supra-physiologic hormonal levels observed during COS.

In frozen-thawed embryo transfer (FET), concerns were raised about the possible deleterious effect of COS on the endometrium, resulting in a poorer obstetric and perinatal outcome in fresh cycles than freeze-all transfers. From these concerns, an idea of "freeze-all strategy" was supported by several researchers. Researchers have demonstrated that the freeze-all approach has assisted in overcoming an endometrial problem.

Birth of freeze-all strategy

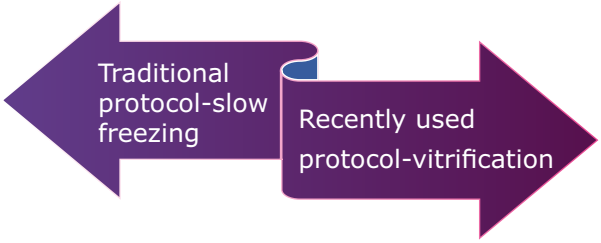
Weon-Young Son and Seang-Lin Tan. Comparison between slow freezing and vitrification for human embryos. Expert Rev. Med. Devices. 2009; 6(1):1–7.

Maheshwari A and Bhattacharya S. Elective frozen replacement cycles for all: ready for prime time? Hum Reprod. 2013;28(1):6–9.

Evolution

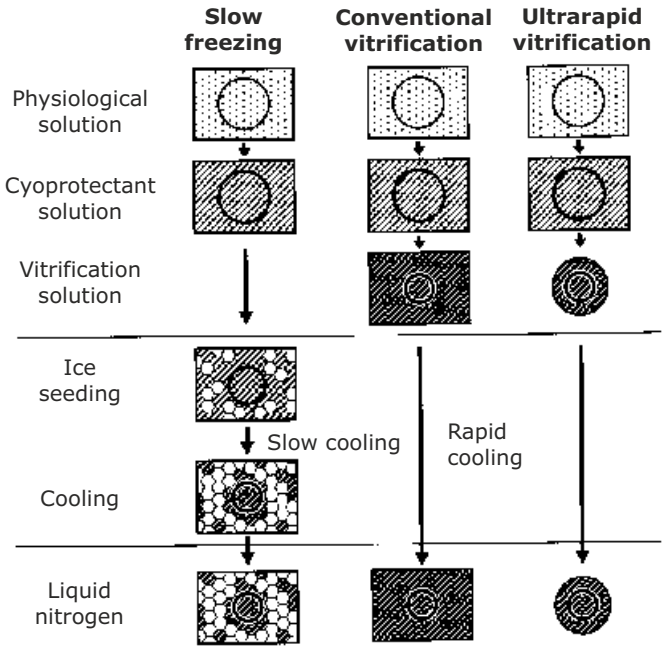
- COS with multi-follicular development leads to supra-physiologic levels of estrogens by growing follicles, which can have negative impact on endometrial angiogenesis and implantation. COS also leads to disruption of transcriptional genes involved in endometrial receptivity.
- Thus, it has been suggested that transfer of frozen-thawed embryos in a non-stimulated cycle is more conducive to early placentation and embryogenesis in comparison with COS cycle.
- Also, physical effects of freezing and thawing may filter out those embryos of borderline quality. This would allow the more robust embryos to survive and develop, resulting in more optimal fetal growth.

- Embryo cryopreservation has several potential advantages in human IVF. The goal of the cryopreservation procedure in human assisted reproductive technology should be to ensure high survival and viability of human embryos after thawing.
- The determining parameters for the success of any cryopreservation protocol: the way cells regain equilibrium in response to cooling and the speed of freezing.
- The field of cryobiology has been progressed. The slow-freezing protocols have been replaced by vitrification, which is a very short and more effective procedure, and it is envisaged that the time will come when vitrification will be used more commonly and widely for storage of all kinds of human embryos.



Slow freezing	Vitrification
Used to freeze-all kinds of human embryos	Used to freeze all kinds of human embryos
Clinical results are not consistent and satisfactory	Consistent and clinically more effective
Concentration of the cryoprotectant is low and the cooling rate is very slow	Concentration of the cryoprotectant is high with ultrarapid cooling rate
Requires expensive equipment	It does not require specialized expensive equipment and so economic

Figure 1. Schematic representation of an oocyte/embryo (circle) during slow freezing, conventional vitrification and ultrarapid vitrification. White hexagons represent ice crystals. The concentration of cryoprotectant is shown by the darkness of shading.



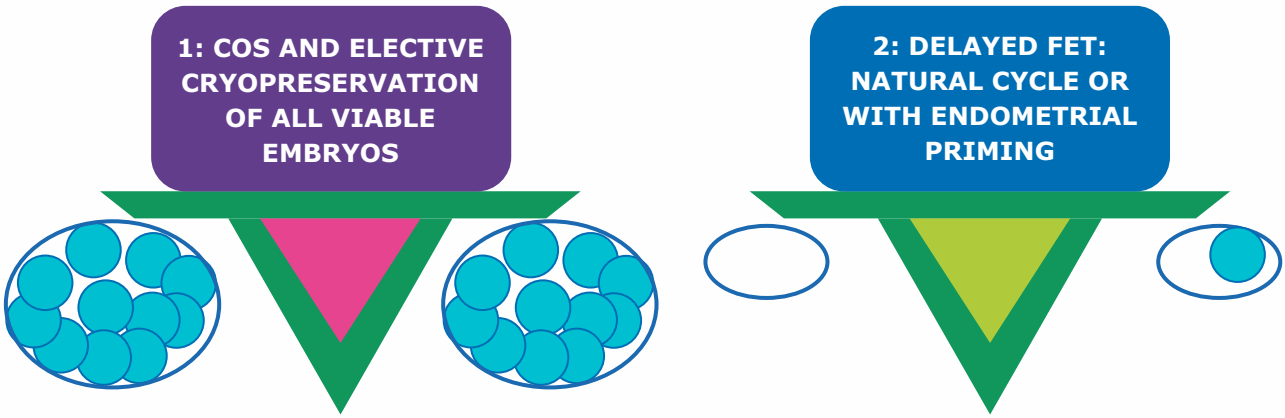
As per the evidence, up to 100% survival and high pregnancies were obtained after thawing of the vitrified blastocysts. Therefore, vitrification has become a viable and promising alternative to traditional approaches in cryopreservation of highlight **"Vitrification is the future in IVF."**

The freeze-all technique is an emerging strategy

Roque M, Valle M, Kostolias A, Sampaio M, Geber S. Freeze-all cycle in reproductive medicine: current perspectives. JBRA Assist Reprod. 2017;21(1):49–53.

Kasai M. Advances in the cryopreservation of mammalian oocytes and embryos: Development of ultrarapid vitrification. Reproductive Medicine and Biology 2002; 1: 1–9.

- The improvement in cryopreservation techniques associated with the suspected impairment in endometrial receptivity due to the supra-physiologic hormonal levels observed during fresh transfer started the freeze-all strategy discussion.
- The freeze-all strategy has emerged as an alternative to fresh-embryo transfer (FET) during IVF cycles.
- In the freeze-all strategy, the entire cohort of embryos is cryopreserved (Step 1) and not just the "second best", and the best embryos are transferred in a posterior cycle with a more physiologic endometrium (Step 2).



FET: Frozen-embryo transfer, COS: Controlled ovarian stimulation

The freeze-all strengths, weaknesses, opportunities and threats (SWOT) analysis

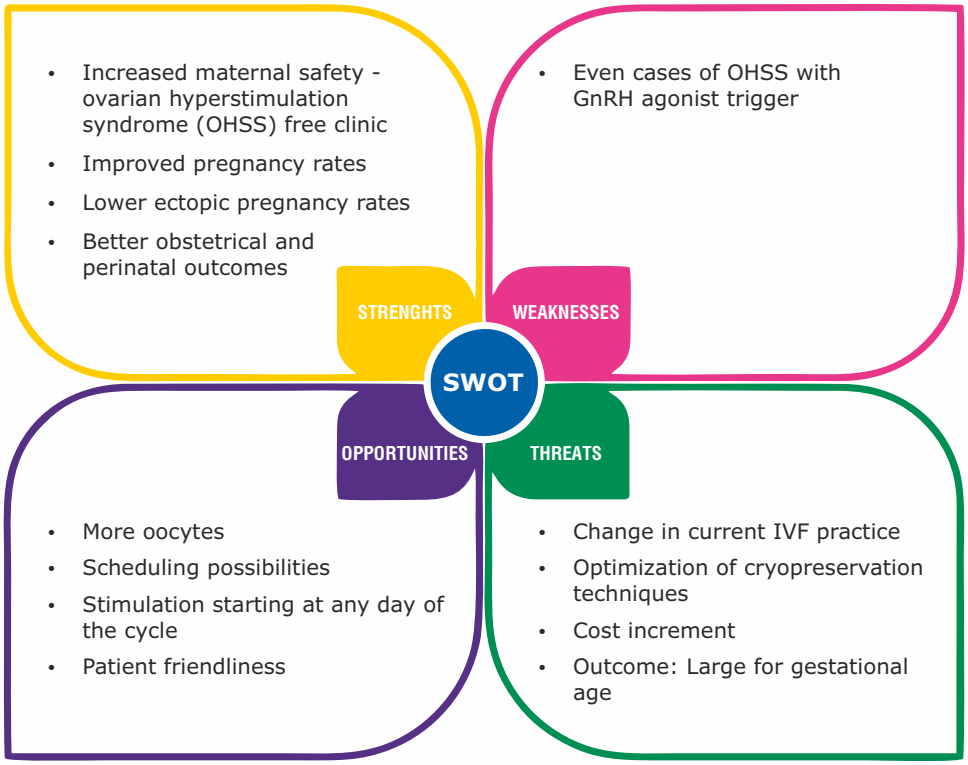
Blockeel, C. A fresh look at the freeze-all protocol: a SWOT analysis. Human Repro. 2016;31(3):491–97.

An emerging "freeze-all" strategy resulted in the segmentation of ovarian stimulation (using a gonadotropin-releasing hormone (GnRH) antagonist protocol ovulation triggering (with a GnRH agonist), the elective cryopreservation of all embryos (by vitrification) and a frozen-thawed embryo transfer in a subsequent natural or artificial cycle (Figure 2).

In this regard, it is imperative to shed some light on freeze-all strategy by performing the SWOT analysis before it becomes a gold standard in IVF treatment.

Figure 2. The freeze-all protocol

Figure 3. SWOT analysis of a freeze-all strategy



SWOT analysis has given the insights on the freeze-all strategy that might become the gold standard for IVF stimulation soon.

crucial points to remember for freeze-all policy

Roque M, Nuto Nóbrega B, Valle M, et al. Freeze-all strategy in IVF/ICSI cycles: an update on clinical utility. Panminerva Med. 2018.

- During the implementation of the freeze-all strategy, two crucial issues need to be considered, namely,

The method of endometrial priming for transfer.

The duration of exogenous progesterone administration before frozen-embryo transfer.

- There seem to be **no differences in reproductive outcomes of frozen-embryo transfer cycles** when comparing different strategies for priming the endometrium. Thus, r**esults seem to be similar when comparing natural cycle, modified natural cycle, and artificial cycle with or without GnRH agonist.**
- The standardization of the timing between the start of progesterone administration and the day of the embryo transfer based on the development stage of the embryo is the essential factor.
- Importantly, **the frozen-embryo transfer cycle can be performed in a subsequent menstrual cycle** immediately following the cycle in which oocyte retrieval was carried out, as there are no differences in the clinical outcomes when comparing different intervals between the oocyte retrieval and the frozen-embryo transfer cycle.

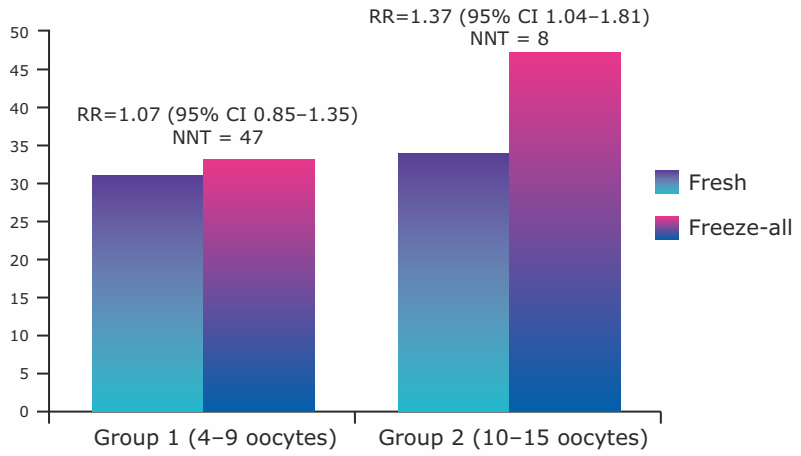
Impact of fresh-embryo transfer on pregnancy outcomes

Roque M, Valle M, Guimarães F, et al. Freeze-all cycle for all normal responders? J Assist Reprod Genet. 2017;34(2):179–185.

- Fresh-embryo transfer is still a routine practice in IVF cycles. However, patients with poorer ovarian response do not benefit from the freeze-all strategy. Since last decade, cryopreservation techniques have improved, which means that the quality and potential for implantation of frozen-embryos are like those for fresh-embryos.

Study purpose	Study design	Study findings
• To evaluate the freeze-all strategy in subgroups of normal responders.	• It was an observational, cohort study performed in a private IVF center. • A total of 938 IVF cycles were included in this study. • The comparison between the fresh-embryo transfer (n=523) and the freeze-all cycles (n=415) was performed in the present study. • The analysis was performed in two subgroups of patients based on the number of retrieved oocytes: group 1 (4–9 oocytes) and group 2 (10–15 oocytes).	• In group 1 (4–9 retrieved oocytes), the implantation rates (IR) were 17.9 and 20.5% (p=0.259) in the fresh and freeze-all group, respectively; the ongoing pregnancy rates (OPR) were 31 and 33% (p=0.577) in the fresh and freeze-all group, respectively. • In group 2 (10–15 oocytes), the IR were 22.1 and 30.1% (p=0.028) and the OPR were 34 and 47% (p=0.021) in the fresh and freeze-all groups, respectively.

Figure 4. Ongoing pregnancy rates with its relative risk (RR) and the number needed to treat (NNT) in fresh *vs.* freeze-all cycles.



As per the above study, the freeze-all policy in normal responders is strongly associated with better IVF outcomes than fresh-embryo transfer, although there is no benefit in performing the strategy in suboptimal responders.

when to do freeze-all?

Roque M, Valle M, Sampaio M, et al. Obstetric outcomes after fresh versus frozen-thawed embryo transfers: A systematic review and meta-analysis. JBRA Assist Reprod. 2018;22(3):253–260.
Roque M, Haahr T, Esteves S, et al. The 'Big Freeze': freeze-all should not be used for everyone. Human Reproduction. 2018;33(8): 1577–1578.

- Roque M, *et al.,* emphasized that the freeze-all policy should not be offered to all the patients, but should be offered to those with a clear indication of the benefits of such strategy.

In patients with high-risk of ovarian hyperstimulation syndrome.

Evidence from randomized controlled trials reported a significant benefit of freeze-all when used in hyper-responders patients.

In patients undergoing preimplantation genetic testing for aneuploidy (PGT-A) at the blastocyst stage.

Freeze-all strategies for the management of ovarian hyperstimulation syndrome

Yuhua Shi, Yun Sun, Cuifang Hao, et al. Transfer of fresh versus frozen embryos in ovulatory women. N Engl J Med. 2018;378:126–36.

- Multicenter randomized controlled trial conducted in 2,157 ovulatory women with infertility undergoing either fresh–embryo transfer or embryo cryopreservation at cleavage stage (day 3) followed by frozen-embryo transfer.
- Frozen-embryo transfer resulted in a significantly lower risk of the ovarian hyperstimulation syndrome than fresh–embryo transfer (0.6% *vs*. 2.0%; RR, 0.32; 95% CI, 0.14 to 0.74; $p = 0.005$). The risks of obstetrical and neonatal complications and other adverse outcomes did not differ significantly between the two groups.
- In this trial, ectopic pregnancies and preeclampsia did not differ significantly between the two groups.
- Youhua *et al.,* found a lower risk of second trimester pregnancy loss in the frozen-embryo group than in the fresh-embryo group (Table 1).

Table 1. Fertility outcomes and treatment complications after first embryo transfer

Outcome	Frozen-embryo Group (N = 1077)	Fresh-embryo Group (N = 1080)	*p*-value
Primary outcome: live birth number (%)	48.7%	50.2%	0.5
Moderate or severe ovarian hyperstimulation syndrome before biochemical pregnancy	0.6%	2%	0.005

There was no statistical difference in live birth rate when comparing frozen-embryo transfer to fresh cycles. **However, the risk of moderate or severe ovarian hyperstimulation syndrome was lower with frozen-embryo transfer.**

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Freeze-all strategy based on progesterone levels on trigger day

Esteves SC, Khastgir G, Shah J. Association between progesterone elevation on the day of human chronic gonadotropin trigger and pregnancy outcomes after fresh embryo transfer in in vitro fertilization/intracytoplasmic sperm injection cycles. Front Endocrinol (Lausanne). 2018;9:1–10.

Some researchers have reported that raised progesterone levels (>1.5 ng/mL) would be detrimental and thus a "freeze-all" embryos policy should be adopted.

The progesterone cut-off points associated with decreased pregnancy outcomes in fresh–embryo transfer cycles were

Furthermore, progesterone elevation is not a universal phenomenon with evidence indicating that its detrimental consequences on pregnancy outcomes do not affect all patient populations equally. An individualized approach should be used in cases of progesterone elevation, which could include fresh-embryo transfers in hyper-responders with low-risk of ovarian hyperstimulation syndrome and in patients with supranumerary embryos undergoing blastocyst transfer. In normal responders with progesterone elevation undergoing fresh-embryo transfers, a "freeze-all" strategy might be considered. As for poor–responders, the optimal strategy in the face of progesterone elevation is yet to be determined.

Impact of freeze-all on preimplantation genetic testing (PGT) for aneuploidies

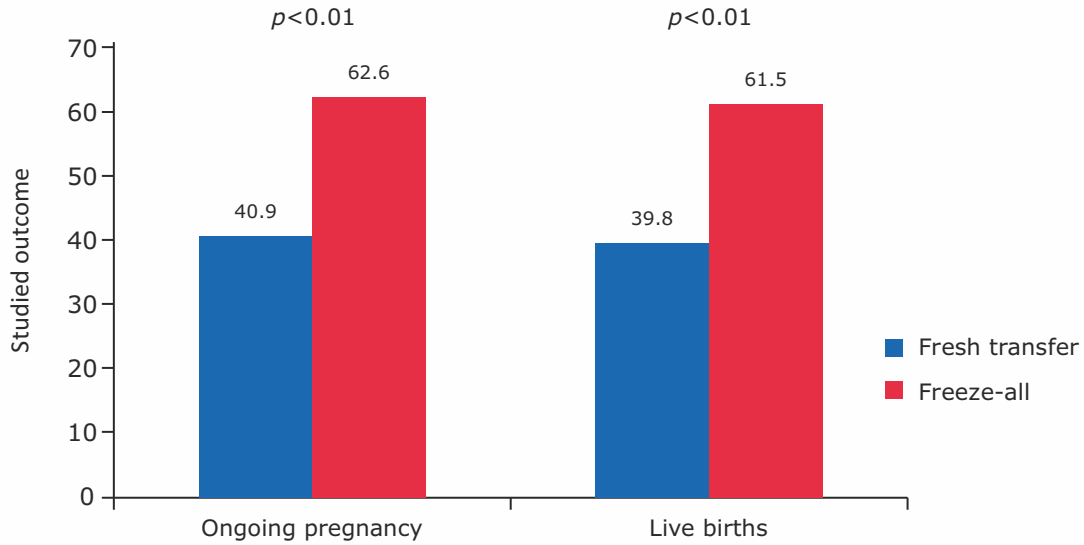
Coates A, Kung A, Mounts E, et al. Optimal euploid embryo transfer strategy, fresh versus frozen, after preimplantation genetic screening with next generation sequencing: a randomized controlled trial. Fertil Steril. 2017;107(3):723–730.

The author compared the fresh *vs.* vitrified protocols used to transfer euploid blastocysts after IVF with preimplantation genetic testing for aneuploidy (PGT-A). In this investigation, total 179 patients were randomized at the time of hCG administration to either a freeze-all cycle or a fresh day 6 embryo transfer during the stimulated cycle. In this study, implantation rates (sac/embryo transferred), ongoing pregnancy rates (OPRs) (beyond 8 weeks), and live birth rate per embryo transfer in the primary transfer cycle were measured.

This randomized controlled trial has demonstrated that the ongoing pregnancy rates and live birth rates were significantly higher in the frozen-embryo transfer group compared with the fresh transfer (Figure 5). In addition, a significantly higher proportion of patients can attain the desired embryo transfer strategy in the frozen-embryo transfer group compared with the fresh-embryo transfer group.

The survival rate of blastocyst embryos has improved significantly, making the transfer of frozen-thawed embryos a pragmatic option for patients and practitioners.

Figure 5. Outcomes compared for fresh *vs.* freeze-all in PGT-A cycles



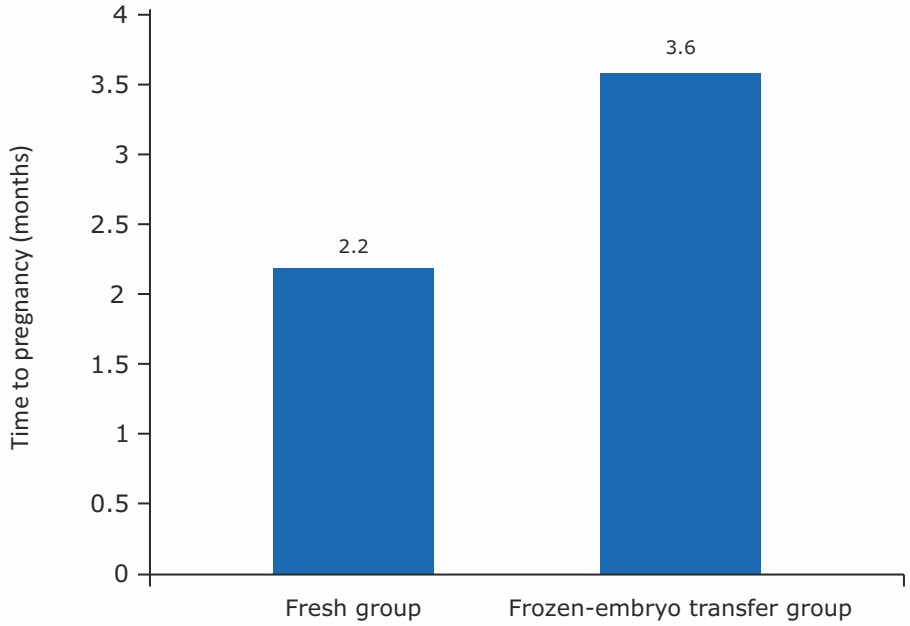
The above study findings suggest a trend toward favoring the freeze-all option as a preferred transfer strategy in PGT-A cycles.

Impact of freeze-all strategy on time to pregnancy

Vuong L, Dang V, Huynh BG, et al. IVF Transfer of Fresh or Frozen Embryos in Women without Polycystic Ovaries. New England Journal of Medicine, 2018; 378 (2): 137–47.

- The study investigated almost 800 women who had infertility not related to polycystic ovarian syndrome (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 happened subsequently without the use of IVF drugs.
- After the first completed cycle of IVF, ongoing pregnancy occurred in 36% of women and livebirth rates after the first embryo transfer was 33.8% in the frozen-embryo group.

Figure 6. Median time to pregnancy in fresh *vs*. frozen-embryo transfer group



In this study, no significant difference was observed in the rate of ongoing pregnancy or live birth between frozen-embryo transfer and fresh-embryo transfer in women without the PCOS who were undergoing IVF.

Freeze-all strategy: concluding comments based on the above evidence

Vuong L, Dang V, Huynh BG, et al. IVF Transfer of Fresh or Frozen Embryos in Women without Polycystic Ovaries. New England Journal of Medicine. 2018; 378 (2): 137–47.
Roque M, Valle M, Kostolias A, Sampaio M, Geber S. Freeze-all cycle in reproductive medicine: current perspectives. JBRA Assist Reprod. 2017;21(1):49–53.

RATIONALE

- Hyperstimulation
- Evolving endometrium-embryo interaction
- Altered gene expression
- Adverse effects of COS
- Progesterone elevation cut-off levels (at present, 1.5 ng/mL)

CLINICAL BENEFITS

- Improves implantation rates in specific groups

SAFETY

- Prevent the development of ovarian hyperstimulation syndrome
- Reduces the risk of low-birth weight and pre-term birth

Overall, individualized approach should be considered in case of IVF treatment but how?

Freeze-all strategy is recommended in hyper-responders, patients with risk of ovarian hyperstimulation syndrome, progesterone rise and preimplantation genetic testing for aneuploidies

Fresh-embryo transfer is recommended to normal-responders

Yet strategy is not defined for poor-responders

recent trends

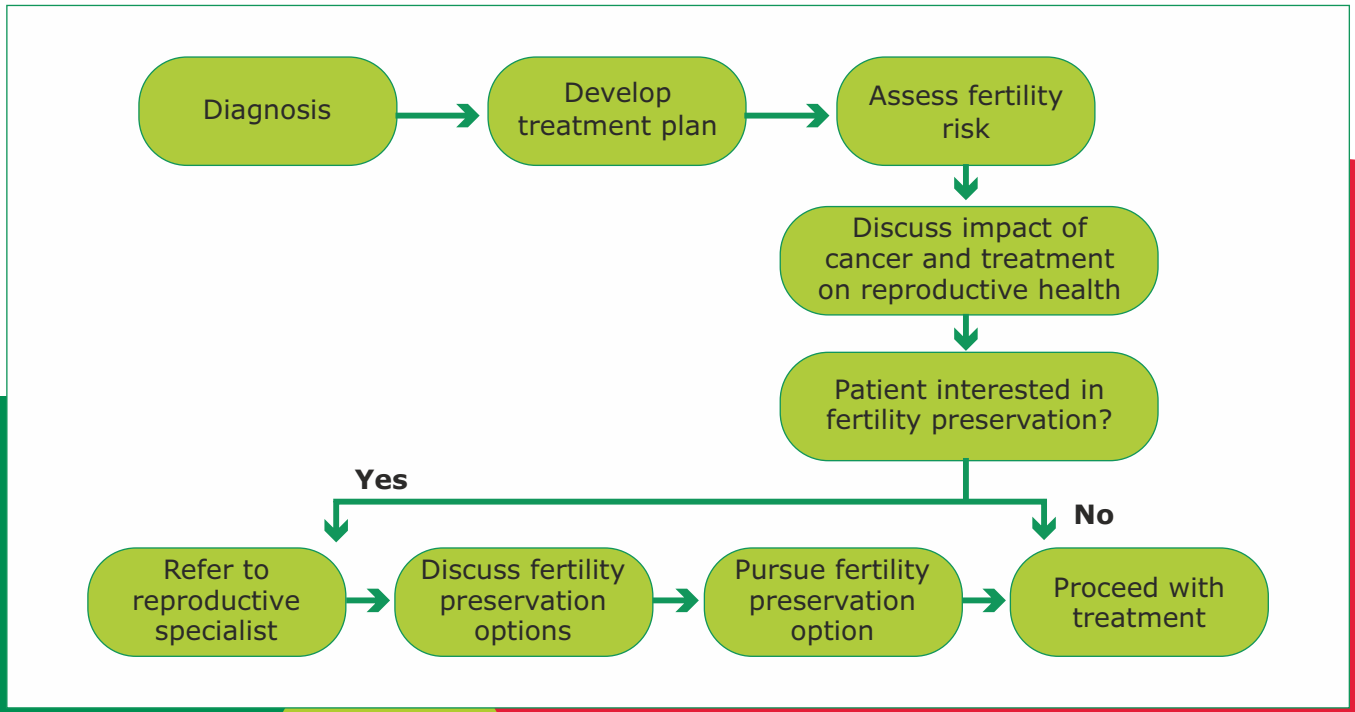
Fertility preservation

Vuong L, Dang V, Huynh BG, et al. IVF Transfer of Fresh or Frozen Embryos in Women without Polycystic Ovaries. New England Journal of Medicine. 2018; 378 (2): 137–47.

- The impact of cancer therapy on future fertility has raised concerns and fertility preservation is becoming an important component in the management of cancer patients. It is known that the loss of the reproductive capacity negatively impacts the quality-of-life.
- The American Society of Clinical Oncology guidelines recommend that oncology patients in reproductive age should be counselled on the options for fertility preservation and future reproduction prior to the initiation of gonadotoxic therapy.
- There are several strategies for fertility preservation in patients with cancer, including preservation of gametes, embryos or gonadal tissue for their use in the future. Cryopreservation of mature oocyte is currently one of the major approaches with acceptable pregnancy rates, providing real options for oncological patients of adolescent age or women who do not have a male partner.

Fertility preservation - Where does it fit?

Fertility Preservation for Women Diagnosed with Cancer. Available at *https://www.savemyfertility.org/ pocket-guides/providers/fertility-preservation-women-diagnosed-cancer.* Accessed on November, 2018.



Indications for fertility preservation

Malignant diseases requiring gonadotoxic chemotherapy, radiotherapy or bone marrow transplantation	a) Hematological diseases (leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma)
	b) Breast cancer
	c) Sarcoma
	d) Some pelvic cancers
Benign conditions	a) Systemic diseases requiring chemotherapy, radiotherapy, or bone marrow transplantation
	b) Ovarian diseases
	c) Bilateral benign ovarian tumors
	d) Severe and recurrent ovarian endometriosis
	e) Possible ovarian torsion
	f) Risk of premature ovarian insufficiency
	g) Family history
	h) Turner syndrome
Personal reasons	a) Age
	b) Delayed childbearing

Fertility preservation in patients with cancer: American Society of Clinical Oncology (ASCO) 2018 guideline update

Oktay K, Harvey BE, Partridge AH. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(19):1994–2001.

- Healthcare providers should initiate the discussion on the possibility of infertility with patients with cancer treated during their reproductive years or with parents/guardians of children as early as possible.
- Providers should be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, providers should advise patients regarding potential threats to fertility as early as possible in the treatment process to allow for the widest array of options for fertility preservation.
- The discussion should be documented. Sperm, oocyte, and embryo cryopreservation are considered standard practice and are widely available. Vitrification showed a better performance than slow freezing.
- There is conflicting evidence to recommend gonadotrophin-releasing hormone agonists (GnRHa) and other means of ovarian suppression for fertility preservation.
- When proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency.
- GnRHa should not be used in place of proven fertility preservation methods. The panel notes that the field of ovarian tissue cryopreservation is advancing quickly and may evolve to become standard therapy in the future.

Social egg freezing: A viable option for fertility preservation

Caitlin Dunne and Jeffrey Roberts. Social egg freezing: A viable option for fertility preservation. BC Medical Journal. 2016;58(10): 573–77.
Petropanagos A, Cattapan A, Baylis F, et al. Social egg freezing: risk, benefits and other considerations. CMAJ. 2015;187(9):666–9.

- Social egg freezing refers to the cryopreservation of mature oocytes on an elective basis for delayed childbearing. As of 2013, the American Society for Reproductive Medicine (ASRM) no longer considers egg freezing experimental, and large organizations such as Apple, Facebook, and the US military have started offering social egg freezing as an employee benefit.

How well does egg freezing work?

- The logistical burden of anonymous egg donation in synchronous IVF cycles can be eased by providing the facility by fertility clinics to often bank the frozen eggs from donors and subsequently distribute them to recipients for warming and fertilization at a more convenient time. In 2016, reports were published for two studies that examined large numbers of elective egg freezing cycles.
- Recently, Cobo and colleagues conducted study included 6362 women who underwent social egg freezing. The researchers found that 9.3% of these subjects had returned to use their eggs, that the average age of those returning was 37.7 years, and that the overall egg survival rate was 85.2%. For women who were 35 or younger at the time of egg freezing and who banked 10 eggs, the average live birth rate when 10 eggs were used was an impressive 60.5% (95% CI, 34.5–89.5%).
- In the group of women 36 or older, the same 10 eggs yielded a significantly lower live birth rate of 29.7% (95% CI, 15.2–34.2%). It means that for women younger than 36, social egg freezing appears to be at least as good as the national IVF averages. Given that social egg freezing is relatively new, most of the eggs retrieved for elective freezing so far are presented in cryostorage.

Social egg freezing is typically offered to women under 38 years of age who want to preserve the option of having healthy, genetically related children later.

What are the potential benefits of social egg freezing and IVF

- Social egg freezing, followed by IVF and embryo transfer, offers two important benefits to women who anticipate becoming pregnant at an advanced age:
  - It provides them with the possibility of becoming a genetic parent using their frozen–thawed eggs.
  - It reduces the risk of having children with chromosomal abnormalities associated with ovarian aneuploidy.
  - In addition, for women who do not have a partner or for women who have moral concerns about the status of a developing embryo, egg freezing may be a preferable alternative to embryo freezing.

The best chance for a future pregnancy appears to result from freezing at least 8 to 10 eggs before age 36. Social egg freezing is a safe and viable option for women in our society. It does not provide women with the same reproductive longevity that men enjoy, but it can allow women that delay childbearing for 2 to 10 years to increase their chance of having a baby in the future and may be a reasonable choice for women wishing to do this. Women may regard social egg freezing as a reproductive insurance policy or just as a backup plan.

technology corner

GAVI® The world's first automated vitrification instrument

Merck. Available at https://www.merckgroup.com/content/dam/web/corporate/non-images/press-releases/2016/oct/en/Merck_Fertility_Gavi_oocytes_Geri_medium_EN.pdf. Accessed on November, 2018.

Sole M, Polyzos M, Gonzalez Llagostera C. Automatic vs manual vitrification of human oocytes. preliminary results of the first randomised controlled trial using sibling oocytes. Fertility and Sterility. 2017; 108(3):e57.

Gavi Whitepaper. Available at s://www.geneabiomedx.com/ GeneaBioMedx/media/GeneaBioMedx/Downloads/QRTM184-Gavi-White-Paper.pdf?ext=.pdf. Accessed on January, 2019.

In 2016, Merck, a leading science and technology company, announced the launch of two innovative fertility technologies, Gavi® oocyte protocol and Geri® medium. Both products help to improve key steps of assisted reproductive treatment (ART) an area where laboratory technologies play a vital role in treatment success.

- Gavi® allows freezing of oocytes and embryos at key stages (Figure 7).
- Geri® medium supports undisturbed embryo growth (Figure 8).
- Launches in line with Merck's healthcare strategy to deliver innovation through best-in-class assets for the benefit of patients.

Figure 7. Gavi® the automated vitrification instrument

Figure 8. Geri® Benchtop incubator

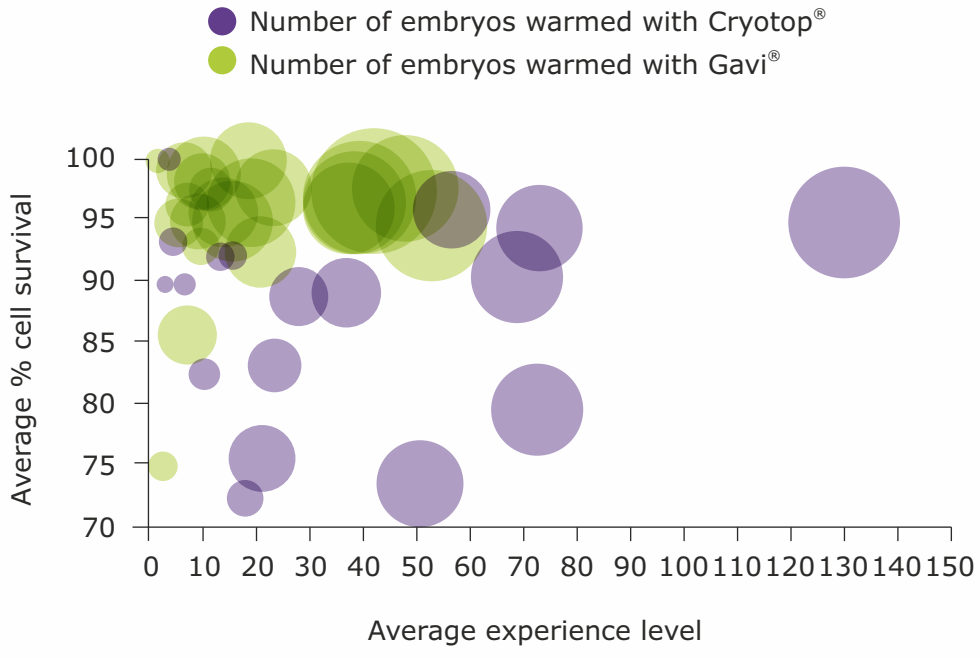
- Preserving oocytes or embryos for future IVF and embryo transfers by cooling them to deep sub-zero degrees is a key step in the laboratory. Gavi® is the world's first automated instrument for this preservation technique, also called vitrification. With its latest product innovation, Gavi® provides clinicians with added flexibility when taking important treatment decisions with and for their patients.
- An embryo survival with Gavi® is ≥95% as compared to Cryotop® (36%), $p<0.001$ (Figure 9). As shown in **Table 2** post warming survival rates were comparable between groups.
- Geri® medium was developed to help improve another critical factor for successful treatment, embryo cultivation. After fertilization, the embryo needs to grow and develop before it is transferred into a woman's womb. With the single-step culture medium, now it is possible to support undisturbed incubation and optimal embryo development.

GAVI® clinical data

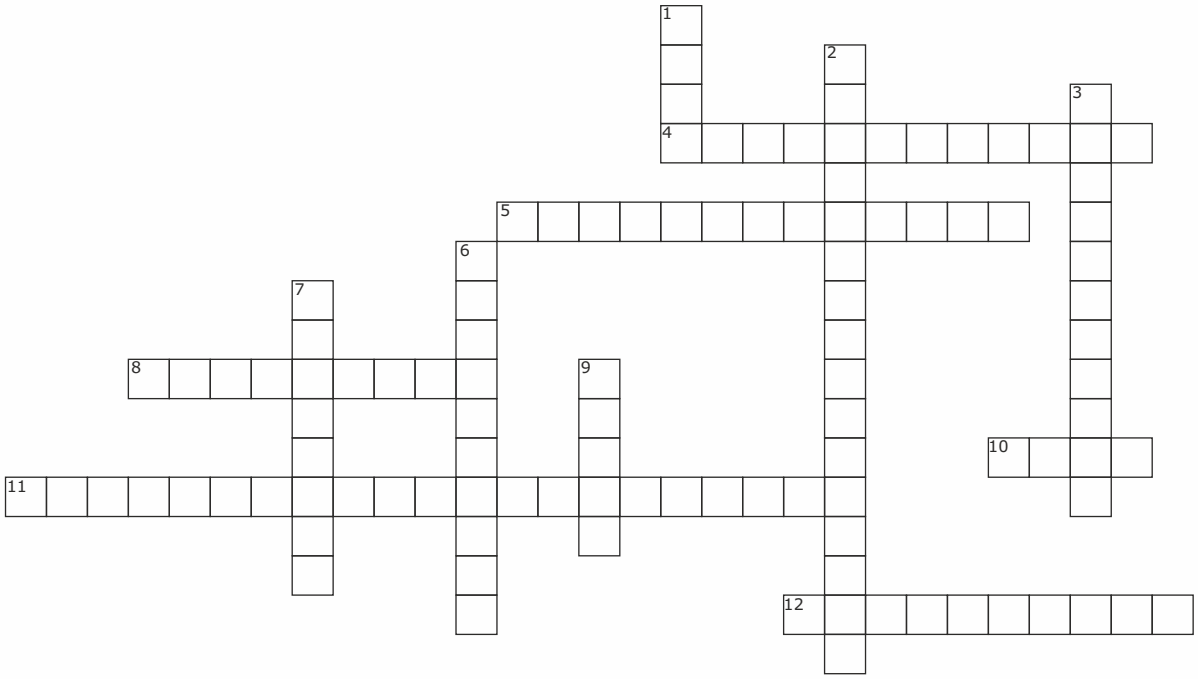
Table 2. GAVI® generates comparable oocyte survival rate and increased embryo quality

Early stage development	Cryotop®	Gavi®
Oocyte donation cycles (n)	11	11
Number of metaphase II (MII) oocytes	68	70
Warming cycles	7	7
Warming oocytes	38	42
Survival rate	**76.3**	**78.6**
Fertilization rate	**65.5**	**75.8**
Good quality embryos on D3 (%)	**15.8**	**32**
Multinucleated D2-D3 (%)	**47.4**	**32**
Ongoing embryos (%)	**57.9**	**64.0**

Figure 9. Recovered embryo survived by freezing. Gavi® *vs.* Cryoyop®



CROSSWORD



Across

4. Progesterone cut-off of 1.75 ng/mL is categorized as .....responders.
5. A process in which concentration of the cryoprotectant is high with ultra-rapid cooling rate.
8. Geri® is a benchtop.....
10. .....analysis should be done before implementation of freeze-all policy.
11. .....is not a universal phenomenon.
12. A.....strategy has emerged as an alternative to fresh-embryo transfer during IVF cycles.

Down

1. .....is product innovation of Merck.
2. The freeze-all policy in.....is strongly associated with better IVF outcomes than fresh-embryo transfer.
3. Endometrial receptivity is affected in.....cycles.
6. Ovarian hyperstimulation syndrome is an .....complication of assisted reproduction technology.
7. Preserving oocytes or embryos for future *in-vitro* fertilization and embryo transfers by cooling them to deep.....degrees is a key step in the laboratory.
9. Freeze-all strategy should be considered as an ideal option for.....responders.

Across
4. Intermediate
5. Vitrification
8. Incubator
10. SWOT
11. Progesterone elevation
12. Freeze-all

Down
1. GAVI®
2. Normal responders
3. Stimulation
6. Iatrogenic
7. Sub zero
9. Hyper

FEEDBACK FORM

Steps to scan QR code

1) Open the Camera application either from the lock screen or tapping on the icon from your home screen.
2) Hold your device steady for 2-3 seconds towards the QR Code.
3) Click on the notification to open the content of the QR Code.

THREE CENTURIES OF TRANSFORMATION

MERCK
350th ANNIVERSARY

2018

2015 — Acquisition of Sigma-Aldrich

2014 — Acquisition of AZ Electronic Materials

2011 — We take up the fight against schistosomiasis, aiming to eliminate this tropical disease in Africa

2010 — Acquisition of Millipore

2007 — Acquisition of Serono

1995 — Initial public offering

1969 — The Institute for Experimental Drug Research is established

1955 — We enter the field of bio-technology, assuming a pioneering role in Germany

1950/60 — Our subsidiaries are founded or reestablished around the world

1945 — All foreign subsidiaries are lost and the company starts up again from the ruins in Darmstadt

1917 — Our U. S. subsidiary Merck & Co, is expropriated as a consequence of World War 1

1900 — Merck from Darmstadt, Germany is represented on all continents

1827 — Emanuel Merck begins production on an industrial scale

1668 — Friedrich Jacob Merck purchases the "Angel pharmacy" (Engel-Apotheke) in Darmstadt

Merck Specialities Pvt. Ltd.
Godrej One, 8th Floor, Pirojshanagar Nagar, Eastern Express Highway,
Vikroli East, Mumbai, Maharashtra 400079, India.

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