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Strategies for Maximizing FET Outcomes

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Disclosures

Founder of Innovative Cryo Enterprises LLC

We focus on all aspects of cryopreservation and offer vitrification media, free advise on all things cryobiological, and consulting services.

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Why FET???

Has the time come for a freeze-all strategy in ART?

CRB 2016

To Freeze or not to freeze: A debate on the freeze-all strategy

PCRS 2017

Bruce Shapiro, M.D., Ph.D.

Evidence for FET

Fresh vs. FET preg rates

2005-2006 FET live birth rates around the country began to surpass those with fresh transfers.

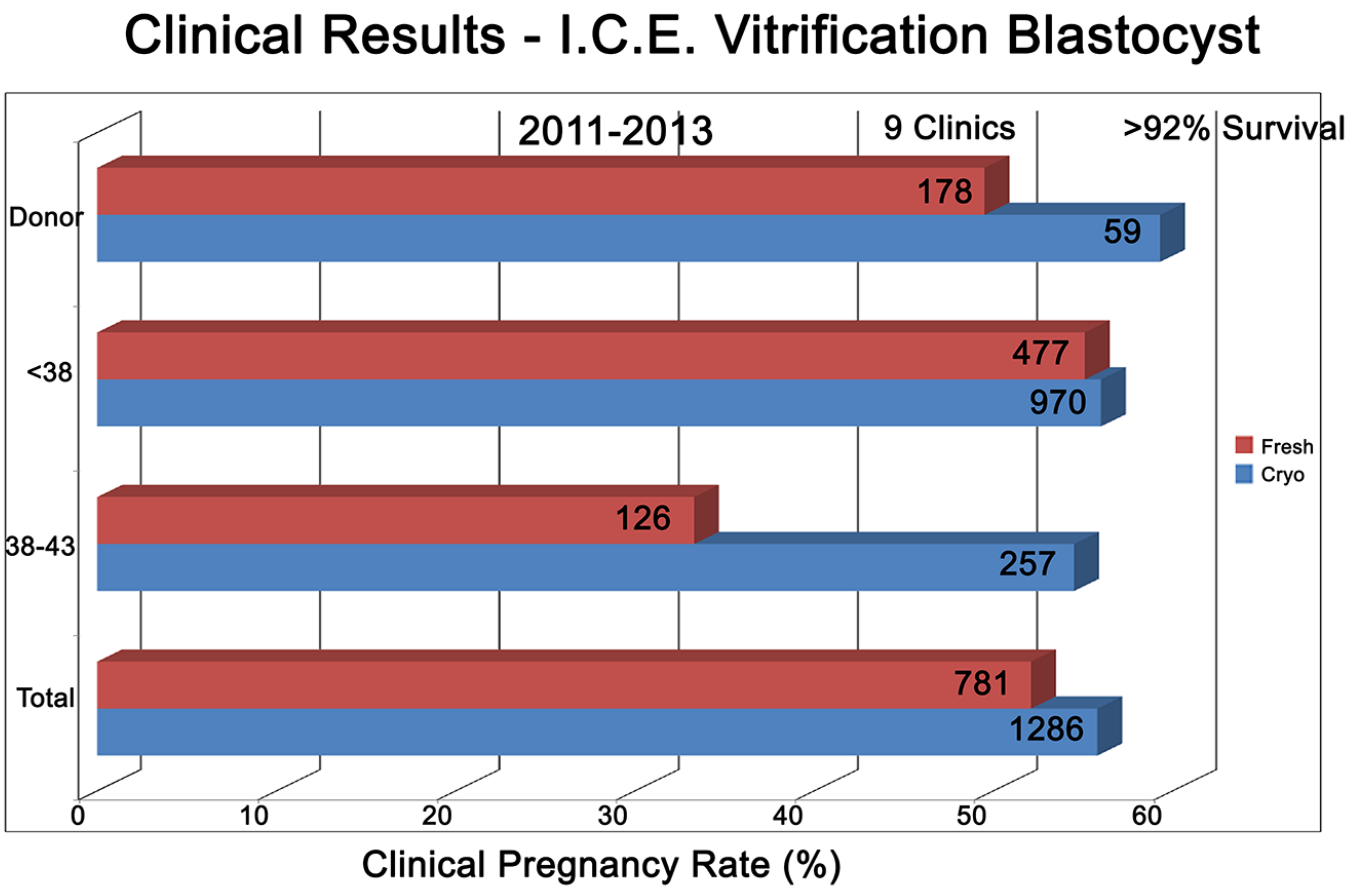
Despite the fact that the best embryos were transferred fresh!

Age	Survival	Transfer	Clin. Preg Rate	Fresh Preg Rate
<35	745/819 (91.0%)	501	246/501 (49.1%)	187/337 (55.5%)
35-37	287/312 (92.0%)	189	98/189 (51.8%)	76/140 (54.3%)
38-40	195/215 (91.2%)	110	57/110 (51.8%)	32/78 (41.0%)
41-41	39/45 (86.7%)	23	6/23 (26.1%)	9/44 (20.4%)
43+	12/12 (100%)	9	4/9 (44.4%)	1/4 (25%)
Donor	112/121 (92.6%)	59	35/59 (59.3%)	102/178 (57.3%)

Data from 8 clinics from 2010 using ICE vitrification system.

Evidence for FET

Fresh vs. FET preg rates



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Rationale for FET Cycles

If second best frozen embryos did as well and better than fresh embryos, could we do even better if all embryos were frozen?

Ovarian Stimulation

Numerous studies have identified detrimental effects of COS on emdometrial development, embryo implantation, placentation, and birthweight.

Progesterone receptors are down-regulated earlier in COS cycles.

Advanced endometrial histology correlates with premature P4 elevation and implantation failure.

Nikas et al., 1999 HR; Kolibianakis et al, 2002 FS; Develioglu et al, 1999 FS; Mirkin et al, 2004 Clin Endo Metab.

Impact of COS

Following COS the endometrium is “histologically advanced, biochemically different, and genomically dysregulated.”

Horcajadas et al, 2007 Semin Reprod Med.

Day 5 vs. Day 6 Blastocysts

Different implantation potential of D5 vs. D6 blastocysts is consistent with advanced endometrial development in COS cycles, so that slower embryos are less likely to implant because they miss the window of implantation.

Richter et al, 2006 FS; Shapiro et al, 2008 FS.

Embryo – Endometrial Asynchrony

Shapiro investigated the timing of blastulation, degree of expansion and the elevation in P4.

Insert table here

Shapiro et al, 2008 & 2013 FS.

FET in young patients vs. fresh young donor cycles

Similar implantation rates (65.9% vs. 62.1%)

Similar ongoing pregnancy rates (79.7% vs. 75.0%)

“In the absence of cryodamage, embryos in FET cycles can implant as readily as those in fresh oocyte donor cycles.”

Shapiro et al, 2010 FS.

Randomized Control Trials: Fresh vs. FET

All 6 RCT's comparing fresh transfer to freeze-all, (3,102 patients) reported a greater main outcome measure with freeze-all. The difference was significant in 4 studies.

The first study was withdrawn by ASRM.

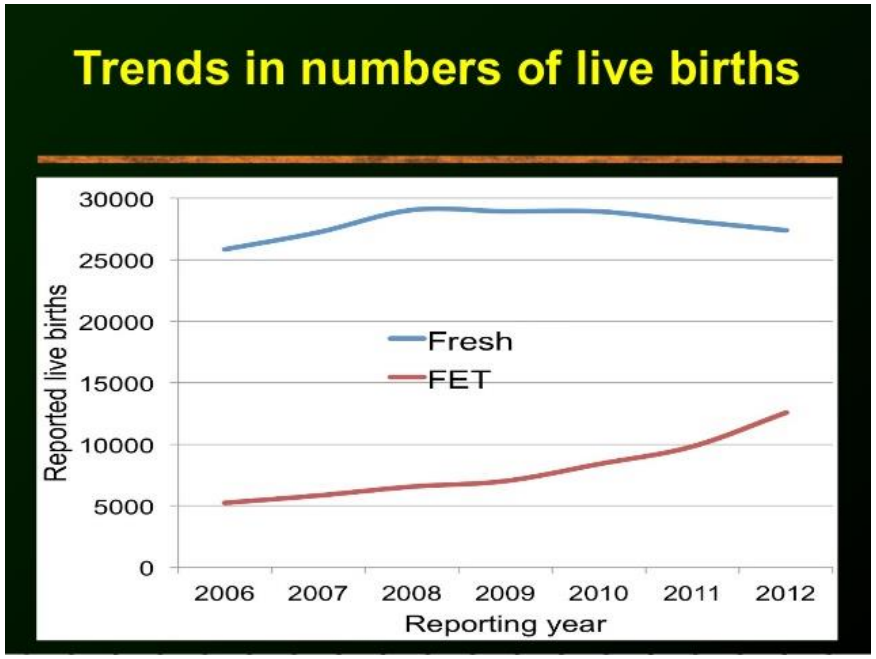
The risk ratio for main outcomes and live birth was in favor of freeze-all.

Shapiro et al, 2017 PCRS.

Success of FET

In the US the success with FET has been rising more rapidly than those with fresh transfer.

2014 implantation rates and percentage of transfers resulting in live births with FET exceeded those with fresh embryos in every age group. And, the increases become more significant with age.
CDC 2014.



Comparison of matched fresh and freeze-thaw transfers.

TABLE 2

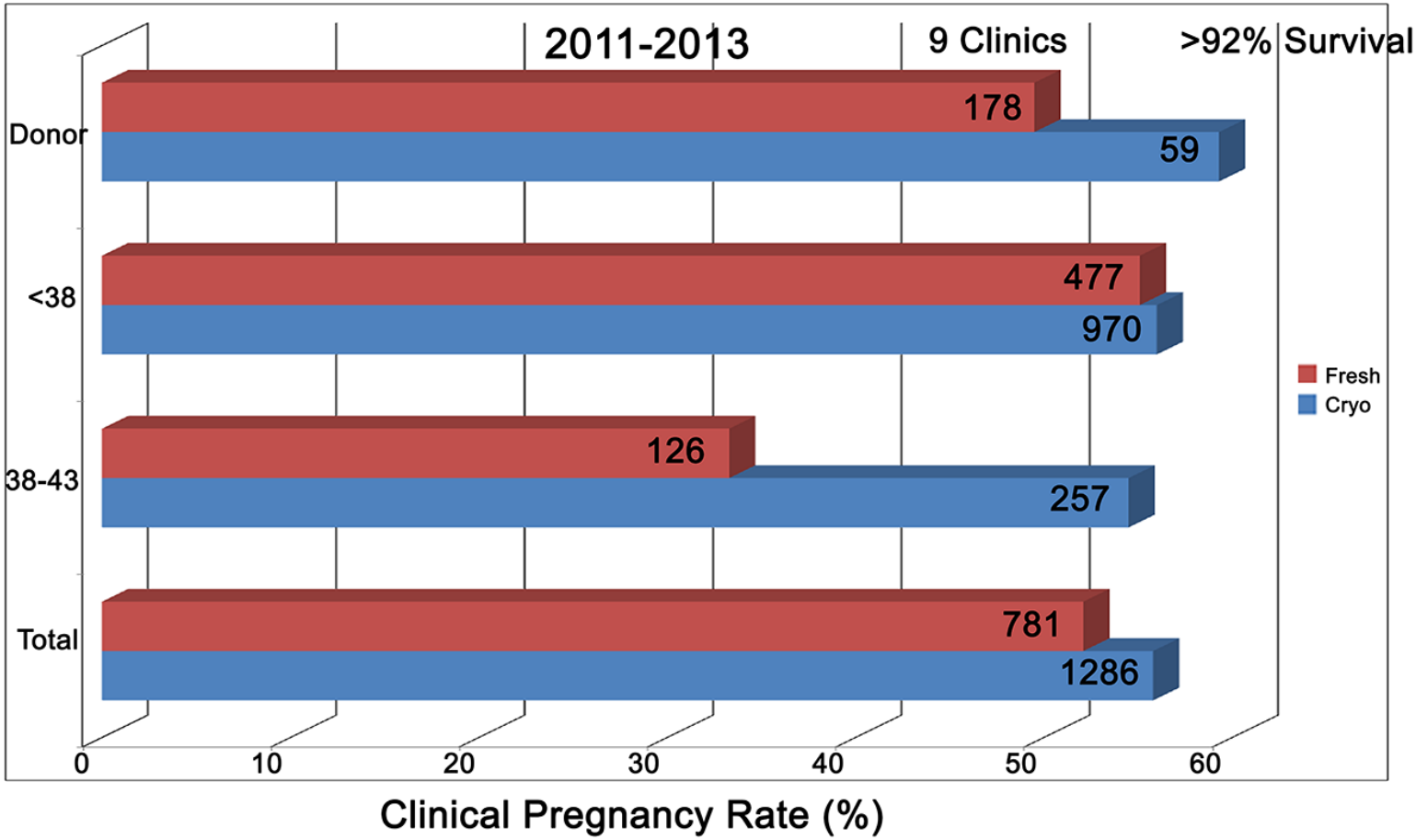
Comparison of outcomes following matched fresh and freeze-thaw single-blastocyst transfers.

	Fresh	Freeze-thaw	*P* value
Transfers, n	93	93	
Pregnancy, n (%)	38 (40.9)	72 (77.4)	<.0001
Clinical pregnancy, n (%)	25 (26.9)	52 (55.9)	<.0001
Early pregnancy loss, n (%)	13 (34.2)	20 (27.8)	NS
Ongoing pregnancy, n (%)	25 (26.9)	52 (55.9)	<.0001

Note: Percentages are proportions of transfers, except pregnancy losses, which are proportions of pregnancies.

Shapiro. Embryo-endometrium asynchrony. Fertil Steril 2012.

Clinical Results - I.C.E. Vitrification Blastocyst



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Risks of FET

What are the risks of FET???

Risks of FET

Perinatal Risks:

- Greater mean birthweight (only 167g greater than fresh transfers and 11g greater than natural conception) Shih et al 2008

- Reduced risk of low birthweight & small for gestational age

- Reduced risk of pre-term birth & low pre-term birthweight

- Reduced risk of antepartum hemorrage, placenta previa, placental abortion, & perinatal mortality

- Higher risk of placenta accreta

Maheshwari et al, 2012 FS; Pinborg et al, 2013 HR; Li et al., 2014 HR; Ishihara et al., 2014 FS; Kaser et al., 2015 FS; Kalra et al, 2011 Ob Gyn; Pelkonen et al., 2010 HR; Sullivan et al., 2013 BMC Preg Childbirth; Roque et al, 2017 JBRA

Risks of FET

Maternal Risks:

Compared to fresh ET, FET has been associated with:

- Reduced risk of late-onset OHSS
- Reduced risk of ectopic pregnancy
- Reduced risk of pre-eclampsia

ASRM practice committee 2008 FS; Ng et al, 1998 J ObGyn; Ishihara et al, 2011 FS; Shapiro et al, 2012 FS; Maheshwari et al, 2012 FS, Imudia 2013 FS.

Risks of FET

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Risks of FET

Cost Risks:

• 2 cost-effectiveness studies published reported better cost-effectiveness (lower cost per live birth) with freeze-all than with fresh transfer.

• Neither study considered costs of perinatal risks (prematurity) and maternal risks (OHSS) following fresh transfer.

Papaleo et al 2016

Shapiro's Conclusions

• Published evidence indicates endometrial development and receptivity are impaired by ovarian stimulation.

• Success rates and cost-efficiency are improved via a freeze-all strategy.

• National average implantation rates with FET exceed those with fresh transfer.

• Infants are generally healthier and closer to ideal birthweight following FET.

Shapiro's Conclusions cont.

• Ovarian stimulation impairs endometrial receptivity, particularly through embryo-endometrium asynchrony.

• Freeze all circumvents the compromised endometrium.

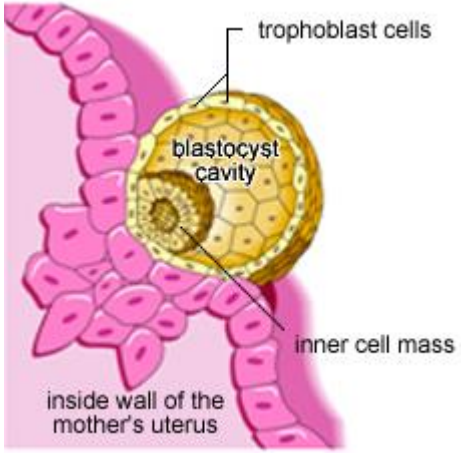
• FET is associated with many reduced maternal and perinatal risks when compared to fresh autologous transfers.

• Some or all of these risks differences appear to be due to uterine effects of COS.

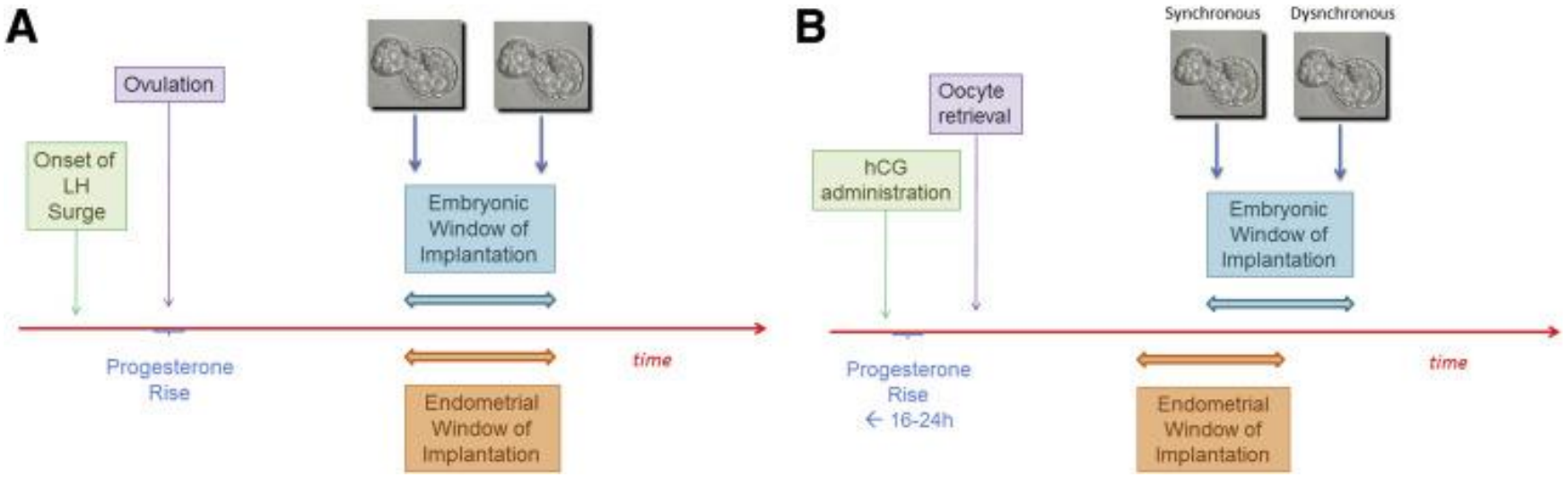
Why is there a reduced endometrial receptivity following ovarian stimulation?

The COS reduction of implantation of slow and normal developing embryos is consistent with embryo-endometrium asynchrony.

Shapiro et al, 2013 FS.



Oocyte/embryo timeline in a natural cycle



Increasing asynchronous transfers in fresh cycles with age

Retrospective study showing asynchrony factors increasing with age

	≤30 years	31-34 years	35-40 years
Transfers	419	436	486
Day 5 transfers	276	242	222
Day 6 transfers (%) a	143 (34.1)	194 (44.5)	264 (54.3)
Elevated P4 (%) a	96 (22.9)	110 (25.2)	152 (31.3)
Asynchronous transfers (%) a	200 (47.7)	257 (58.9)	335 (68.9)
a= Proportions differ significantly across age groups (P<0.05)			

Shapiro et al, 2013

Are there issues with FET's

So if we believe all the data and studies that FET is the way to go versus fresh transfer, than how come all FET's don't result in a pregnancy?

Some labs do not have good pregnancy rates with FET vs. fresh transfer.

Are there issues with FET's

In some clinics the fresh pregnancy rate is greater than the FET rate.

And/or the biochemical rate is greater in the FET cycles.

What should the pregnancy and biochem rates be with FET's

• Pregnancy rates should be within 5% Fresh & FET, and realistically the FET should be the same or higher, especially with increasing maternal age.

• Biochem rates should be equal or lower in FET cycles compared to fresh transfers .

FET Problem Areas

- Cryopreservation
- Embryo Culture
- Embryo Transfer
- Uterine Preparation

FET Problem Areas: Cryopreservation

With current vitrification systems (DMSO and non-DMSO) survival of blastocysts is on average over 85% nationally.

In many clinics it is over 90-95% .

With these relatively high survival rates, it is unlikely that the cryopreservation system is to blame. Especially when one considers that only surviving good quality blastocysts are transferred.

Additionally, some or most of the blasts transferred are euploid, and preg rates should be even greater.

FET Problem Areas: Embryo Culture

With current culture systems (incubators and media) blastulation rates are higher than ever.

Although some embryos do not culture (or freeze) well, related to a patient specific issue, this should only make up a very small proportion of results.

Furthermore, stimulation protocols resulting in poor quality oocytes/embryos would effect both fresh and frozen cycles.

Bergh & Navot, 1992 FS; Franasiak et al, 2016 FS; Meldrum 2016 FS; Meldrum & De Ziegler, 2016 FS

FET Problem Areas: Embryo Transfer

- Patient specific issues
- Contamination of the catheter
- Retained or expelled embryos
- Type of catheter
- Media
- Adjuvants
- Timing
- etc…

Schoolcraft 2016 FS; Meldrum 2016 FS; Meldrum & De Ziegler, 2016 FS

FET Problem Areas: Uterine Preparation

Considering that the vitrification, embryo culture, and embryo transfer are in order, the next logical cause of reduced implantation and/or pregnancy rate would be associated with the uterine preparation regime.

Indeed, improper uterine preparation leads to an increase in both failed and biochemical pregnancies.

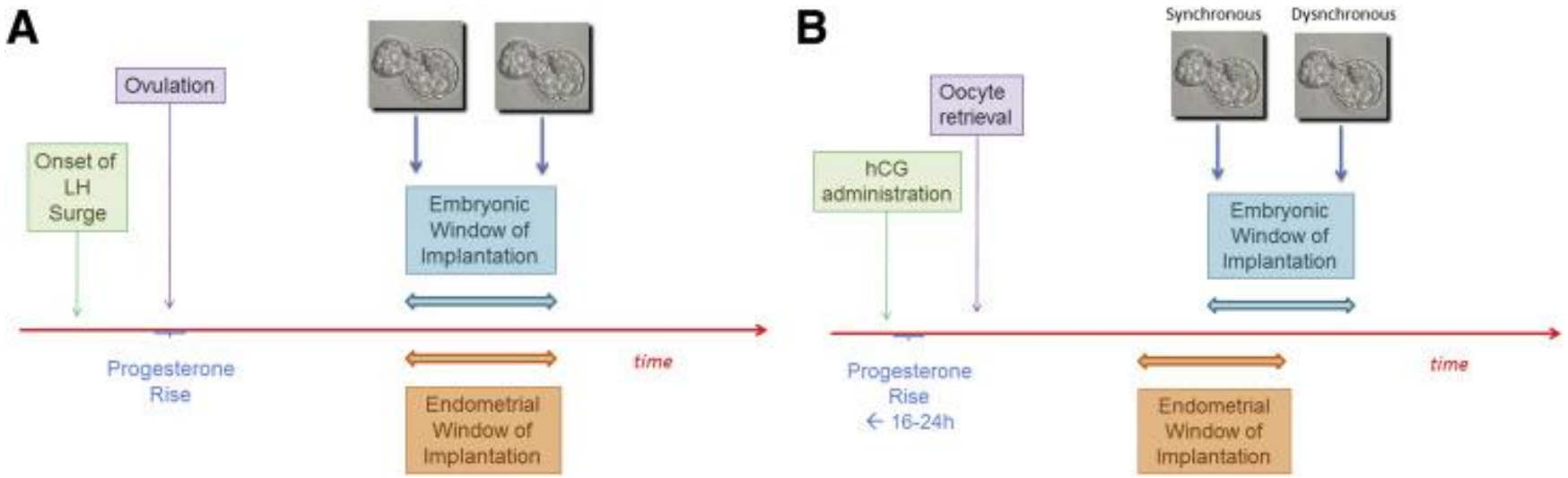
An overall increase in biochemical pregnancies and decrease in fetal heart beats and/or delivery rates over a period of time can be a strong indicator of poor uterine preparation.

Casper & Yanushpolsky, 2016 FS

FET: Uterine Asynchrony

Similar to the embryo-endometrium asynchrony that occurs with COS, and leads to a reduction of implantation; a similar scenario can occur with FET.

Shapiro et al, 2013 FS.



Window of Implantation

A pregnancy will initiate only when the embryo is ready to implant and only when the uterus is ready for implantation.

This window of implantation, although 12-24h wide varies and can be different between patients.

Proper uterine preparation is key to synchronizing the implantation windows of the uterus and embryo.

Berg & Navot, 1992 FS; ***Casper & Yanushpolsky, 2016 FS***; Franasiak et al, 2016 FS

Window of Implantation

Endometrial morphology is an appropriate predictor of receptivity for implantation.

Hormonal control of endometrial receptivity includes an estrogen priming phase followed by progesterone (P4) secretion, which leads to the necessary endometrial changes.

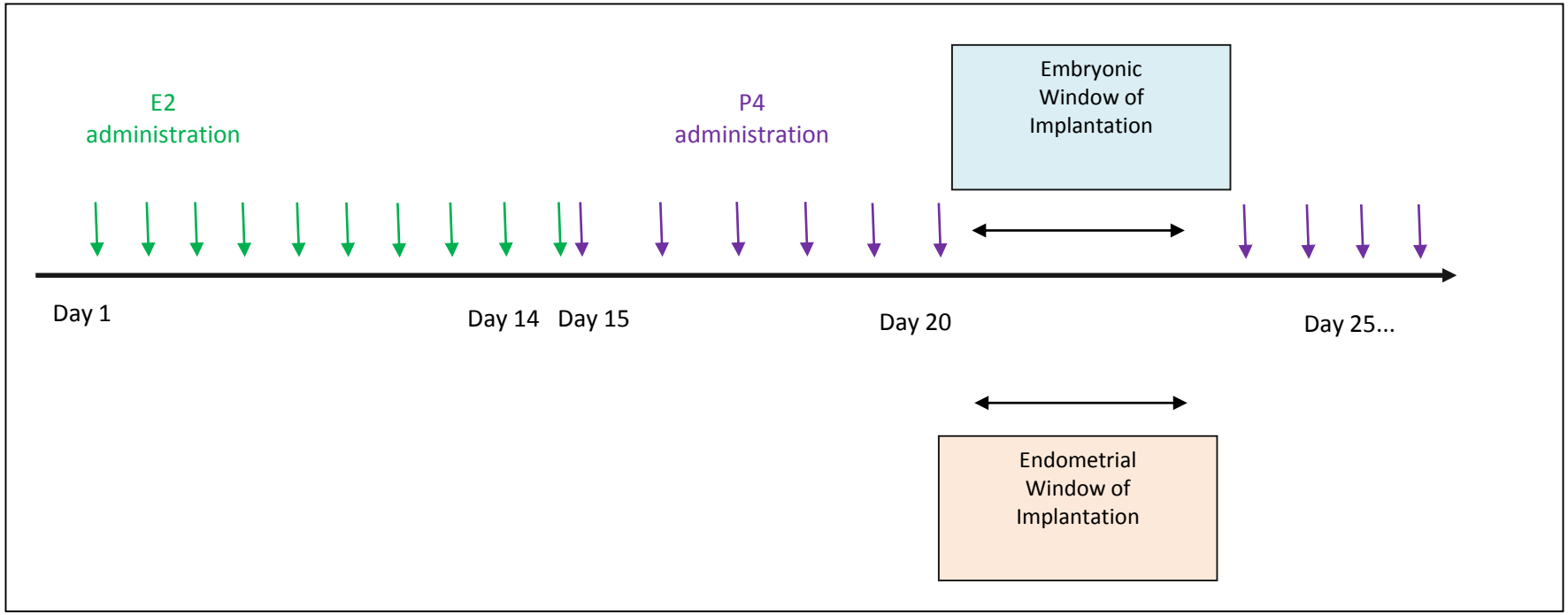
De Ziegler et al, 1994 Anal NY Acad Sci; De Ziegler et al, 1998 J Reprod Imm.

Timing of Estrogen and P4 Administration

Estrogen increases endometrial thickness and is given for approximately 15 days until thickness reaches 7-8mm.

At this time P4 administration begins for the number of days proportional to the embryo stage.

Paulson, 2011 FS.



Timing of Progesterone P4 Administration

A Day 5 blastocyst would require approximately 5 full days of P4.

Therefore, it is widely suggested to do the thaw and transfer (D5 blast) on D6 of P4 administration.

It is known that approximately 25% of women can be out-of-phase and would require longer P4 treatment.

The idea here is to not advance the endometrium using P4 (especially Crinone and other vaginal progesterone) and close the window of implantation too early.

Murray et al, 2004 FS; Coutifaris et al, 2004 FS ; Gomaa et al, 2015 RBMO.

Type of Progesterone

The type of P4 is important. Vaginal vs. I.M.

Randomized control studies have shown vaginal and IM P4 to be equally effective.

However there are pros and cons of both types of P4.

Shapiro et al, 2014 HR; Shapiro et al, 2015 HR; Kaser et al 2012 HR; Casper 2014 FS; Kahraman et al, 2010 FS; DalPrato et al, 2008 RBMO; Yanushpolsky et al, 2010 HR; Leonard et al, 2015 JRM; van der Linden et al, 2015 Coc Data Syst Rev.

Vaginal Progesterone

The short half life of natural P4 (used in vaginal supplements) dictates multiple daily usage (2-3x/day) in order to maintain natural P4 serum levels.

Immediate effect.

Messy transfers, need to lavage first.

Be careful not to close window of implantation with too long exposure before transfer.

IM Progesterone

The long half life of IM P4 in oil (>1 Day; continuous release over time) requires only once daily injections (40-60mg), and will lead to higher serum levels than vaginal P4.

It takes much longer for IM P4 to start effecting the uterus, which can lead to a longer administration period prior to transfer.

Painful injections; however not as painful as giving birth (or raising a teenager).

Casper, 2014 FS; Cicinelli et al, 2000 ObGyn.

Type of Progesterone: Timing

IM P4:

Day 1	Day 2……..	Day 5	Day 6 (Transfer day)
10am	10am……..	10am	10am inj & transfer 10am-2pm

Vaginal P4:

Day 1	Day 2	Day 5	Day 6 (Transfer day)
am &/or pm	am & pm	am & pm	am & transfer 10am-2pm

Start time of P4 may effect transfer timing!

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Uterine Contractions

Progesterone (serum levels) can effect uterine contractility and influence implantation and pregnancy rates!

Increased myometrial contractions are associated with decreased pregnancy rates and tubal ectopic pregnancies.

Higher serum P4 levels equate to low uterine contractility (better pregnancy outcomes) and vise versa.

Nawroth & Ludwig, 2005 HR; Fanchin et al, 1998 Cont Fert Sex; Fanchin et al, 1998 FS; Fanchin et al, 2001 FS

Uterine Contractions

Estrogen increases uterine contractility and subendometrial wave action whereas P4 antagonizes this action.

Endometrial concentrations are higher with vaginal P4 versus IM P4.

The gap between administration of vaginal P4 and the actual time of FET the following day, can result in a low P4 concentration in the uterus and greater contractions.

This gap does not occur with IM P4, thus IM P4 may quiet endometrial activity better.

Cincielli et al, 2000 ObGyn; Casper, 2014 FS.

Vaginal vs. IM Progesterone: insights

• We have noted that many issues occur in clinics using only vaginal progesterone and no IM.

• Some IM has been suggested, even if most is vaginal.

• We have heard from various clinics that doctors that allow patients to dictate their preference as vaginal progesterone only for luteal support have more variable outcomes and increased loss rates.

• Greater than 90% of labs contacted use at least some IM P4.

Stachecki 2016 personal communications

Clinic Case #1:

Original protocol:

6 days of vaginal P4 with FET on the 6th day.

Revised protocol:

3 days of vaginal P4, then 3 days of P4 IM followed by transfer. Ultrasound on day prior and day of transfer showed no wave activity in endometrium. Switch back to vaginal P4 1-2 days post ET.

Result: higher clinical pregnancy rates.

Casper, 2014 FS.

Clinic Case #2:

Retrospective Study:

P4 IM every other day plus 400mg vaginal P4 daily

5 days vs. 6 days P4 prior to ET

Result:

The mean implantation rate of vitrified-warmed blastocysts was higher (p-value=0.03) when P4 was started five days before transfer (36.6%; N=117) compared to the implantation rate when P4 was started six days before transfer (26.3%; N=112).

Anderson et al, 2016, abstract

Clinic Case #3:

Original protocol:

Revised protocol:

Result:

Conclusions

• It is important to know what your pregnancy rates are for both your fresh and cryopreserved transfers, in order to determine if there is a problem.

• If thaw rates are >90% and embryo culture is good, then uterine preparation for FET should be looked at.

• The differences between vaginal and IM P4 will determine dosage and length of treatment prior to transfer.

• The effect of P4 on endometrial contractions can play a role in successful implantation and ongoing pregnancies.