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The Case for More Active Management of Endometrial Development in IVM: Decreasing the Miscarriage rate and Increasing the Clinical Pregnancy Rate

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Abstract

This review looks at the problem of pregnancy loss after in vitro maturation IVF (IVM) cycles as it may relate to the development of the endometrium during that cycle. The management of the endometrial lining in IVM cycles is currently primarily informed by what has worked in the past rather than by designed experimental studies. The IVF literature on the use of estradiol in artificial cycles prior to cryopreserved embryo transfer cycles and fresh donor-recipient cycles can provide some context in which to evaluate practices in IVM. Endogenous estradiol, exogenous estradiol, and estradiol induced by FSH priming all potentially effect the development of the endometrium during an IVM cycle. These vary in part between programs based on patient selection and cycle management choices, making it harder to use the medical literature to guide decision making in this area. In particular, the short duration of functional estrogen exposure and the diminished endometrial thickness typical of many IVM cycles may contribute to an increased pregnancy loss rate and a lower implantation rate than seen with conventional IVF.

Keywords: IVM; *in vitro* maturation; miscarriage; pregnancy loss; endometrium; endometrial thickness; estradio

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Introduction

Investigators have raised the possibility of there being an increase in miscarriages of pregnancies conceived with in vitro maturation IVF (IVM) compared to conventional IVF [1,2]. There is little specific published research on this topic in the literature on IVM. However, there is considerably more information available in the conventional IVF literature and especially with respect to the development of an artificial endometrium in preparation for use of donor embryos or cryo-preserved embryos.

Review

Buckett et al looked at the issue of increased pregnancy loss after IVM in the IVM and IVF programs at McGill University. They found that pregnancy losses were increased with IVM compared to IVF, but likely attributable to differences in patient populations [3]. The pregnancy loss rate for clinical pregnancies after IVM at McGill was 25.3% and the miscarriage rate for the IVF program was 15.7% (p = .0049). However, IVM was primarily undertaken in patients with PCOS. A comparable subpopulation in McGill's conventional IVF program had a miscarriage rate of 24.7%, which was not statistically different from the incidence of pregnancy loss in their IVM program. The medical literature on the clinical pregnancy and live birth rates for individual IVM programs sheds little light on this issue since loss rates vary greatly in published reports **(Table 1)**. Further difficulty is created by the use of different "priming" approaches, which may impact embryo competence and, indirectly, the development of the endometrial lining [16]. Child et al, using hCG priming, showed that endometrial lining thickness on the day of embryo transfer was predictive of pregnancy [17]. In another study, Child et al showed that a higher estradiol level (greater than 27 pg/ml) at the start of a cycle was more predictive of pregnancy than a lower one [18]. Mikkelson et al, using no priming, found that pregnancies only occurred if the estradiol level at least doubled from the start of the cycle to oocyte aspiration (mean of 40 pg/ml increasing to 117 pg/ml) [11]. Estrogen levels during an IVM cycle depend in part on endogenous FSH production in patients and

Table 1 Pregnancy Data from Selected Publications.

Publication	Patient selection	Number of cases aspirated	Number of cases transferred	Clinical pregnancy rate[1]	Live birth rate[1]	Miscarriage rate[2]
Bos-Mikich 2011 [4]	PCOS or PCO[3]	34	34	32.4%	29.4%	9.1%
Cha 2005 [5]	PCOS and clomiphene failure	203	187	21.9%[4]	12.8%	36.8%[4]
Child 2001 [6]	Normal, PCOS or PCO	180	169	20.1%	11.8%	41.2%
Fadini 2009 [7]	normal	379	300	18.3%	15.3%	16.4%
Gremeau 2012 [9]	PCO	97	96	19.8%	16.7%	15.8%
Junk 2012 [10]	PCOS or PCO	66	62	46.8%	45.2%[5]	3.4%
Le Du 2005 [8]	PCOS	45	40	22.5%	15%	33.3%
Mikkelsen 2000 [11]	Normal	85	62	17.7%	14.5%	18.2%
Rose 2014 [12]	PCOS or PCO	75	72	37.5%	23.6%	37%
Soderstrom-Anttila 2005 [2]	Normal, PCOS or PCO[1]	239	184	26.6%	19.6%[5]	26.5%
Son 2008 [13]	PCOS or PCO[1]	171	171	29.8%	22.2%[5]	25.5%
Vitek 2012 [14]	PCOS, HAFC[6], Hx OHSS	20	20	45%	40%	11.1%
Zhao 2009 [15]	PCOS	152	140	38.6%[7]	34.3%[5]	11.1%[7]
Totals or averages		1746	1537	26%	19.4%	22.1%

[1]Per transfer; multiples counted as one
[2]Per clinical pregnancy
[3]Polycystic pattern on ultrasound only
[4]Three clinical pregnancies were lost to follow-up
[5]Includes ongoing pregnancies
[6]High antral follicle count
[7]Two ectopic pregnancies were not counted as clinical pregnancies or losses

on the endometrial response to that estradiol as modulated by a patient's ovaries, which is a reflection of the patient's underlying diagnosis. More explicitly, non-PCO patients, PCO pattern only patients, PCOS patients with ovaries able to respond to low doses of FSH, and PCO patients with an ovarian environment requiring a high FSH threshold for ovulatory response, all likely produce different estrogen profiles during the course of an IVM cycle. Estrogen production is also modulated with the use of FSH priming during an IVF cycle. FSH priming increases the thickness of the endometrial lining as well as estrogen levels [19,20]. IVM programs vary in their use of priming with FSH **(Table 2)**. The primary parameter discussed in the IVM cacalbri this type of observation is reassuring if a transfer needs to done in a patient with a thin endometrial lining (e.g., a patient with a history of Asherman's syndrome), it is not clear that this is the best approach for all patients. As pointed out in the meta-analysis of Momeni et al, in spite of at least 484 articles on the subject, there are too few patients having extremes of endometrial thickness to arrive at a truly robust cut-off thickness for transfer decision making [21]. The most informative part of the IVF literature for understanding the endometrium in IVM were studies concerning artificial cycles for embryo transfer after cryo-preservation (CET) or before recipient cycle transfers utilizing fresh donor oocytes (FDT). In this setting, the endometrium develops without being affected by a developing pre-ovulatory follicle or a post-ovulatory corpus luteum. These studies are still significantly different from IVM in that much higher levels of estrogen may be present for a longer period of time than during IVM.

Publications about the significance of a thin endometrial lining for CET or FDT show conflicting results, with most publications finding a decreased pregnancy rate with endometrial linings less than a given thickness on the day of starting progesterone. For example, El-Toukhy et al showed a 1.9 fold increase in the clinical pregnancy rate when the endometrial lining thickness was 9 to 14 mm compared to 7 to 8 mm [25]. In addition, for the 13 cases with endometrial linings less than 7 mm, the clinical pregnancy rate was only 7%. In contrast, Remohi et al, in a study involving 465 cases of FDT, found no impact of endometrial lining thickness on the pregnancy rate.[26}. Remohi observed that normal pregnancies occurred in patients with very thin endometrial linings (less than 4 mm) and in women with very low estrogen levels (less than 50 pg/ml). They stated that endometrial lining thickness should not be a criterion to cancel embryo transfer. Detti et al, also found no correlation between endometrial lining thickness and the pregnancy rate [27]. However, Detti et al did find a difference in endometrial lining thickness between the early pregnancy loss patient subgroup and those patients with ongoing pregnancies.

For IVM, two parameters commonly used to determine the timing of the oocyte retrieval are the size of the largest antral follicle and the thickness of the endometrial lining **(Table 2)**. Never-the-less, on the day of follicle aspiration, greater than 25% [20] or greater than 50% [2] of patients have endometrial lining thicknesses less than 6 mm. Thus programs may treat patients with exogenous estrogen at different times to enhance endometrial lining thickness and/or support the luteal phase. Generally, orally administered estradiol is used. Estrogen may be given from the start of the cycle, in late cycle before the oocyte retrieval decision to help develop the lining, on the day that the decision for oocyte retrieval is made, or on the day of the oocyte retrieval **(Table 2)**. For most IVM programs, progesterone is usually started on the day of the first fertilization. The number of days during which

Table 2 IVM cycle details from selected publications

Publication	Oocyte Retrieval Criteria	FSH priming approach	hCG priming	Use of estrogen starts	Estrogen dose	Endometrial line management
Bos-Mikich 2011 [4]	EL[1] ≥ 7 mm on day 6-8	None	Yes	Day of retrieval	Oral estradiol 6 mg	Not given
Cha 2005 [5]	Day 10-13 Lead follicle <11 mm	None	No	Day of retrieval	Oral estradiol 4 mg	Cryo if EL < 7 mm on day of transfer
Child 2001 [6]	All follicles ≤ 10 mm on day 9-14	None	Yes	Day of retrieval	Oral estradiol 6- 10 mg	10 mg if EL < 6 mm
Fadini 2009 [7]	Lead follicle <14 mm and EL > 4 mm	Half had 150 IU on days 3-5	Yes for half	Day of retrieval	Oral estradiol 6 mg	Not given
Gremeau 2012 [9]	All follicles < 14 mm on day 8-16	None	Yes	Day of retrieval	Oral estradiol 8 mg	Not given
Junk 2012 [10]	Largest follicle 10-12 mm	100-150 IU on days 3-5	No	Two days before retrieval	Oral estradiol 6-9 mg[2]	Higher dose if EL < 6 mm
Le Du 2005 [8]	Lead follicle size 7 mm	None	Yes	Day of retrieval	Oral estradiol 6- 10 mg	10 mg if EL < 5 mm; cryo if EL < 7 mm at transfer
Mikkelsen 2000 [11]	Lead follicle ≥ 10 mm and EL ≥ 5 mm	None	No	Day of retrieval	Oral estradiol 6 mg	Not given
Rose 2014 [12]	Lead follicle < 13 mm	Letrozole 2.5 mg day 3-7 or FSH 50 U day 3 to hCG	Yes	Day of retrieval unless thin EL	Oral estradiol 4 mg	Early additional estradiol; 4-12 mg
Soderstrom-Anttila 2005 [2]	Lead follicle ≤ 10 mm and EL ≥ 5 mm	None	No	Day of retrieval	Oral estradiol 6 mg	Not given
Son 2008 [13]	EL ≥ 7 mm after day 7	None	Yes	Day of retrieval	Oral estradiol 6- 10 mg	Increased estrogen if EL < 8 mm
Vitek 2012 [14]	All aspirated on day 16	None	Yes	Cycle day 3	Oral estradiol 6 mg	Not given
Zhao 2009 [15]	Lead follicle < 10 mm on day 9-14	None	No	Cycle Day 3-5 if EL < 5 mm	Oral estradiol 4 mg	Increased to 6-10 if EL < 7 mm on later ultrasounds

[1]Endometrial lining thickness
[2]Transdermal estrogen also used

estrogen was available to develop the endometrial lining prior to the start of progesterone administration depends both on when the patient began to produce enough endogenous estrogen to stimulate growth of the endometrial lining (related to the patient's diagnosis and the program's use of priming) and on the program's protocol for exogenous estrogen use. For at least occasional patients, the duration of time that estrogen is available to stimulate growth of the endometrial lining may be short. During the historical development of therapies CET and FDT, researchers looked at factors that might impact the success of these procedures. One of the factors looked at was the number of days required to prepare the endometrium with estrogen prior to starting progesterone. Researchers examined the impact that short, intermediate, or long treatment with estradiol had on the pregnancy rates after the procedure. In an experimental study, Navot et al [28] looked at different length artificial cycles, and in particular, found that cycles with a short duration estrogen exposure (six days of 6 mg of micronized estradiol) had endometrial biopsies consistent with those of patients having estrogen exposures modeling the natural cycle. Early luteal biopsies on both short and normal length artificial cycles were out of phase with the glands being two days behind the stroma. Late luteal histology became normal after longer progesterone exposure. Histochemical studies were similar for both and similar to results seen in normal cycling women of proven fertility. Borini et al looked at the duration of endometrial estrogen exposure prior to progesterone for FDT [29]. They evaluated five subgroups of patients with different lengths of estrogen exposure and found miscarriage rates (41%) in patients with only 6 to 10 days of exposure to be statistically higher than some (but not all) of the other subgroups. Younis et al reviewed 51 recipient FDT cycles and found that the pregnancy rate correlated with the length of estrogen stimulation in the follicular phase with a pregnancy rate of 7.7%, 52%, and 7.7% after short, intermediate, and long cycles [30]. Again, this impairment of the pregnancy rate occurred in spite of a thick endometrial lining. For example, Simon et al showed that after seven days of treatment with 6 mg of micronized estradiol prior to CET, the thickness of the endometrial lining was 9.3 mm in the average patient (SD 1.8 mm) [31]. For some IVM programs, oocyte aspiration occurs on average as early as day 7.1 [32] or day 8.7 [2]. In a later publication, Younis et al reported on a preliminary unpublished study of Younis and Laufer in which ovarian failure patients were randomized to a short or an intermediate period of estrogen exposure prior to embryo transfer utilizing donor oocytes [33]. In the intermediate estrogen exposure group, there were two delivered pregnancies out of eight transfers. In the short estrogen exposure group, there were two biochemical pregnancies out of eight transfers. Peak hCG levels in these biochemical pregnancies were 23 and 89 mIU/ml. Navot et al compared CET after short estrogen exposure cycles (5 to 10 days) to long exposure cycles (21 to 42 days) and found no difference in the implantation rate. [34]. They also showed that a

normal pregnancy could occur using donor oocytes after only 5 days of endometrial preparation. However, the early pregnancy loss rate was 52.9% in the short duration estrogen exposed cycles compared to 18.8% in the long duration estrogen exposed cycles. Thus, in spite of histologically normal appearing endometrial tissue and normally thick endometrial linings after short duration estrogen exposure, most authors have recommended that the minimum duration of estrogen exposure prior to the introduction of progesterone in CET cycles should be at least 11 days [31, 33]. This estrogen duration is longer than occurs during some IVM cycles. Many IVM cycles likely have a functional estrogen exposure period less than 8 days, which based on the preceding referenced literature, raises some concerns about pregnancy loss attributable to endometrial development. Does the short duration of functional estrogen exposure that occurs in some IVM cycles have an impact on the live birth rate after IVM? Some of the programs that use a longer duration of estrogen treatment than the standard 6 mg dose starting on the day of oocyte retrieval appear to have lower miscarriage rates (and higher clinical pregnancy rates). Vitek et al [14] and Zhao et al [15] routinely administer estradiol from cycle day 3 and Junk and Yeap [10] start estradiol two days before oocyte retrieval in non-hCG cycles **(Table 2).** De Vos et al found a higher clinical pregnancy rate in patients who had their embryos vitrified, warmed, and transferred into a routine artificial (longer) CET cycle than if transferred during the primary IVM cycle [35]. Son et al had a high live birth rate while starting estrogen on the day after oocyte aspiration, but the day of oocyte aspiration was delayed up to 18 days depending on endometrial thickness [36]. Do the low estrogen levels that occur during an IVM cycle affect the clinical pregnancy rates? Low estrogen levels certainly impact the thickness of the endometrial lining [26,32,37]. De Paula Martins et al performed a cross-over designed experiment to evaluate multiple aspects of the endometrial lining in mock IVM cycles in PCOS patients [37]. They compared increasing doses of estrogen over 14 days prior to starting progesterone as typically done prior to a CET cycle with the typical preparation for a non-primed IVM cycle where 6 mg of estradiol is given 2 days prior to starting progesterone. On cycle day 14 of a standard or typical (for IVM) estradiol treatment cycle, the average endometrial lining thickness was 5.11±1.50 mm with only 10% of patients having a lining thicker than 7 mm with the standard approach. One week later, with this standard approach, the endometrial lining thickness averaged 7.41±2.24 mm with only three patients having a lining thicker than 9 mm. In contrast, when the lining preparation was typical of that used for a CET cycle (estradiol starting on day 1), the endometrial thickness on day 14 averaged 9.96±2.22 mm and a week later it averaged 10.52±2.43 mm. Russell et al compared endometrial preparation for IVM with estrogen given from the beginning of the cycle to endometrial preparation when estrogen was started in the mid-follicular phase of the cycle [38]. Early estrogen use was viewed as inferior because of a decreased maturation rate (39.7% versus 61.5%) and an increased failure to cleave (36% versus 8.3%) in the early estrogen group. The cleavage problem could be due to differences from current IVM practice. At the time the Russell study was done, ISCI was performed on all mature oocytes 52 to 58 hours after oocyte retrieval, no matter when the oocytes became mature. Also the early estrogen group in the Russell study contained only seven patients compared to the 160 patients in the Vitek and Zhao studies, which did not experience either a maturation or a cleavage problem [14,15]. The body of evidence from conventional IVF and the limited evidence directly from IVM suggest that there is potential to enhance the pregnancy rate and decrease the pregnancy loss rate by introducing more estrogen to the follicular phase of the IVM cycle for a longer period of time. There are many approaches that an IVM program could take to increase the duration of functional estradiol exposure to the endometrium prior to the introduction of progesterone, but the challenge is that each approach will likely impact other aspects of that IVM program [20]. Increased estrogen exposure may be direct or indirect through FSH, but the functional impact of the estrogen appears be more important than the absolute level of estradiol. An alternative before introducing estrogen earlier in an IVM cycle would be to wait for a study comparing the use of early estrogen to the use of late estrogen in an IVM program (using or not using FSH priming). However, since some patients produce normal levels of estrogen and thick endometrial linings, the patient numbers required for such a study would be large. Assuming that 50% of patients are low endogenous estrogen producers, that pregnancy losses with IVM are about 26% **(Table 1 and 2)** that we want the study to have an 80% power to detect a 30% decrease in the pregnancy loss rate for IVM, and that a type I error of 5% is optimal, then the number of patients required for the study would be 991. It is more likely that insight into the potential benefit of endometrial lining management in IVM could be gained indirectly. For example, it could be useful to compare IVM patient cycles with a combined low peak estradiol and thin endometrial lining before oocyte aspiration to those with high estradiol levels and thick endometrial linings. Similarly, one could compare results from ultra-short cycles to long cycles within a program.

Conclusion

To summarize, both the IVF and IVM literature propose that patients can get pregnant with very low peak estradiol levels and very thin endometrial linings. The literature also shows that normal thickness endometrial linings with normal histology can be achieved with short duration exposure to estrogen. However, the conventional IVF literature and the DET/CET literature suggest that thin endometrial linings, low peak estradiol levels, and short duration exposure to estradiol may not be optimal in terms of clinical pregnancy and pregnancy loss rates. The examination of different approaches to endometrial preparation in the CET literature found an increased pregnancy loss rate in the setting of short estradiol exposure during the development of the endometrial lining in spite of that lining appearing normal both clinically and histologically. This has led most practitioners to utilize estradiol for 11 or 12 days prior to adding progesterone to prepare the endometrial lining for CET. These issues are particularly worrisome for IVM cycles since is it not uncommon to have IVM cycles with a thin endometrial lining prior to oocyte aspiration, low peak estradiol levels, or a short duration of estradiol exposure before the start of progesterone. Clinical IVM programs also appear to vary significantly in their clinical pregnancy loss rate. An objective of this paper was to raise the question of whether or not some of the clinical pregnancy losses seen in IVM cycles could be eliminated by a different management of the development of the endometrium.

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