Endometrial preparation for third-party parenting and cryopreserved embryo transfer

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The advent of third party parenting ushered in the era of artificial stimulation of the endometrium. Initially intended only for patients with ovarian failure, exogenous induction of endometrial receptivity was quickly shown to be as good as natural endometrial preparation, with the advantage that the timing of embryo transfer could be controlled. It is perhaps surprising that even though the ovary produces a variety of steroids, that estradiol (E2) and progesterone (P) alone would be needed to achieve optimal receptivity; no other substance has ever been shown to improve on the basic regimen of E2 and P. A variety of routes of administration are available for both E2 and P and physiologic (or supraphysiologic) serum or endometrial tissue levels of both can be achieved. The optimal duration of E2 stimulation and the timing of the onset of P administration continue to be debated, but it appears that imitating the sequence that normally occurs in nature leads to optimal results. The poorly responsive endometrium and cases of recurrent implantation failure remain a challenge, but the clear majority of patients can successfully achieve pregnancy as long as embryos of adequate quality are transferred. (Fertil Steril® 2019;111:641–9. ©2019 by American Society for Reproductive Medicine.)

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Embryo implantation is the successful invasion of the endometrium by the hatching blastocyst. Successful embryo implantation is thus dependent on embryonic competence as this invasion is an active process on the part of the embryo. The endometrium, which undergoes a series of structural and biochemical changes during the reproductive cycle, must also be in a receptive phase, because a normal, healthy endometrium will resist implantation in all other phases of the cycle.

In a normal ovulatory cycle, endometrial development is controlled by the hormonal secretions of the ovaries, which undergo a series of predictable changes associated with follicular development, ovulation, and transformation to a corpus luteum. Each of these stages is associated with a concomitant sequence of hormonal signals that are transported through the circulation to stimulate the endometrium to initially proliferate, and then transform to a secretory and, ultimately, receptive state.

Third-party parenting, in which the source of oocytes is separated from the endometrium, led to the development of strategies to induce endometrial receptivity with exogenous steroids. In addition to the correct dose and route of administration of estradiol (E2) and progesterone (P), the timing of both steroids had to be adjusted to synchronize with embryo development in the laboratory. The successful achievement of a pregnancy in a woman with ovarian failure in 1983 (1) provided the proof of concept that endometrial receptivity could be generated and controlled by exogenous means. Eventually, it became clear that not only could embryo implantation be achieved in the absence of ovaries, but that the use of E2 and P produced receptivity that was essentially identical to that generated by endogenous ovarian steroids. Since there are many steroids produced in the ovary, it is perhaps surprising that E2 and P are the only hormones that appear to be needed (2). With the increasing use of embryo cryopreservation, an increasing proportion of in vitro fertilization (IVF) cycles utilize artificial cycles to prepare the endometrium for embryo implantation.

There is, in current usage, a wide variety of regimens that can be used to attain endometrial receptivity. Varying doses and routes of administration are available for both E2 and P, as well as quite wide variations in the duration of administration of E2 prior to initiating P, and even some (small) variability in the duration of P
administration prior to embryo transfer. Two Cochrane Reviews, from 2011 and 2016, concluded that there is “insufficient evidence to recommend one particular protocol for endometrial preparation over another about pregnancy rates after embryo transfers” (3, 4). Therefore, we are left with a consideration of the ease of administration and pharmacokinetic data in deciding on a specific regimen, particularly in difficult situations of poor response to steroid stimulation. Additionally, one recent clinical trial has suggested that regimens that include only vaginal progesterone may be associated with lower implantation rates (5).

ENDOMETRIAL PROLIFERATION: ESTROGENIC STIMULATION

The hallmark of the first phase of the natural menstrual cycle is the development of a dominant follicle, a concomitant rise in E2, and consequent proliferation of the endometrium. More specifically, it is the granulosa cells of the developing follicle that produce E2 in response to gonadotropin stimulation. Although the ovary is, anatomically, near the uterus, E2 must travel through the circulation to reach the endometrium (6). Therefore, peripheral serum E2 levels accurately represent the E2 stimulation that is experienced by the endometrium (except in cases of E2 receptor antagonism, such as occurs with clomiphene citrate or tamoxifen). Early attempts at artificial cycles all used increasing doses of E2 designed to mimic the natural rise of E2 during the follicular phase (1, 7–10), and it remains the common practice to this day, even though varying the dose may not be necessary (7).

How Should Estrogen be Administered?

Estradiol can be administered via many routes—oral, transdermal, intramuscular, and vaginal. The oral route of administration is simple, well-tolerated, and has been extensively studied. Oral E2 is extensively metabolized by both the intestinal mucosa and liver. Ingested E2 is converted to estrone (E1) and estrone sulfate (E1S), with steady-state E1 levels some 3 to 6 times higher than those of E2 (11, 12). E1 is a weaker estrogen as compared to E2, with lower binding affinity for both α and β estrogen receptors. However, despite this, normal circulating E2 levels are achieved as, at equilibrium, 17βE2-dehydrogenase, sulfotransferase and aryl sulfatase can convert these varying forms of estrogen (E2, E1 and E1S) into one another. These specific enzymes are found both in the liver and endometrium, the latter of which has its activity modulated by progesterone (11) (Fig. 1).

FIGURE 1

Interconversion between E2, E1, and E1 sulfate in the circulation and in the endometrium.

To circumvent first-pass hepatic metabolism, E2 can also be administered via various parenteral routes: transdermal, intramuscular (IM), or vaginal. The transdermal route affords the most stable steady-state levels of E2 as less of the transdermally absorbed E2 is converted into E1, with E2/E1 ratios of 1–2 (13). As such, the endometrium may respond differently to oral versus transdermal administration owing to E2’s stronger binding affinity for both estrogen receptors than E1. Because of this differential in E2/E1 ratios, transdermal E2 has been suggested to be superior to oral estrogen for inducing endometrial receptivity and is certainly an excellent alternative in those cases in which oral E2 does not provide adequate endometrial proliferation (14). Since transdermal absorption of E2 is variable, serum E2 levels may be useful for monitoring the response to stimulation, especially if an appropriate endometrial response is not achieved.

Vaginal E2 administration is an alternative parenteral regimen that results in high serum and endometrial levels of E2, confirming that steroids are readily absorbed by the vaginal epithelium (15–17). Furthermore, there appears to be selective uptake of vaginally administered E2 by the endometrium and only a small fraction of the absorbed E2 is converted to E1 (15, 18, 19). This allows for both higher E2 levels and even higher (supraphysiologic) endometrial tissue levels (16). In most cases, either the oral or transdermal routes achieve adequate endometrial proliferation. Thus, vaginal E2 is generally reserved for those cases in which the former modalities are ineffective (20).

How Long Should Estrogen be Administered?

In a natural menstrual cycle, the follicular phase is about 14 days, but may vary quite widely, and still be followed by a normal luteal phase and normal endometrial receptivity. While most artificial protocols utilize a duration of 10 to 14 days of E2 stimulation, most normal responders will have an adequate endometrial priming by 5 to 7 days (7). In those patients who do not respond by 10 to 14 days, the duration of E2 administration may be extended. Pregnancies have been reported after prolonged (4–5 weeks) of vaginal E2 administration (20). In a study using histologic evaluation, 5 weeks of E2 priming was shown to result in optimal luteal phase endometrial histology after progesterone was added (7). Therefore, there does not appear to be an upper limit on the duration of estrogenic stimulation and patients who fail to respond to standard regimens may benefit from an extended course of E2.

The purpose of E2 priming and attainment of endometrial proliferation is the induction of P receptors, which allows subsequent P stimulation to induce endometrial receptivity. Therefore, adequate E2 priming is best confirmed by an endometrial biopsy performed during the subsequent luteal phase to document appropriate histologic endometrial luteinization (9, 10, 21, 22). While many clinics still utilize a practice cycle of hormonal stimulation to document this luteal transition, the measurement of endometrial thickness on transvaginal ultrasound alone may have sufficient predictive value to be used in lieu of an endometrial biopsy (23). Nevertheless, it must be kept in mind that estrogenic stimulation may have a significant effect on the subsequent luteal phase, and the luteal progression of the endometrium depends on not only on the duration and strength of P stimulation, but also on the prior E2 priming. Therefore, an apparent endometrial delay in response to P may be reflective of insufficient P receptors resulting from inadequate E2 priming.

LUTEINIZATION AND THE INDUCTION OF ENDOMETRIAL RECEPTIVITY: ROLE OF PROGESTERONE

With an adequate estrogen regimen, the endometrium and, more precisely, its P receptors, are primed and ready to induce a receptive environment for the developing embryo. Upon the addition of P, the endometrium undergoes both conformational and biochemical changes to produce an environment capable of supporting embryo implantation (24, 25).

Natural cycle P levels are generally less than 0.5 ng/mL. However, in terms of absolute concentrations, circulating P levels are higher than those of E2, as 500 pg/mL of P exceeds the typical 20 to 300 pg/mL of E2 observed in the natural follicular phase (26). Thus, there must be a P threshold below which no luteinization takes place. While the precise level at which this transition occurs has not been firmly established, it appears that luteinization occurs with circulating P levels between 1 ng/mL and 5 ng/mL (27). Conversely, there does not appear to be an upper limit of serum or tissue P in terms of inducing endometrial receptivity. Both IM and vaginal P administration result in higher serum and tissue levels, respectively, than occur in a natural cycle. Yet, there is no evidence of excessive luteinization or a more rapid luteal progression. Pregnancies can be established with both routes of administration (18).

The effect of intermediate serum levels of P, meaning at or near the 1 to 5 ng/mL threshold, in inducing luteinization has not been fully characterized. Previously, it was thought that inadequate P stimulation would cause a “luteal phase defect,” meaning inadequate luteinization to support an implanting blastocyst (28). However, a study examining cycles with exogenously generated low levels of P (approximately 5 ng/mL) found no difference between these cycles and those with control levels of mean ± standard deviation, 19.2 ± 6.6 ng/mL. The lower levels of P resulted in an appropriate endometrial histologic progression, as well as many other markers of endometrial receptivity (endometrial integrins and qRT-PCR analysis for nine putative functional markers) (29). A follow-up study by the same group (30) found that lower levels of P (3 ng/mL) produced normal histological change, but altered endometrial gene expression, confirming an intermediate response to an intermediate low level of P. Thus, current data suggest that a serum level of less than 1 ng/mL is below the endometrial luteinization threshold, while 5 ng/mL is sufficient to induce normal luteal transition and receptivity. Levels between 1 and 5 ng/mL produce intermediate results, whereas levels of P>5 ng/mL will not produce any additional endometrial effects.
How Should \( P \) be Administered?

Unlike \( E_2 \), the routes of administration of \( P \) are limited, given that a higher quantity of the steroid must be delivered to the circulation. Despite extensive first pass metabolism, oral \( P \) can produce adequate serum \( P \) levels (31). However, clinical studies have shown this route to be inadequate, at least in the realm of assisted reproduction (32). Thus, a parenteral route must be used for administration. Transdermal administration is not practical as patches or creams would need to cover large portions of the skin to allow for adequate administration of \( P \). Moreover, transdermally applied \( P \) is metabolized by local 5α-reductase in the skin. Several other routes have been investigated, including intranasal (33), rectal (34), and sublingual (35). These have demonstrated low bioavailability and have yet to be tested in assisted reproduction. Therefore, there are only two practical routes of \( P \) administration for artificially inducing a receptive endometrium—intramuscular and vaginal.

Each of these parenteral routes has advantages and disadvantages. Intramuscular \( P \) provides the highest levels of circulating serum \( P \), yet requires a painful injection. Vaginal \( P \) is readily absorbed by the vaginal epithelium and there appears to be selective uptake of vaginally administered steroids by the endometrium (18, 19, 36). While previous studies showed no difference in outcome of oocyte donation or frozen embryo transfer cycles when either IM or vaginal \( P \) was used (3), a more recent study of three progesterone regimens as called this into question (5). In this most recent study of frozen embryo transfer cycles, a regimen that included only vaginal progesterone was inferior to those that included intramuscular \( P \) (5). Thus, despite the pain and inconvenience of an intramuscular \( P \), many programs continue to use this route of administration for frozen embryo transfer and agonadal replacement cycles. Like \( E_2 \), \( P \) is subject to metabolism in the endometrium (Fig. 2).

How Should \( P \) Administration be Timed?

Exogenous \( P \) administration has made it possible to observe the likelihood of embryo implantation during specific times after \( P \) is first administered. Thus, it became clear that embryo implantation can take place only during a specific period, commonly referred to as the “window of implantation” (37, 38). While the exact timing and duration of this window in humans is not entirely clear, early studies in assisted reproduction demonstrated that this period may be quite large, as cleavage stage embryos resulted in pregnancies after transfers on days 1–6 after the initiation of \( P_4 \) administration (39, 40). Even though the precise timing of the moment of optimal embryo–endometrial synchrony has not been established (41), and it may not exist, the progression of \( P \) secretion in the natural cycle should provide a guide for the timing of exogenous \( P \) administration.

Serum \( P \) levels begin to rise in the late follicular phase of a natural cycle, prior to the luteinizing hormone surge. However, at the time of ovulation, serum \( P \) levels are in the range of 1 ng/mL, which is still below the luteinization threshold (26). Thus, the endometrial luteal transition in natural cycles begins only after ovulation. Levels above the luteinization threshold are likely not achieved for at least another 12 hours. Therefore, \( P \) should most logically be started several hours after egg retrieval.

Despite this argument, clinical experience in assisted reproduction has not always been consistent with these observations (41). In a study by Prapas et al. (42), day 2 embryo transfers were carried out on various days after the start of \( P \) stimulation, from day 2 up to day 6. Rather than finding optimal implantation rates on day 2 or 3 (as would be expected based on the preceding paragraph), there were no pregnancies with transfers that occurred on day 2. Instead, they observed optimal implantation rates on day 4 or 5 of \( P \). Other studies have found good pregnancy rates with the timing of the transfer closer to what would be expected in the natural cycle. For instance, Lelaïdier et al. (43) found good pregnancy rates with transfers of cryopreserved blastocysts on day 5 of \( P \). However, it has been suggested that frozen-thawed embryos have potentially slower development and may benefit from an earlier transfer to synchronize the embryo with the endometrium, thus explaining Lelaïdier’s findings.

Other studies have evaluated starting \( P \) both before and after oocyte retrieval in oocyte donation cycles. Escriba et al. (44) started \( P \) in the recipient on the day prior to donor’s egg retrieval, the day of, and one day after. While they found no difference in pregnancy rates among the groups, there was a trend towards lower ongoing pregnancy in the group that initiated \( P \) prior to egg retrieval (44). In line with this study, a Cochrane Review found evidence of a lower pregnancy rate in fresh oocyte donation cycles when \( P \) was started on the day before egg retrieval rather than the day of or one day after (3). The timing of initiation of \( P \) based on these studies corresponds to day 3 embryos being transferred on day 3 or 4 of \( P \) and blastocysts on day 5 or 6.

Is Estrogen Necessary in the Artificial Luteal Phase?

Most regimens utilize a combination of \( E_2 \) and \( P \) in the luteal phase, consistent with natural cycles. However, several studies have examined the endometrium in cycles primed with \( E_2 \) alone and then with \( P \) alone in the luteal phase. In a cohort of women with no ovarian function, DeZiegler et al. (45) administered vaginal \( P \) with and without transdermal \( E_2 \) in artificial cycles. On endometrial biopsy, they found normal secretory histology in both groups. However, the group without exogenous \( E_2 \) experienced earlier luteal bleeding. In a similar study, Younis et al. (46) studied women in ovarian failure, administering intramuscular \( P \) with and without oral \( E_2 \) after appropriate \( E_2 \) priming. There were no differences in endometrial histology between the two groups even though \( E_2 \) levels were quite different, 21 pg/mL versus 692 pg/mL (46).

Using a different approach to examine the role of \( E_2 \) in the artificial luteal phase, Groll et al. (47) suppressed normally cycling women with a GnRH agonist and then divided the women into 3 groups: no supplemental \( E_2 \); physiologic \( E_2 \) supplementation; and supraphysiologic \( E_2 \) supplementation. Everyone received intramuscular \( P \). On subsequent examination of an endometrial biopsy, they found no difference in the
expression of putative biomarkers of endometrial function between the three groups (47). However, the group with no supplemental E2, serum levels were still 21.9 pg/mL, almost identical to those found in the Younis study. The results of these studies suggest that a very low level of E2, in the range of 20 pg/mL, is sufficient for a normal luteal phase progression. Moreover, given that both studies found E2 levels of about 20 pg/mL without any E2 administration, it appears that some of the exogenous P may undergo conversion to E2. Based on P levels of 20 ng/mL along with these E2 levels, this suggests a conversion rate of about 0.1%. It is tempting to speculate that the increased vaginal bleeding observed in IVF cycles supplemented with vaginal (rather than intramuscular) P without exogenous E2 is due to lower E2 levels since intramuscular P produces higher serum P levels, and thus greater conversion to E2 (48, 49).

POORLY RESPONSIVE ENDOMETRIUM AND OTHER SUBSTANCES

In general, the response of the endometrium is interpreted by its thickness and pattern on trans-vaginal ultrasound, with a tri-laminar endometrium over 7 mm being ideal and a thinner endometrium associated with lower implantation...
rates [50, 51]. However, there is no absolute cut-off for endometrial thickness, since good pregnancy rates have been reported in IVF cycles with endometrial thickness of < 6 mm [51], and a successful pregnancy with an endometrial thickness of just 4 mm [52]. Artificial cycles may differ from IVF cycles, given the absence of ovarian stimulation and reliance only on exogenous hormones to induce a receptive endometrium. For instance, in recipients of oocyte donation, one study found a marked decrease in pregnancy rates in those with an endometrium of less than 7.5 mm [53]. Another study of 465 oocyte donation cycles found a positive correlation between endometrial thickness and implantation rates [54]. However, no minimum value for endometrial thickness could be determined since 50% of recipients with an endometrium less than 4 mm conceived as did 60% of those with an endometrial thickness of 6 to 6.9 mm. From this, the authors concluded that while implantation rates did correlate with endometrial thickness, the success of oocyte donation could not be predicted by endometrial thickness alone. Friedler et al.’s [55] comprehensive review of endometrial thickness concluded that “the usefulness of ultrasonographic parameters in monitoring improvements in uterine receptivity still remains to be proved by controlled prospective studies”.

Despite these data, most practices prepare the endometrium with exogenous estrogen and start P only after the endometrium as reached 7 to 8 mm in thickness [23]. If this thickness is not being reached after a standard two weeks, one approach is to simply extend the duration of the E2 stimulation for a longer period. Alternately, the vaginal route can be used to maximize endometrial delivery [17]. As with other routes of administration, there does not appear to be a maximum time for vaginal E2 administration, and a study by Tourgeman et al. [20] demonstrated an endometrial thickness of > 7 mm in all study subjects given 4–6 weeks of vaginal E2 (n = 10) and an ongoing pregnancy rate of 70%.

Various approaches have been investigated to increase uterine blood flow and, thereby, increase delivery of E2 to the endometrium to potentially prevent an “inadequate” endometrial thickness. Low dose aspirin has been shown to improve uterine blood flow while still yielding satisfactory pregnancy rates [56]. In contrast, another study of 28 recipients of oocyte donation who failed to achieve an endometrial thickness of 8 mm in a practice cycle found no improvement in endometrial thickness in a subsequent cycle in which low dose aspirin was added to the regimen. However, despite no increase in endometrial thickness, the aspirin group did have a statistically significant increase in implantation rate compared to controls [57]. In those recipients with an endometrial thickness less than 8 mm, the effect of aspirin on the pregnancy rate was more pronounced, with the aspirin group having an 83% pregnancy rate versus 25% in the non-aspirin group. Although a Cochrane review did not find aspirin helpful for endometrial preparation, low dose aspirin is a low cost, easy, and relatively harmless intervention with a potential benefit [3].

In addition to aspirin, vaginal sildenafil (Viagra), a smooth muscle relaxant, has been investigated in terms of its ability to increase uterine blood flow. In a group of patients undergoing IVF with an inadequate endometrium, defined as less than 9 mm, vaginal sildenafil was found to increase both uterine blood flow and endometrial thickness [58]. In contrast, a retrospective analysis of the use of vaginal sildenafil in oocyte donation cycles saw no improvement in the recipient’s endometrial thickness or pregnancy rates [59].

Another potential adjunctive treatment for the inadequate endometrium has been the use of a combination of pentoxifylline 800 mg per day with tocopherol (vitamin E) 1,000 mg per day, as this regimen was found to reverse radiation induced uterine fibrosis and improve endometrial thickness [60]. However, it should be noted that this was seen after an entire year of this supplementation. A subsequent study in which subjects with an unresponsive endometrium received 6 months of pentoxifylline and tocopherol did show an increase in endometrial thickness post-treatment, from 4.9 mm to 6.2 mm [61]. Of their 18 subjects, 13 had an improved response and 5 of those conceived.

Some have postulated that endogenous, fluctuating luteinizing hormone levels may be associated with disturbed endometrial maturation and, thus, have investigated the use of GnRH agonists in artificial cycles. El-Toukhy et al. [62] found an increased pregnancy rate in frozen embryo transfer cycles that included a GnRH agonist (buserelin) as part of the artificial endometrial preparation regimen. Yet, a Cochrane review that using a GnRH analog in artificial cycles offered no benefit over regimens that did not include an analog [3]. Tesarik et al. [63] investigated exogenous human chorionic gonadotropin (HCG) as a tool to enhance endometrial receptivity. In their study, recipients of oocyte donation were randomized to receive either HCG 5,000 units or no HCG two days prior to the donor’s egg retrieval. They found improved endometrial thickness and implantation rates in those that received HCG. Thereafter, another group conducted a prospective randomized trial investigating three adjuvant HCG injection regimens versus no HCG in 165 patients undergoing frozen embryo transfers [64]. They found no difference between the study groups in terms of endometrial thickness or pregnancy rates. Likewise, a Cochrane review found no benefit of HCG in artificial endometrial preparation cycles [3].

Endometrial biopsy, or “scratching,” has been studied as another intervention that may aid in implantation. Barash et al. [65] performed four sequentially time biopsies on patients during the luteal phase of the cycle prior to the IVF cycle. They found that those patients who had undergone a biopsy in the prior cycle had a higher implantation rate twice as high as controls, thus concluding that the endometrial injury and repair allowed for enhanced embryo implantation [65]. In turn, another group performed endometrial biopsies during the follicular phase of an IVF cycle, finding improved implantation and pregnancy rates after embryo transfer [66]. To further assess the mechanism by which endometrial injury may aid in implantation, Gnainsky et al. [67] performed sequential endometrial biopsies on patients and examined them histologically. The later biopsies showed an influx of macrophages and inflammatory cytokines, suggesting that a pro-inflammatory environment may make the endometrium more receptive in subsequent cycles.

Recent large, prospective studies and meta-analyses have called into question the efficacy of the “endometrial scratch.”
In a recent double-blind randomized controlled trial of an unselected sub-fertile population, endometrial injury in the luteal phase of the cycle preceding embryo transfer did not result in improved pregnancy rates and, rather, a lower live birth rate (68). In contrast, a 2015 Cochrane review suggested endometrial injury in the month prior to an IVF cycle improved the chances of pregnancy in women with a history of two or more previously failed embryo transfers (69). However, another review highlighted the clinical heterogeneity of studies involving this intervention and, called into question the effect of the endometrial scratch (70). A recent multicenter randomized clinical trial has confirmed the lack of utility of the endometrial scratch (71).

The endometrial receptivity array (ERA) analyzes 238 genes associated with endometrial receptivity in endometrial biopsies obtained on the 5th and 7th days of P in artificial cycles (72). The results are used to estimate the timing of the window of implantation and thus to individualize the timing of the embryo transfer. Utilization of the ERA assumes that the window of implantation is small, that its occurrence is different in different patients, that endometrial progression is similar in each individual patient in repetitive cycles, and that duration of P stimulation is the only parameter that influences the timing of the window of implantation. Whereas a retrospective study of good prognosis patients showed no benefit of the ERA in improving ongoing pregnancy rates, another study showed that a significant number of those with recurrent implantation failure had a displaced window of implantation as determined by the ERA (73, 74). Those patients who subsequently underwent a transfer of cryopreserved embryos with timing based on the ERA showed improved implantation and pregnancy rates. However, those results did not reach statistical significance (73).

CONCLUSIONS AND RECOMMENDATIONS

Successful human reproduction is dependent upon a receptive endometrium. Receptivity to implantation can be induced with exogenously administered E2 and P utilizing a variety of regimens, doses, durations and routes of administration. Adequate E2 priming is necessary for both endometrial proliferation and the induction of P receptors. Thereafter, P action on those receptors causes profound conformational and biochemical changes that induce luteinization and open the window of implantation. Timing of the embryo transfer is adjusted to the embryonic development to achieve synchrony between the implanting embryo and endometrium. Although it appears in natural cycles the window of implantation is quite wide, implantation rates may be improved by optimizing the timing of the transfer. From studies of fresh oocyte donation cycles, it seems that P should be initiated on the day of or day after egg retrieval, with lower pregnancy rates seen when P is started prior to oocyte retrieval of the donor. Adjunctive treatments to exogenous steroids, such as low dose aspirin, GnRH agonists, sildenafil, and HCG, have been investigated and, at present, their value is unproven. The mechanical disruption of the endometrium (“scratch”) is not supported by most recent studies. Adjusting the timing of the transfer with the ERA is also not adequately supported by the data.

For E2 administration, the simplest regimen may be the best approach. Most patients will respond to oral E2 in increasing doses for 10 to 14 days. Should the endometrium not respond adequately, the duration of priming can be extended. If this is not successful, the route of administration can be changed to transdermal, and vaginal E2 may be added. Once an adequate endometrial thickness is achieved, P can be started, usually as a daily dose of 50 mg IM or 100 mg P4 vaginally, to achieve serum levels above the luteinization threshold. Since there appears to be no disadvantage (nor advantage) of higher doses, practitioners may err on the side of higher (or more frequent) doses as a margin of safety. Day 3 embryos should be transferred on day 3 or 4 of P and blastocysts on day 5 or 6. In fresh oocyte donation cycles, this corresponds to the recipient starting P on the day or day after the donor’s oocyte retrieval.

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