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Defining the Proliferative Phase Endometrial Defect

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Abstract

Objective—To evaluate proliferative phase endometrial development in a heterogeneous infertility population.

Design—Retrospective study.

Patient(s)—246 treatment cycles.

Setting—University-based infertility practice.

Intervention(s)—Clomiphene citrate or FSH ovarian stimulation, followed by intrauterine insemination or in vitro fertilization.

Main Outcome Measures(s)—Endometrial thickness by transvaginal ultrasonography. Clinical pregnancy rate.

Result(s)—Endometrial growth began from a nadir of approximately 4.5 mm on cycle day 4, and increased linearly to a plateau of approximately 10 mm on cycle day 9. This same pattern was observed in all cycles, regardless of pregnancy, drug, or underlying diagnosis. FSH stimulated cycles showed a significantly increased endometrial thickness compared to clomiphene citrate cycles (10.1 vs. 8.3 mm, $p < 0.001$). Maximum endometrial thickness achieved showed a correlation with age, BMI, and maximum estradiol level. Subjects who carried a primary diagnosis of PCOS, endometriosis, or RPL all achieved a significantly lower peak endometrial thickness than control subjects. There was a trend toward increased endometrial thickness in cycles resulting in pregnancy than those not (10.1 versus 9.6 mm respectively).

Conclusion(s)—Endometrial development follows a predictable pattern, with a plateau in growth at cycle day 9. Diseases associated with infertility manifest a proliferative phase defect that can be recognized clinically.

Keywords

Endometrium; Endometrial development; Proliferative phase; clomiphene; FSH; endometriosis; Polycystic ovary syndrome; Recurrent pregnancy loss

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Introduction

The normal endometrium increases in thickness during the proliferative phase of the menstrual cycle in response to estrogen. Following ovulation, the endometrium provides an attachment site for and a source of nourishment to an early embryo until the placenta develops. Therefore, the development of the endometrium through the follicular phase is critical to the function of the uterus as a reproductive organ (1).

Because of the importance of endometrial development to successful pregnancy, ultrasound monitoring of the growth of the uterine lining has become a common part of all assisted reproductive technologies, and transvaginal ultrasound has been shown to accurately evaluate the endometrial thickness in menstruating women (2–4). However, there has not been a focus to date on the dynamic changes of the endometrial lining prior to ovulation in women undergoing infertility treatment. Furthermore, controversy exists regarding the clinical significance of variation in endometrial thickness observed among patients undergoing assisted reproductive technologies (1).

Clomiphene citrate (CC) is a very frequently used drug for ovulation induction and controlled ovarian hyperstimulation. It is easily administered, has relatively few side effects, and the risk of multiple pregnancy is relatively low. The mechanism of action is as an anti-estrogen agent exerting effects on the hypothalamus, pituitary, and uterus (5–8). Of clinical importance is the effect of CC on endometrial thickness and quality as detected sonographically. There is evidence that endometrial thickness is reduced by CC, with multiple studies showing that the agent does have a negative impact (9–11). However, these studies have focused on a comparison of endometrial thickness while taking CC to placebo. It has been suggested that some of the harmful effects on the endometrium can be countered by the addition of Follicle Stimulating Hormone (FSH) to the stimulation regimen. Multiple studies have shown that women treated with a combination of these drugs develop thicker endometrial linings than with CC alone in a dose responsive fashion (12–14). Nonetheless, a review of the literature finds little comparison of CC to FSH directly in terms of the development of the endometrium through the proliferative phase.

In addition to the drugs utilized in cycle stimulation, underlying endocrine and reproductive diagnoses can often play a role in endometrial development as well. For instance, many changes have been found in both the ultrastructural morphology and the molecular composition of the endometrium in patients with endometriosis, providing the basis for a uterine factor in infertility (15–17). Likewise, polycystic ovary syndrome has also been characterized with specific alterations in the endometrium, including a change in the ratio of estrogen and androgen receptors (18,19). Recurrent pregnancy loss is also a reproductive disorder that has been characterized at the molecular level in the endometrium. Both differentiation and adhesion markers have been found to be altered in women with recurrent pregnancy loss believed to be of other etiologies, such as the antiphospholipid syndrome (20,21).

In this study, we attempted to perform a thorough analysis of the sonographically detected development of the endometrium throughout the proliferative phase of treatment cycles. Specifically, we wished to examine the effects of patient demographics, drugs used for stimulation, underlying disease processes known to be characterized by endometrial defects, and eventual pregnancy outcomes on both the rate of development of endometrial thickness as well as the maximum thickness achieved.

Materials and Methods

After IRB approval for chart review was obtained, the charts of randomly selected patients undergoing assisted reproduction at the Yale Fertility Center between 2001 and 2007 were

reviewed. Subjects eligible for selection had undergone at least one cycle of ovulation induction with either clomiphene citrate or follicle stimulating hormone (FSH) during the time period. Patients who had undergone only in vitro fertilization cycles were excluded. A total of 246 treatment cycles from 100 subjects were reviewed.

Stimulation Protocols

Clomiphene Citrate

Patients underwent ovulation induction or superovulation with 50 – 200 mg clomiphene citrate daily beginning at day 3, 4, or 5 of the menstrual cycle. Recombinant human chorionic gonadotropin (r-hCG) was administered with a leading follicle ≥ 18 mm on transvaginal ultrasound. Intrauterine insemination (IUI) was performed approximately 12 and 36 hours later. Pregnancy was determined by urine hCG approximately 18 days after r-hCG administration.

Follicle Stimulating Hormone

Patients underwent ovulation induction or superovulation with a physician selected dose of recombinant or urinary derived FSH beginning at day 3 of the menstrual cycle after baseline ultrasound examination. Recombinant human chorionic gonadotropin (r-hCG) was administered with a leading follicle 18 mm on transvaginal ultrasound. Intrauterine insemination (IUI) was performed approximately 12 and 36 hours later. Pregnancy was determined by urine hCG approximately 18 days after r-hCG administration, and then confirmed by serum hCG.

In Vitro Fertilization

Patients underwent controlled ovarian hyperstimulation with the use of recombinant FSH. R-hCG was administered when three or more leading follicles were ≥ 18 mm. Oocytes were retrieved 36 hours later, after which supplementary progesterone was begun. Oocytes were inseminated by either conventional insemination or intracytoplasmic sperm injection (ICSI), as appropriate. Embryos were cultured in vitro, using sequential culture media, and transferred on either day 3 or 5 following oocyte retrieval. All patients undergoing IVF received saline infusion sonography to assess the endometrial cavity within 12 months prior to treatment. Pregnancy was determined by serum hCG approximately 15 days after oocyte retrieval.

Measurement of Endometrial thickness

Maximal ET in the sagittal plane was measured on each day of physician determined monitoring with an office ultrasound (GE Healthcare, Chalfont St. Giles, United Kingdom), using a 5-MHz endovaginal probe. The endometrial pattern was not recorded. Serum estradiol (pg/ml) was also measured on each day of monitoring. Patient age, gravidy, parity, diagnosis, semenanalysis result, BMI, duration of infertility, day 3 FSH level, and treatment regimen were also recorded for each cycle.

ET curves were developed by plotting the mean $\pm$ standard error of the mean (SEM) ET measurement for all results of ultrasound monitoring from a particular day of the menstrual cycles. Woman with a sole diagnosis of male factor infertility were utilized as a control population.

Comparisons of means between 2 independent groups for continuous variables were made with Student's t-test, and the paired t-test was used for comparison of means between 2 dependent groups. Comparison of categorical variables was made by Chi-Square test. 1 way ANOVA with Holm-Sidak post-hoc analysis was used for multiple comparisons. Analysis of covariance (ANCOVA) was used for multiple comparisons with dependency correction. Correlations were

calculated using multiple linear regression. All statistical analysis was performed using SigmaStat version 10.0 (SyStat).

Results

Population and cycle characteristics

The baseline characteristics of our study population, including demographics, infertility diagnosis, and cycle type, are described in Table I. A diagnosis of PCOS was derived from the Rotterdam consensus criteria (2003).

Patterns of Endometrial Development

A composite representation of follicular phase endometrial development was constructed for all cycles in the study (see Figure 1A). Endometrial growth began from a nadir of approximately 4.5 mm on cycle day 4, and increased linearly by 1 mm per day to a plateau of approximately 10 mm by cycle day 9. Endometrial thickness appeared to stay at a mean of close to 10 mm from cycle day 9 onward regardless of follicular phase length. The mean endometrial thickness measured on each day of the proliferation curve correlated closely with the mean estradiol levels measured on that day (coefficient 0.00524, $p < 0.001$). This same trajectory was observed in cycles resulting in pregnancy, and those that did not. Cycles resulting in pregnancy did have an increased plateau thickness; however, this result did not reach statistical significance.

A comparison of all cycles utilizing clomiphene citrate to those using FSH showed that while the overall trajectories of growth and plateau were similar, cycles resulting from FSH had significantly increased endometrial thickness (see Figure 1B). This difference was additionally demonstrated in a subgroup of subjects who had undergone multiple cycles utilizing both drugs (see Figure 1C). In these patients, subsequent cycles using FSH for ovarian stimulation had significantly increased plateau thickness when compared to their previous cycles with clomiphene.

Similarly, subjects who underwent treatment cycles who had diagnoses of PCOS or endometriosis also achieved maximum endometrial thickness by approximately cycle day 9, similar to the control (male factor diagnosis only) patients (see Figure 2A,B). Subjects with Recurrent Pregnancy Loss (RPL), however, had a delay in the achievement of plateau thickness, taking until approximately day 12 to plateau (see Figure 2C). In all of these subgroups, the plateau thickness was significantly less than in the control patients.

Evaluation of Peak Endometrial Thickness

The peak, mean endometrial thickness of all clomiphene cycles compared with all non-IVF FSH cycles showed a significantly increased endometrial thickness with FSH use (10.1 vs. 8.3 mm, $p < 0.001$). This difference persisted when corrected for serum estradiol level using ANCOVA. The peak endometrial thickness did not vary linearly with dose of clomiphene citrate from 50–200 mg (coefficient 0.00774, $p = 0.554$). When evaluating subjects who had separately utilized both FSH and clomiphene citrate over multiple cycles of ovarian stimulation, the cycles utilizing FSH resulted in a significantly higher endometrial thickness (10.7 vs. 8.6 mm respectively, $p < 0.001$).

For all included treatment cycles, the mean maximum endometrial thickness achieved during the follicular phase was 9.8 mm. Maximum endometrial thickness achieved showed a significant positive correlation with age (coefficient 0.107, $p = 0.002$), BMI (coefficient 0.0625, $p = 0.024$), and maximum estradiol level (coefficient 0.000864, $p < 0.001$), although there was no significant correlation with cycle day 3 FSH (coefficient -0.0319 , $p = 0.550$).

Subjects who underwent treatment cycles who carried a primary diagnose of PCOS, endometriosis, or RPL all achieved a significantly lower peak endometrial thickness than the male factor control subjects (see Figure 3). This difference was observed despite a similarity of the proportion of clomiphene citrate cycles within each subgroup ($p = 0.369, 0.461$, and 0.447 , respectively). This difference also persisted in all individual subgroups when an analysis of covariance was performed to correct for the confounding variables of age, BMI, and peak estradiol levels.

Analysis of pregnancy rates excluded IVF cycles, so as to limit the impact of factors outside of method of ovarian stimulation and maximum endometrial thickness. When controlling again for maximum estradiol level, age, and BMI, there was a trend toward increased endometrial thickness in cycles resulting in pregnancy than those not resulting in pregnancy (10.1 versus 9.6 mm respectively, $p = 0.303$).

Discussion

We performed an analysis of the development of proliferative phase endometrium in 246 cycles. We have described the dynamics of the pattern of growth of the endometrium throughout the follicular phase in a large, heterogeneous, infertile population, as well as how this growth pattern is affected by different treatment medications and underlying diagnoses. As our study population was very heterogeneous with respect to age, treatment, and medication used, our data and conclusions should be applicable to a large proportion of patients.

Endometrial growth plateau

In this population, endometrial growth begins at approximately cycle day 4 after the conclusion of menses, and grows at a linear rate of approximately 1 mm/day until approximately cycle day 9, at which point growth plateaus. This plateau is an interesting and novel observation for several reasons. First, the plateau appears to occur in all settings, regardless of treatment regimen, drug, underlying diagnosis, or success. This phenomenon suggests that there is a critical window for intervention in the first several days following the cessation of menses in which to affect the development of the endometrium. Interventions occurring after this window may not allow for any significant additional growth.

The plateau phenomenon is also a novel concept that may be interesting at the molecular level. There may be a biological mechanism responsible for the prevention of growth of the functional endometrium beyond a certain thickness, or stated another way, a certain distance from the basalis layer. One could imagine a soluble factor that may be responsible for the functional “height” of the endometrium. This factor could be expressed over a diffusible gradient, thus establishing a set point for endometrial thickness. As investigators continue to study the differential expression of genes in the endometrium in diseases such as endometriosis, such a functional factor could be further explored.

Effect of clomiphene citrate

It has been well established that CC has an anti-estrogenic effect on the endometrium. Clomiphene has been shown to reduce the number of estrogen and progesterone receptors and glandular density in the endometrium, and increase the number of vacuolated cells (6,8). All of these features are consistent with a hypoestrogenic effect (5). It has also been shown that CC has a detrimental effect on endometrial thickness and implantation rate, and a few reports suggest these effects may be ameliorated by the addition of exogenous estradiol (22–25). Nonetheless, we observed a significantly decreased endometrial thickness with CC use even when corrected for estradiol levels. These data would suggest that there are additional effects of CC on the physiology of the endometrium beyond suppression of global estradiol levels.

This difference could explain why CC is much more successful at inducing ovulation than resulting in ongoing pregnancy, and why there are lower pregnancy rates seen with using CC for superovulation than with gonadotropins (23). At our institution, clomiphene citrate start date varies from cycle day three to five, and we cannot exclude the possibility that this variation could have affected our results. Furthermore, it is possible that clomiphene citrate use may result in a permanent change in the endometrium beyond the particular treatment cycle. Our study is unable to address this possibility; nonetheless, these results confirm that the utilization of FSH for ovulation induction or superovulation is a viable treatment strategy for patients who are found to have poor endometrial development with CC.

Effect on pregnancy rates

In this study, we observed a trend toward increased endometrial thickness in cycles resulting in pregnancy, although this difference did not achieve statistical significance. The lack of statistical significance is likely due to the very small sample size of cycles resulting in pregnancy available in this study. Thus our study was not adequately powered to examine this secondary outcome. Nonetheless, our results agree with data described recently for a large series of cycles which showed significant correlations between maximum endometrial thickness and pregnancy rates for IVF (1).

Effect of diagnosis

While we cannot exclude the possibility that patients with a male factor diagnosis do not also have an underlying endometrial disorder, this group is the best possible control group that is generally available for evaluation in a typical infertility practice. Thus, the inclusion of subjects with male factor infertility in this study allowed for an evaluation of the effects of endocrine dysfunction and reproductive pathology on endometrial development.

Not surprisingly, several disease states that have been previously associated with endometrial pathology were all found to have significant differences in endometrial development detected sonographically. Endometriosis has been previously characterized as having a eutopic endometrial component, with the eutopic endometrium of women with endometriosis showing changes in molecular markers for inflammation (26,27) and steroid metabolism (28). Both of these pathways could lead to aberrant endometrial development through the proliferative phase.

It is also interesting that women with PCOS also appear to have deficient endometrial development. It has been previously suggested that women with PCOS had a higher incidence of dysynchrony between endometrial glands and stroma on biopsy after CC treatment than controls (29), suggesting a mechanism for lower implantation and pregnancy rates. Our data suggest that there is abnormal development in the proliferative phase as well. Likewise, the uterine component of recurrent pregnancy loss has been traditionally believed to be due to a defect in implantation, and recently, deficiencies in adhesion molecule expression have been found in these patients (21). However, our data suggests that the endometrial component of RPL may occur much earlier than the implantation window. It is possible that this component could be due to deficient proliferation resulting from scar tissue or fibrosis following procedures such as D&C's or resections of myomas and polyps, however the occurrence of this defect in subjects without a history of such interventions argues for an inherent endometrial defect.

The "Proliferative Phase Defect"

Our data suggest a "proliferative phase defect" in patients with diseases associated with infertility that can be recognized in clinical practice. Prakash et al. recently attempted to identify a "follicular phase defect" in patients with recurrent pregnancy loss, and found no differences in the serum concentrations of many biochemical markers, including anti-Mullerian hormone,

inhibin B, FSH, luteinizing hormone, and progesterone (31). However, we have described a limitation in the maximum endometrial thickness that can be achieved in a subset of infertile patients, despite no change in the time course to reach peak endometrial thickness. This difference suggests that the proliferative phase defect in these patients is indeed a defect in endometrial proliferation. Despite the fact that most studies of uterine factor infertility focus on the luteal phase, these data suggest that attention should be paid to growth and proliferation as well. More studies are warranted to better evaluate the true extent of this proliferative phase defect clinically, as well as at the histological and molecular level. Nonetheless, the fact that the endometrial defect we have identified can be measured non-invasively by sonography makes it a potentially useful clinical tool for reproductive endocrinologists.

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Figure 1.

A) Pattern of follicular phase endometrial development: composite of all 246 cycles. B)

Comparison of all cycles using clomiphene citrate to those using FSH. C) Subgroup comparison

limited to only subjects who underwent multiple cycles with both clomiphene citrate and FSH.

Figure 2.
Comparison of endometrial growth between control (male factor diagnosis only) subjects and subjects with: A) Polycystic Ovary Syndrome, B) Endometriosis, and C) Recurrent Pregnancy Loss.

Figure 3. Comparison of peak endometrial thickness in patients with PCOS, endometriosis and RPL to the control group. * $p < .05$, ** $p < .01$.

Table 1

Characteristics of the study population.

	Mean (Range)
Age (years)	34.2 (22 – 46)
BMI	25.8 (16.6 – 43.2)
Duration of Infertility (months)	22.9 (0 – 96)
CD 3 FSH	6.06 (1.4 – 18.4)
Abnormal SA (%)	24.6
Infertility (%)	
-Primary	48
-Secondary	52
Primary Diagnosis (%):	
-PCOS [*] /Ovulatory dysfunction	28
-Male Factor	19
-Unexplained	18
-DOR/Age related	8
-RPL	7
-Endometriosis	7
Method of ovarian stimulation (%):	
-Natural	2
-Clomiphene citrate	23
-FSH	75
Pregnancy Rate (%)	22.9

^{*} Defined by Rotterdam Criteria, 2003.