*Clinical Medicine Research*
2024, Vol. 13, No. 6, pp. 68-76
https://doi.org/10.11648/j.cmr.20241306.11

Research Article

# Evaluation of Endometrial Receptivity in Unexplained Infertility After Clomiphene Citrate by Shear Wave Elastography

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## Abstract

Objective: This study utilized shear wave elastography (SWE) to evaluate endometrial receptivity (ER) in cases of unexplained infertility (UI) following treatment with clomiphene citrate (CC). The aim was to establish a reliable imaging reference for clinical treatment. Methods: This investigation encompassed 68 patients with UI who attended our hospital from October 2023 to May 2024. Participants were allocated to either a CC group (28 participants) or a normal control (NC) group (40 participants) according to the treatment protocols they followed. During the LP phase (days 13-16) and the MP phase (6-9 days post-ovulation), both groups underwent transvaginal ultrasound and SWE assessments. The evaluated parameters included endometrial thickness (EMT), uterine artery parameters (UA-PI, UA-RI, UA-S/D), average endometrial elasticity (E-mean), and mean shear wave velocity (SWV-mean). Additionally, clinical pregnancy outcomes were tracked. Results: Significant variations were observed between the CC and NC groups in E-mean, SWV-mean, EMT, UA-PI, UA-RI, and UA-S/D during both evaluated phases, with statistical significance ($P<0.05$). Nevertheless, there were no significant variations found in clinical pregnancy rates among the groups ($P>0.05$). Significant statistical differences were observed in E- mean and SWV-mean between pregnant and non-pregnant patients within each group ($P<0.05$). Conclusions: After CC treatment, the endometrium in UI patients showed decreased thickness, increased hardness, reduced blood flow, and increased difficulty in implantation. Despite these effects, CC did not significantly impact clinical pregnancy rates. Future studies should expand the sample size to determine the threshold of endometrial hardness that optimally balances its effects.

## Keywords

Clomiphene Citrate, Endometrial Receptivity, Shear Wave Elastography, Unexplained Infertility

## 1. Introduction

Unexplained infertility (UI) is characterized as the inability of a couple to achieve pregnancy despite regular sexual intercourse for more than one year. After a comprehensive diagnostic assessment, an identifiable cause for the couple's inability to conceive remains unidentified [1]. Endometrial receptivity (ER) is defined as the changes in the endometrial stroma necessary for embryo positioning, adhesion, penetration, and implantation [2]. These changes are essential for the embryo's ability to attach and implant within the uterus and are considered the primary factor contributing to UI [3-6].

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**Received:** 10 October 2024; **Accepted:** 28 October 2024; **Published:** 22 November 2024

Currently, there is no standardized strategy for the clinical treatment of UI. Treatment typically begins with oral medication. Clomiphene citrate (CC) has been the principal pharmaceutical agent used in managing infertility [7]. Its primary mechanism of action includes competitive binding to estrogen receptors, stimulation of ovarian follicular activity, and increased availability of potential oocytes for fertilization, thereby enhancing the cycle pregnancy rate.

Shear wave elastography (SWE) is an emerging technique that quantifies tissue elasticity by measuring SWV-mean [8, 9]. It offers the benefits of being non-invasive, providing real-time imaging, and being repeatable. Recent research suggests that the elasticity of the endometrium, which plays a vital role in supporting embryo implantation, can be effectively measured using SWE. This holds true for both women with UI and those who are healthy [10, 11]. Thus, this study utilized SWE to assess the elasticity of the endometrium in patients with UI during the late-proliferative (LP) and mid-secretory (MP) phases after CC treatment, with a particular emphasis on their clinical pregnancy outcomes. The aim was to provide clinicians with a reliable imaging reference for treatment decisions.

## 2. Materials and Methods

University-Town Hospital's Institutional Ethics Committee (LL-202337) of Chongqing Medical University approved this retrospective study, which followed the guidelines laid down in the Declaration of Helsinkis.

### 2.1. Research Subjects

The 121 UI patients who visited the University-Town Hospital of Chongqing Medical University for fertility counseling or preconception examinations between October 2023 and May 2024 were the subjects of the analysis. This group included 54 UI patients treated with CC group (n=54) and 67 treated with a normal control (NC group, n=67). Inclusion criteria were: (1) age 20-40; (2) bilateral tubal patency and normal uterine and ovarian morphology and ovulation as confirmed by transvaginal ultrasound; (3) no use of vasoactive drugs or gynecological surgery within two months prior to examination. Exclusion criteria included: (1) abnormal uterine or ovarian development or trauma, or a history of surgery; (2) hypertension; (3) autoimmune disease; (4) endocrine disorders such as diabetes mellitus and thyroid dysfunction; (5) abnormal semen analysis in the male partner; (6) prior administration of clomiphene. In the end, the study included 28 patients from the CC group and 41 patients from the NC group (Figure 1)

Beginning on day 10 of the menstrual cycle, patients were observed for ovulation every other day using routine transvaginal ultrasonography. Once the follicle diameter reached 16 mm, the monitoring was increased to daily. During the ovulatory (LP; days 12 – 16) and implantation (MP; 6 – 9 days post – ovulation) phases, transvaginal ultrasonography (TVS) and SWE were performed. The CC group, comprising 28 participants, was segmented into the LPCC and MPCC subgroups based on the timing of their assessments during these phases. Similarly, the NC group, with 41 participants, was divided into LPNC and MPNC subgroups.

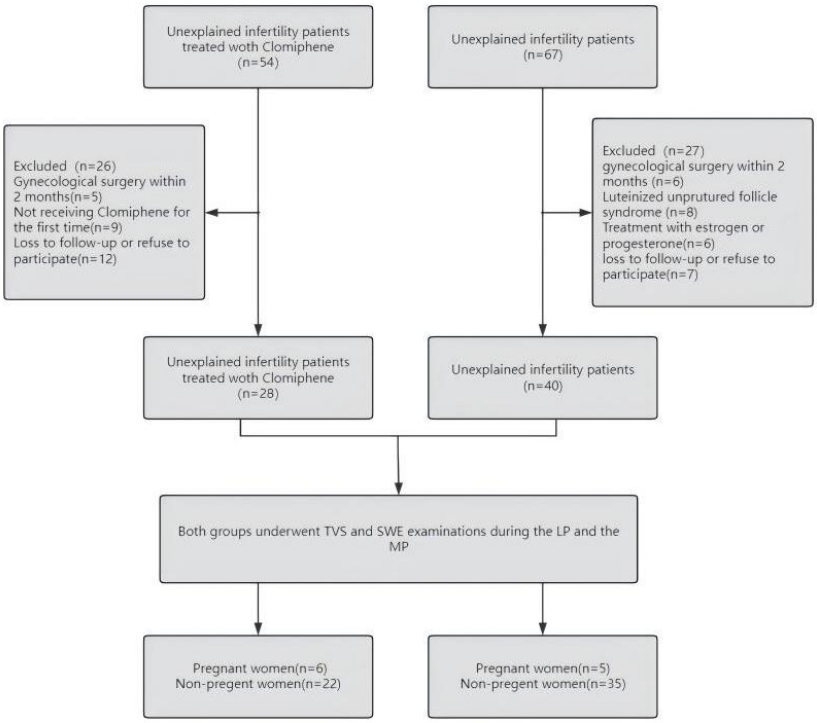


***Figure 1.*** *Flow chart of the study population. TVS transvaginal ultrasonography. SWE shear wave elastography. LP late-proliferative phase. MP mid-secretory phase.*

## 2.2. Clomiphene Citrate

Participants in the CC group were administered oral CC (produced by Shanghai Hengshan Pharmaceutical Co., Ltd., approved by the National Medical Products Administration, No. H31021107), at a dosage of 50 mg/day for five days beginning on the fifth day of the menstrual cycle.

## 2.3. Clinical Pregnancy Outcome Determination

About 35 to 40 days following the last menstrual cycle, a transvaginal ultrasound and human chorionic gonadotropin (HCG)

blood test were conducted. Ultrasound confirmation of a gestational sac in the uterus and a positive HCG blood test established a clinical pregnancy. Without these signs, the pregnancy was deemed a failure.

## 2.4. TVS and SWE Acquisition

An intracavitary probe SE12-3 (3-12 MHz) and the Supersonic Imagine AixPlorer (Aix-en-Provence, France) were used for imaging. The same physician with over five years of ultrasonography experience performed all TVS and SWE evaluations using the same equipment settings. Prior to the operations, all subjects were asked to provide their informed permission.

The patients were told to empty their bladders, get into the lithotomy position, and breathe calmly before the exams. A complete sagittal two-dimensional image of the uterine cavity was obtained by inserting the SE12-3 endocavity probe into the posterior vaginal fornix. In order to assess EMT, the biggest longitudinal slice was used, which was 2 cm away from the uterine fundus. After that, a transverse piece of the cervix was captured by rotating the probe 90 °. At the outer lower boundary of the cervical junction, uterine artery blood flow parameters were examined. These included the pulsatility index (PI), resistance index (RI), and the ratio of peak systolic velocity to end-diastolic velocity (S/D).

Starting on the upper sagittal portion of the uterus, the sample box was positioned to completely encircle the endometrium for a duration of three seconds during SWE. Once the picture had stabilized and frozen, the region of interest (ROI) diameter was set at 2 mm, and the ROI was positioned 2 to 4 cm from the probe surface. The ROI was found at the middle of the uterine cavity line, halfway between the myometrium-endometrial boundary and the typical sagittal section of the uterus. Furthermore, symmetrically and uniformly spaced, three spots were noted throughout the middle and top segments of the endometrium on both the front and posterior walls (Figure 2). The endometrium's mean E-mean and SWV-mean were computed automatically by the Q-box system. Measurements were taken thrice at the same site, and the mean value was computed.

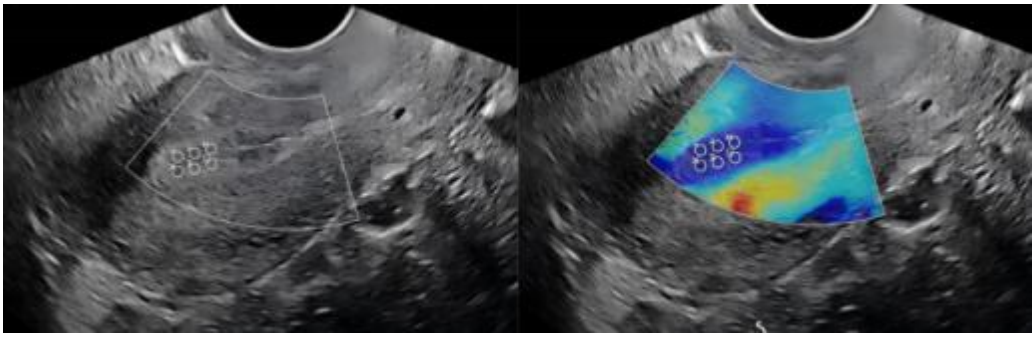

***Figure 2.*** *Sonographic image of endometrial elastography measurement. In a standard sagittal section of the uterus, the middle and upper segment of the endometrium is completely covered by the white sampling frame. The white circles represent the six sampling sites for SWE.*

## 2.5. Clinical Data

The endometrium's mean E-mean and SWV-mean were computed automatically by the Q-box system. Measurements were taken thrice at the same site, and the mean value was computed. It is imperative to gather and document all pertinent clinical data, including demographic characteristics (Table 1). It is also crucial to note the individuals' baseline levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) on days 2-3 of their menstrual cycles.

## 2.6. Statistical Analysis

The data analysis was performed using SPSS version 25.0. Assessing the normality of the data was done using the Shapiro- Wilk (SW) test. The data was expressed as the mean plus or minus the standard deviation. Comparisons between groups were made using the two-independent-sample t-test, while within-group comparisons across different time points were made using the paired t-test. For data that didn't follow a

normal distribution, we used the median (P25, P75) to represent it. To compare groups, we used the Mann-Whitney U test, and for comparisons within the same group at different time points, we used the Wilcoxon rank sum test. Data were presented as counts or percentages, and the X2 test was used to compare groups. A P-value of < 0.05 was considered to be statistically significant.

# 3. Results

## 3.1. Population Characteristics

There were no statistically significant differences between the two groups of pregnant women in terms of age, height, gestational age, maternal weight, abdominal wall fat thickness, BMI, fetal birth weight, and 1-minute Apgar score (p>0.05) (Table 1).

***Table 1.*** *Clinical data between Clomiphene citrate group and Normal control group.*

| Groups | Age (years) | Year of infertility | BMI ($kg/m^2$) | Follicle-stimulating hormone (mIU/mL) | Luteinizing hormone (mIU/mL) | Estradiol (ng/mL) |
|---|---|---|---|---|---|---|
| CC (n=28) | 29.07±3.92 | 2.48±0.44 | 22.25±1.77 | 6.23±0.88 | 4.38±0.47 | 37.65 (37.18, 38.03) |
| NC (n=40) | 29.23±4.12 | 2.45±0.32 | 22.91±2.00 | 5.91±0.73 | 4.58±0.70 | 37.30 (26.38, 46.80) |
| Z/t | -0.154 | 0.296 | -1.417 | 1.666 | -1.307 | -0.237 |
| P | 0.878[a] | 0.768[a] | 0.161[a] | 0.101[a] | 0.196[a] | 0.813[b] |

CC Clomiphene citrate, NC Normal control, BMI Body mass inde
a Student's test
b Mann-Whitney U test
p < 0.05, indicating statistical significance

## 3.2. TVS and SWE Results

In both the LP and MP stages, EMT was consistently lower in the CC group compared to the NC group (P<0.05) (Table 2). In addition, across all groups, EMT measures during the LP phase were higher than those during the MP phase (P<0.05). The CC group showed slight increases in uterine artery blood flow measures, such as UA-PI, UA-RI, and UA-S/D, compared to the NC group at both time points of observation (P<0.05). In both groups, these characteristics declined when the LP phase transitioned into the MP phase (P<0.05). Figure 3 shows that during the LP and MP phases, the CC group had significantly higher average E-mean and SWV-mean values than the NC group (P<0.05). Both groups had lower E-mean and SWV-mean values during the MP phase compared to the LP phase (P<0.05).

***Table 2.*** *Parameters of CC and NC group during the late-proliferative and mid-secretory phase.*

| Groups | EMT (mm) | UA-PI | UA-RI | UA-S/D | E-mean (kPa) | SWV-mean (m/s) |
|---|---|---|---|---|---|---|
| CC | | | | | | |
| LPCC | 6.55 (5.53, 8.33) | 2.64 (2.30, 2.90) | 0.88 (0.85, 0.91) | 8.05 (6.51, 9.94) | 32.05 (19.53, 37.87) | 3.24 (2.53, 3.52) |
| MPCC | 9.40 (8.50, 11.18) | 2.31 (1.85, 2.52) | 0.85 (0.78, 0.87) | 7.18 (6.55, 9.09) | 12.46 (7.28, 21.15) | 1.92 (1.62, 2.16) |
| NC | | | | | | |
| LPNC | 8.60 (7.93, 9.68) | 2.27 (2.07, 2.64) | 0.85 (0.81, 0.89) | 7.14 (5.38, 8.39) | 16.32 (11.95, 21.01) | 2.32 (1.98, 2.63) |
| MPNC | 11.55 (10.43, 12.50) | 1.97 (1.74, 2.15) | 0.81 (0.77, 0.83) | 6.25 (5.37, 7.10) | 8.69 (6.84, 9.63) | 1.67 (1.37, 1.85) |
| PLPCCvsLPNC | 0.000[b] | 0.003[b] | 0.018[b] | 0.034[b] | 0.000[b] | 0.000[b] |

| Groups | EMT (mm) | UA-PI | UA-RI | UA-S/D | E-mean (kPa) | SWV-mean (m/s) |
|---|---|---|---|---|---|---|
| PMPCCvsMPNC | 0.000[b] | 0.001[b] | 0.023[b] | 0.002[b] | 0.000[b] | 0.004[b] |
| PLPCCvsMPCC | 0.000[C] | 0.000[C] | 0.002[C] | 0.030[C] | 0.000[C] | 0.000[C] |
| PLPNCvsMPNC | 0.000[C] | 0.000[C] | 0.000[C] | 0.006[C] | 0.000[C] | 0.000[C] |

CC Clomiphene citrate, LPCC Late-proliferative phase of clomiphene citrate, MPCC Mid-secretory phase of clomiphene citrate, NC Normal control, LPNC Late-proliferative phase of normal control, MPNC Mid-secretory phase of normal control, EMT Endometrial thickness, E-mean Mean elasticity (ormean Young's modulus), SWV-mean Mean shear wave velocities, UA-PI, Uterine artery pulsatility index; UA-RI, Uterine artery resistance index; UA-S/D, Peak systolic velocity/end diastolic velocity of the uterine artery

b Mann-Whitney U test

C Wilcoxon rank sum test

$p < 0.05$, indicating statistical significance

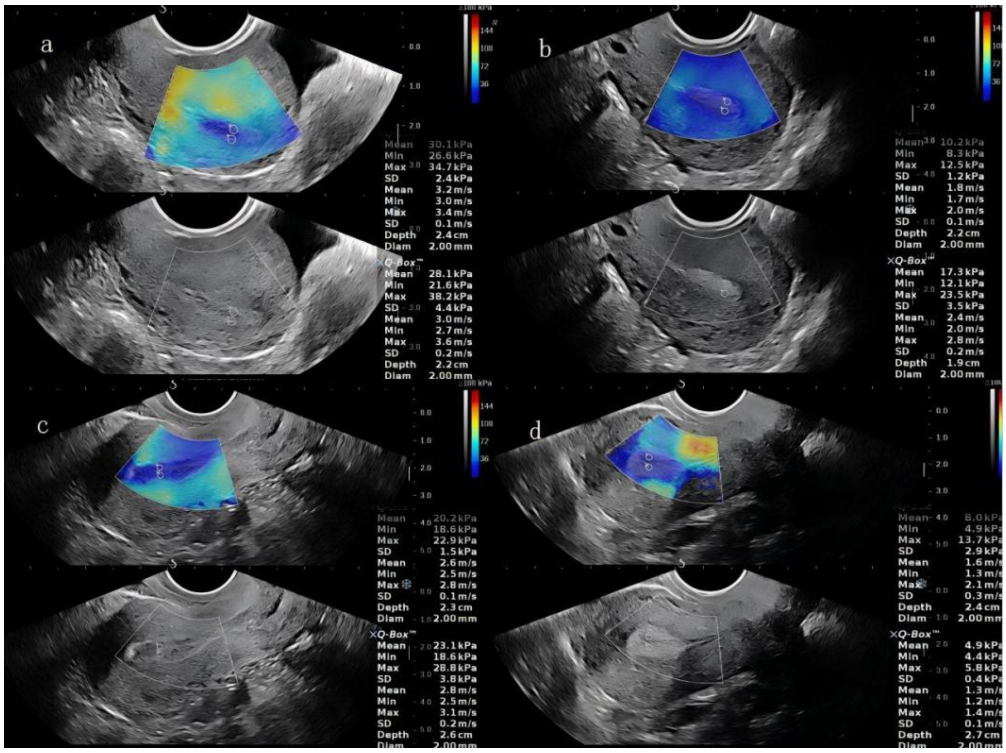


***Figure 3.*** *Representative images of one person in group CC during LP(a) and MP(b). a In the LPCC group, the mean elasticity (E-mean) and mean shear wave velocity (SWV-mean) at the two ROIs of the upper endometrial segments were 30.1 kPa and 28.1 kPa and 3.2 m/s and 3.0 m/s. b In the MPCC group, the E-mean and SWV-mean at the two ROIs of the upper endometrial segments were 10.2 kPa and 17.3 kPa and 1.8 m/s and 2.4 m/s. Representative images of one person in group NC during LP(c) and MP(d). c In the LPNC group, the mean elasticity (E-mean) and mean shear wave velocity (SWV-mean) at the two ROIs of the upper endometrial segments were 20.2 kPa and 23.1 kPa and 2.6 m/s and 2.8 m/s. d In the MPNC group, the E-mean and SWV-mean at the two ROIs of the upper endometrial segments were 8.0 kPa and 4.9 kPa and 1.6 m/s and 1.3 m/s.*

## 3.3. Clinical Pregnancy Outcome and Ultrasound Assessment

The CC group was divided into a pregnancy group (PCC group, 6 cases) and a non-pregnancy group (NCC group, 22 cases) based on clinical pregnancy outcomes. The NC group was further segmented into a pregnancy group (PNC group, 5 cases) and a non-pregnancy group (NNC group, 35 cases). Table 3 shows that compared to the NC group, the CC group had a greater clinical pregnancy rate; however, this difference was not statistically significant (P>0.05). As compared to non-pregnant patients, pregnant patients in both groups had lower E-mean and SWV-mean values (P<0.05). The results of EMT, UA-PI, UA-RI, and UA-S/D were not significantly different between the pregnant and non-pregnant groups of patients (P>0.05) (Table 4).

***Table 3.*** *Comparison of clinical pregnancy between CC group and NC group.*

| Groups | Cases (n) | Clinical pregnancy rate [n (%)] |
|---|---|---|
| CC | 28 | 6 (21.4) |
| NC | 40 | 5 (12.5) |
| $X^2$ | | 0.422 |
| P | | 0.516[d] |

CC Clomiphene citrate, NC Normal control
d $X^2$ test

***Table 4.*** *Clinical pregnancy and ultrasound parameters during MP in the CC and NC groups.*

| Groups | EMT (mm) | UA-PI | UA-RI | UA-S/D | E-mean (kPa) | SWV-mean (m/s) |
|---|---|---|---|---|---|---|
| CC | | | | | | |
| PCC | 9.50 (9.03, 10.53) | 2.24 (1.68, 2.86) | 0.85 (0.76, 0.91) | 6.45 (5.24, 6.89) | 9.42 (8.41, 9.84) | 1.52 (1.39, 1.62) |
| NCC | 9.40 (8.15, 11.58) | 2.31 (1.85, 2.52) | 0.85 (0.78, 0.87) | 7.83 (6.70, 9.20) | 13.48 (11.45, 22.94) | 1.97 (1.82, 2.53) |
| NC | | | | | | |
| PNC | 11.60 (10.35, 12.35) | 1.95 (1.79, 2.14) | 0.81 (0.77, 0.83) | 6.30 (5.10, 7.10) | 6.12 (5.39, 6.96) | 1.27 (1.18, 1.32) |
| NNC | 11.50 (10.40, 12.60) | 1.97 (1.74, 2.15) | 0.81 (0.77, 0.83) | 6.25 (5.37, 7.10) | 8.85 (6.88, 10.38) | 1.68 (1.51, 1.97) |
| PPCCvsNCC | 0.694[b] | 0.889[b] | 0.633[b] | 0.017[b] | 0.004[b] | 0.001[b] |
| PPNCvsNNC | 0.854[b] | 0.413[b] | 0.226[b] | 0.919[b] | 0.000[b] | 0.004[b] |

CC Clomiphene citrate, PCC Pregnancy in the clomifene citrate, NCC No pregnancy in the clomifene citrate, NC Normal control, PNC Pregnancy in the normal control, NNC No pregnancy in the normal control, EMT Endometrial thickness, E-mean Mean elasticity (ormean Young's modulus), SWV-mean Mean shear wave velocities, UA-PI, Uterine artery pulsatility index; UA-RI, Uterine artery resistance index; UA-S/D, Peak systolic velocity/end diastolic velocity of the uterine artery
b Mann-Whitney U test
$p < 0.05$, indicating statistical significance

## 4. Discussion

Previous research has documented histological alterations in the endometrium of patients with UI, such as reduced glandular density, the formation of straight tubes, and an enlargement of the structural matrix [12]. A decrease in glandular density and an increase in stromal fibres are associated with increased stiffness [13]. Initially, this research group used SWE to determine that, compared to women of typical childbearing age, the mean E-mean of the endometrium in UI patients is higher, endometrial hardness is greater, and the embryo's ability to implant is reduced [11].

In this study, EMT in the CC group was found to be reduced during both the LP and MP phases compared to the NC group, aligning with findings reported by Rani et al. [14]. CC inhibits estrogen's negative feedback mechanism by interacting with hypothalamic estrogen receptors. This leads to inadequate upregulation of estrogen and progesterone receptors by estrogen. High levels of progesterone post-ovulation continue to inhibit the synthesis of these receptors, resulting in reduced endometrial proliferation and a thinner endometrium [15-17]. Montenegro et al. [18] found that in women with infertility undergoing ovulation induction with CC, the endometrium developed earlier than in a spontaneous cycle, but the secretory intermediate glands matured later, leading to asynchronous development and maturation of the endometrium and making successful embryo implantation challenging [19].

This study confirms previous findings that the CC and NC

groups had lower UA-PI, UA-RI, and UA-S/D values during MP compared to LP. This indicates that the endometrial blood flow perfusion is better during MP, which is good for embryo implantation [20, 21]. The CC group also had higher UA-PI, UA-RI, and UA-S/D indices than the NC group during the LP and MP phases. This elevation may stem from the anti-estrogenic properties of CC, which potentially curtail angiogenesis during the proliferative phase and hinder the vasodilatory capacity of estrogen [22-24], leading to increased uterine artery resistance, poor endometrial perfusion, and poor embryo implantation [25, 26].

Additionally, the data showed that endometrial stiffness was increased in the CC group compared to the NC group during both stages, with continuously higher mean E-mean and mean SWV-mean values. Sereepapong et al. [27-29] conducted mid-cycle secretory endometrial biopsies on patients treated with CC and observed a deficiency in endometrial glands, which were sparsely distributed and featured small, infrequently tortuous lumina. Furthermore, the glandular epithelium was noted to be low columnar, and the stroma was dense. This suggests that the increased endometrial stiffness in the CC group is due to a reduction in glandular components and increased stromal density, attributable to the anti-oestrogenic effect of CC [23, 28]. Some studies have indicated that higher endometrial stiffness reduces the likelihood of embryo implantation [30, 31].

Relative to the NC group, the CC group exhibited a thinner endometrium, heightened uterine artery blood flow parameters, and increased endometrial stiffness during the MP phase. Embryo implantation could be hindered by these conditions. The clinical pregnancy rates of the CC and NC groups did not differ significantly according to the follow-up clinical pregnancy results of the present study. Hughes et al. [32] also found no significant advantage of clomiphene in treating UI compared to no treatment or placebo. This is attributed to CC's induction of gonadotropin-releasing hormone (GnRH) secretion, which increases FSH and LH levels, exerting a pro-ovulatory effect. While CC stimulates the ovaries and promotes ovulation, enhancing pregnancy rates, it also thins and hardens the endometrium and increases uterine artery resistance, hindering embryo implantation. Future research will aim to determine the endometrial hardness threshold that balances the positive and negative effects, providing a reliable imaging reference for clinical treatment of UI patients.

The caveats of this study must be clearly stated. The main reason for limiting the sample to Chinese women was the need to account for the specific characteristics of the UI population. A larger, multi-center study is needed in the future. Secondly, this study monitored only clinical pregnancy and did not include outcomes such as multiple pregnancies or live births. Future studies should expand follow-up indicators to examine the relationship between endometrial hardness post-CC treatment and various outcomes. Additionally, the reliability of SWE in assessing the endometrium is limited, especially regarding intra-observer and inter-observer consistency. To address this limitation, each participant was assessed three times by the same sonographer to calculate the average values.

## 5. Conclusion

The results of this study demonstrate that following CC treatment, the uterus of UI patients shows a reduction in thickness, a decline in blood perfusion, and an increase in endometrial hardness. These changes are likely to negatively affect embryo implantation. However, no effect on clinical pregnancy rates was identified. Therefore, additional research involving larger populations is necessary to determine the threshold level of endometrial hardness where positive and negative effects are balanced.

## Abbreviations

| | |
|---|---|
| CC | Clomiphene Citrate |
| E2 | Estradiol |
| E-mean | Mean Endometrial Elasticity |
| EMT | Endometrial Thickness |
| ER | Endometrial Receptivity |
| FSH | Follicle-Stimulating Hormone |
| HCG | Human Chorionic Gonadotropin |
| LH | Luteinizing Hormone |
| LP | Late-Proliferative Phase |
| MP | Mid-Secretory Phase |
| NC | Normal Control |
| SWE | Shear Wave Elastography |
| SWV-mean | Mean Shear Wave Velocities |
| TVS | Transvaginal Ultrasonography |
| UA-PI | Uterine Artery Pulsatility Index |
| UA-RI | Uterine Artery Resistance Index |
| UA-S/D | Uterine Artery Peak Systolic Velocity / End Diastolic Velocity |
| UI | Unexplained Infertility |

## Author Contributions

Hui Wang contributed to conceptualization and writing strategies.

Mei He performed the data collection, follow-up, data analyses, and manuscript writing.

Zheng-ying Li contributed significantly to the imaging analysis.

Lu Cai provided assistance with statistical analysis.

Tao Xie and Ling-qing Cui contributed to the data collection.

All authors read and approved the final manuscript.

## Funding

No applicable.

## Conflicts of Interest

The authors declare that they have no competing interests.

## References


[1] Carson, S. A., Kallen, A. N. Diagnosis and management of infertility: a review. JAMA. The Journal of the American Medical Association. 2021, 326(1), 65-76. https://doi.org/10.1001/jama.2021.4788

[2] Lessey, B. A., Young, S. L. What exactly is endometrial receptivity? Fertility and Sterility. 2019, 111(4), 611-617. https://doi.org/10.1016/j.fertnstert.2019.02.009

[3] Achache, H., Revel, A. Endometrial receptivity markers, the journey to successful embryo implantation. Human Reproduction Update. 2006, 12(6), 731-746. https://doi.org/10.1093/humupd/dml004

[4] Messaoudi, S., Kasmi, I. E., Bourdiec, A., Crespo, K., Bissonnette, L., Saint, C. L. 15 years of transcriptomic analysis on endometrial receptivity: what have we learnt? Fertility Research and Practice. 2019, 5(1), 9. https://doi.org/10.1586/era.13.49

[5] Inhorn, M. C., Patrizio, P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Human Reproduction Update. 2015, 21(4), 411-426. https://doi.org/10.1093/humupd/dmv016

[6] Franasiak, J. M., Forman, E. J., Hong, K. H., Werner, M. D., Upham, K. M., Treff, N. R., Scott Jr, R. T. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertility and Sterility. 2014, 101(3), 656-663. https://doi.org/10.1016/j.fertnstert.2013.11.004

[7] Guideline Group on Unexplained Infertility, Romualdi, D., Ata, B., Bhattacharya, S., Bosch, E., Costello, M., Le Clef, N. Evidence-based guideline: unexplained infertility. Human Reproduction, 38(10), 1881-1890. Evidence-based guideline: unexplained infertility. Human Reproduction. 2023, 38(10), 1881-1890. https://doi.org/10.1093/humrep/dead150

[8] Sigrist, R. M., Liau, J., El Kaffas, A., Chammas, M. C., Willmann, J. K. Ultrasound elastography: review of techniques and clinical applications. Theranostics. 2017, 7(5), 1303. https://doi.org/10.7150/thno.18650

[9] Cheng, M. Q., Xian, M. F., Tian, W. S., Li, M. D., Hu, H. T., Li, W,. RGB Three-Channel SWE-Based Ultrasomics Model: Improving the Efficiency in Differentiating Focal Liver Lesions. Frontiers in Oncology. 2021, 11, 704218. https://doi.org/10.3389/fonc.2021.704218

[10] Yu, C. C., Jiao, Y., Wang, J. J., Zhao, X. S., Chen, L. Preliminary application of real-time shear wave elastography to evaluate endometrial receptivity and predict pregnancy outcome. Technology and Health Care. 2024, (Preprint), 1-8. https://doi.org/10.3233/THC-231106

[11] Li, Z. Y., Cai, L., Zhang, Z. J., Zou, H. R., He, M., Qin, M. L., Wang, H. Evaluation of endometrial receptivity in women with unexplained infertility by shear wave elastography. Insights into Imaging. 2024, 15(1), 85. https://doi.org/10.1186/s13244-024-01646-3

[12] Karaoğlan, Ö., Kuyucu, Y., Ürünsak, İ. F., Gümürdülü, D., Tap, Ö. Morphological features of the secretory phase endometrium in women with unexplained infertility. Ultrastructural Pathology. 2021, 45(3), 243-256. https://doi.org/10.21203/rs.3.rs-149936/v1

[13] Stanziano, A., Bianchi, F. P., Caringella, A. M., Cantatore, C., D'Amato, A., Vitti, A. The use of real time strain endometrial elastosonography plus endometrial thickness and vascularization flow index to predict endometrial receptivity in IVF treatments: a pilot study. BMC Medical Imaging. 2023, 23(1), 130. https://doi.org/10.1186/s12880-023-01071-w

[14] Rani, K. U., Gupta, J., Bajaj, B., Das, B., Marwah, S. Comparative Evaluation of Follicular Development and Endometrial Thickness in Spontaneous and Clomiphene Citrate Induced Cycle in Unexplained Infertility. Group. 2020, 15(18), 19-22. https://doi.org/10.1111/j.1471-0528.1989.tb03353.x

[15] Cetin, E., Siblini, H., Al-Hendy, A. What is the mechanism of poor endometrial proliferation in patients with unexplained infertility after clomiphene citrate treatment?. The Journal of Clinical Endocrinology & Metabolism. 2021, 106(11), e4776-e4777. https://doi.org/10.1210/clinem/dgab483

[16] Gingold, J. A., Lee, J. A., Rodriguez, P. J., Whitehouse, M. C., Sandler, B., Grunfeld, L., Copperman, A. B. Endometrial pattern, but not endometrial thickness, affects implantation rates in euploid embryo transfers. Fertility and Sterility. 2015, 104(3), 620-628. https://doi.org/10.1016/j.fertnstert.2015.05.036

[17] Glujovsky, D., Pesce, R., Sueldo, C., Retamar, A. M. Q., Hart, R. J., Ciapponi, A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database of Systematic Reviews. 2020, (10), 31-40. https://doi.org/10.1002/14651858.CD006359.pub3

[18] Montenegro, I. S., Kuhl, C. P., Schneider, R. D. A., Zachia, S. D. A., Passos, E. P. Use of clomiphene citrate protocol for controlled ovarian stimulation impairs endometrial maturity. JBRA Assisted Reproduction. 2021, 25(1), 90. https://doi.org/10.5935/1518-0557.20200056

[19] Basir, G. S., O, W. S., Yu Ng, E. H., Ho, P. C. Morphometric analysis of peri-implantation endometrium in patients having excessively high oestradiol concentrations after ovarian stimulation. Human Reproduction. 2001, 16(3), 435-440. https://doi.org/10.1093/humrep/16.3.435

[20] Zackrisson, U., Brännström, M., Granberg, S., Janson, P. O., Collins, W. P., Bourne, T. H. Acute effects of a transdermal nitric oxide donor on perifollicular and intrauterine blood flow. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1998, 12(1), 50-55. https://doi.org/10.1046/j.1469-0705.1998.12010050.x

[21] Zaidi, J. Blood flow changes in the ovarian and uterine arteries in women with normal and polycystic ovaries. Human Fertility. 2000, 3(3), 194-198. https://doi.org/10.1080/1464727002000198971

[22] Leah, H. B., Fritz, M. A., San-Pin, W., Lingwen, Y., Suzanna, K., Tianyuan, W. Poor endometrial proliferation after clomiphene is associated with altered estrogen action. The Journal of Clinical Endocrinology & Metabolism. 106(9), 2547-2565. https://doi.org/10.1210/clinem/dgab381

[23] Karizbodagh, M. P., Rashidi, B., Sahebkar, A., Masoudifar, A., Mirzaei, H. Implantation window and angiogenesis. Journal of Cellular Biochemistry. 2017, 118(12), 4141-4151. https://doi.org/10.1002/jcb.26088

[24] Zhang, Y., Lin, X., Dai, Y., Hu, X., Zhu, H., Jiang, Y. Endometrial stem cells repair injured endometrium and induce angiogenesis via AKT and ERK pathways. Reproduction. 2016, 152(5), 389-402. https://doi.org/10.1530/REP-16-0286

[25] Jamal, A., Abbasalizadeh, F., Vafaei, H., Marsoosi, V., Eslamian, L. Multicenter screening for adverse pregnancy outcomes by uterine artery Doppler in the second and third trimester of pregnancy. Medical ultrasonography. 2013, 15(2), 95-100. https://doi.org/10.11152/mu.2013.2066.152.aj1fa2

[26] Tong, R., Zhou, Y., He, Q., Zhuang, Y., Zhou, W., Xia, F. Analysis of the guidance value of 3D ultrasound in evaluating endometrial receptivity for frozen-thawed embryo transfer in patients with repeated implantation failure. Annals of Translational Medicine. 2020, 8(15). https://doi.org/10.21037/atm-20-5463

[27] Sereepapong, W., Suwajanakorn, S., Triratanachat, S., Sampatanukul, P., Reinprayoon, D. Effects of clomiphene citrate on the endometrium of regularly cycling women. Fertility and Sterility. 2000, 73(2), 287-291. https://doi.org/10.1016/S0015-0282(99)00509-9

[28] Cook, C. L., Schroeder, J. A., Yussman, M. A., Sanfilippo, J. S. Induction of luteal phase defect with clomiphene citrate. American Journal of Obstetrics and Gynecology. 1984, 149(6), 613-616. https://doi.org/10.1016/0002-9378(84)90244-8

[29] Daly, D. C., Maslar, I. A., Riddick, D. H. Prolactin production during in vitro decidualization of proliferative endometrium. American Journal of Obstetrics and Gynecology. 1983, 145(6), 672-678. https://doi.org/10.1055/s-2007-1023854

[30] Li, M., Zhu, X., Wang, L., Fu, H., Zhao, W., Zhou, C., Yao, B. Evaluation of endometrial receptivity by ultrasound elastography to predict pregnancy outcome is a non-invasive and worthwhile method. Biotechnology and Genetic Engineering Reviews, 2023, 08, 1-15. https://doi.org/10.1080/02648725.2023.2183585

[31] Stanziano, A., Bianchi, F. P., Caringella, A. M., Cantatore, C., D'Amato, A., Vitti, A. The use of real time strain endometrial elastosonography plus endometrial thickness and vascularization flow index to predict endometrial receptivity in IVF treatments: a pilot study. BMC Medical Imaging. 2023, 23(1), 130. https://doi.org/10.1186/s12880-023-01071-w

[32] Hughes, E., Brown, J., Collins, J. J., Vanderkerchove, P. (2010). Clomiphene citrate for unexplained subfertility in women. Cochrane Database of Systematic Reviews. 2000, 65(1), CD000057. https://doi.org/10.1002/14651858.CD000057