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Research Article

The Role of Low-Intensity Pulsed Ultrasound in Enhancing Endometrial Receptivity for Implantation in Infertile Women: A Randomized Controlled Trial

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Abstract

Background: Endometrial receptivity is a crucial factor for embryo implantation, and its deficiency is a major contributor to infertility and failure of in vitro fertilization (IVF). Low-Intensity Pulsed Ultrasound (LIPUS) has emerged as a promising non-invasive treatment for improving endometrial receptivity, with interest due to its affordability and minimal side effects**.** ***Objective***: To assess the efficacy of LIPUS in enhancing endometrial receptivity for embryo implantation in infertile women with thin endometria. ***Methods***: The study included sixty infertile women undergoing IVF treatment. The participants were randomly assigned to receive either LIPUS or traditional estrogen therapy (4 mg/day orally) for 14 days. The study assessed changes in endometrial thickness, blood flow, implantation, and pregnancy rates following treatment as indicators of endometrial receptivity. ***Results***: LIPUS treatment significantly improved endometrial thickness (6.1-9.5mm), compared to a lesser increase in the estrogen group (6.2- 8.6mm, p=0.02). Doppler ultrasound parameters, including peak systolic velocity (PSV) and end-diastolic velocity (EDV), also displayed significant improvements in the LIPUS group (PSV: 36.4 *vs*. 31.3cm/s, p=0.01; EDV: 13.5 *vs*. 11.5cm/s). Although implantation and pregnancy rates were higher in the LIPUS group (60% *vs*. 40% and 53.3% *vs*. 33.3%, respectively), the differences were statistically insignificant. ***Conclusions***: LIPUS may provide a feasible non-invasive alternative approach to traditional estrogen therapy for enhancing endometrial receptivity in IVF patients, potentially improving implantation and pregnancy outcomes, although further studies with larger sample sizes are required.

Keywords: Endometrial receptivity; Endometrial thickness; Infertile women; IVF; LIPUS.

دور الموجات فوق الصوتية النبضية منخفضة الشدة في تعزيز تقبل بطانة الرحم للانغراس لدى النساء العقيمات: تجربة عشوائية محكمة

الخلاصة

الخلفية: تعد قدرة استقبال بطانة الرحم عاملا حيويا في زرع الجنين، ونقصها يساهم بشكل رئيسي في العقم وفشل التلقيح الصناعي (IVF). برزت الموجات فوق الصوتية منخفضة الشدة النبضية (LIPUS) كعلاج واعد غير جراحي لتحسين تقبل بطانة الرحم، مع اهتمام بسبب تكلفته المعقولة وتأثيراته الجانبية القليلة. **الهدف**: تقييم فعالية LIPUS في تعزيز تقبل بطانة الرحم لزرع الأجنة لدى النساء العقم ذوات الانتباذ البطاني الرحمي الرقيق. **الطرائق**: شملت الدراسة ستين امرأة عقيمة خضعن لعلاج التلقيح الصناعي. تم توزيع المشاركين عشوائيا لتلقي علاج إما ب LIPUS أو علاج الإستروجين التقليدي (4 ملغ/يوميا عن طريق الفم) لمدة 14 يوما. تم قياس التغيرات في سمك بطانة الرحم، وتدفق الدم، والانغراس، ومعدلات الحمل بعد العلاج كمؤشرات على تقبل بطانة الرحم. **النتائج**: أدى علاج LIPUS إلى تحسين ملحوظ في سمك بطانة الرحم (9.5-6.1 ملم)، مقارنة بزيادة أقل في مجموعة الإستروجين (8.6-6.2 مم، p=0.02). كما أظهرت معايير الموجات فوق الصوتية دوبلر، بما في ذلك السرعة الانقباضية القصوى (PSV) وسرعة نهاية الانبساط (EDV)، تحسنا كبيرا في مجموعة LIPUS (PSV: 36.4 مقابل 31.3 سم/ث، p=0.01؛ EDV: 13.5 مقابل 11.5 سم/ثانية). على الرغم من أن معدلات الانغراس والحمل كانت أعلى في مجموعة LIPUS (60٪ مقابل 40٪ و53.3٪ مقابل 33.3٪ على التوالي)، إلا أن الفروقات كانت غير ذات دلالة إحصائية. **الاستنتاجات**: قد يوفر LIPUS نهجا بديلا غير جراحي ممكن للعلاج التقليدي بالإستروجين لتعزيز تقبل بطانة الرحم لدى مرضى أطفال الأنابيب (IVF)، مما قد يحسن نتائج الانغراس والحمل، رغم الحاجة إلى دراسات إضافية بعينات أكبر.

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INTRODUCTION

Endometrial receptivity is a crucial factor for embryo implantation, and its deficiency is one of the major contributors to infertility and in vitro fertilization (IVF) failure [1]. A thin endometrium (<7 mm) significantly reduces implantation rates, making it a key factor of recurrent implantation failure (RIF) in assisted reproductive technology (ART) procedures [2]. Current management approaches, including estrogen therapy and platelet-rich plasma (PRP) infusion, intend to improve endometrial thickness and vascularity, but their efficacy varies across patients [3]. For example, PRP has demonstrated potential in improving both angiogenesis and tissue receptivity; however, consistent protocols and confirmation through extensive clinical studies are required [4]. Overall, new regenerative approaches are being investigated to improve implantation success rates, but further randomized controlled trials are required to govern their long-term efficacy [5]. Low-Intensity Pulsed Ultrasound (LIPUS) has emerged as a promising non-invasive treatment for improving endometrial receptivity, drawing increasing attention due to its affordability and minimal side effects. LIPUS has been shown to encourage angiogenesis and tissue regeneration, which are important for making the endometrial environment better and more receptive to embryo implantation [6]. Several studies have investigated the potential of LIPUS in diverse medical fields, highlighting its ability to influence gene expression, promote cell proliferation, and accelerate tissue repair [7,8]. For example, LIPUS has been shown to regulate key markers like Homeobox A10 (HOXA10) and Leukemia Inhibitory Factor (LIF), which are important factors for endometrial receptivity [6]. Furthermore, LIPUS has been compared to conventional therapies such as estrogen and PRP, offering equivalent efficacy with a better safety profile [9,10]. These studies underline the usefulness and therapeutic potential of LIPUS, especially in reproductive medicine [11]. But there is still a lot we don't know, even with these promising findings, because there haven't been any sufficiently large randomized controlled trials that directly study the effects of LIPUS on the ability of women who can't get pregnant to have a uterus that is thin and the baby staying in the uterus. Based on this gap, the current study was intended to test the hypothesis that LIPUS therapy improves endometrial receptivity more effectively than conventional estrogen therapy alone in infertile women undergoing IVF. Specifically, our study aimed to evaluate the effect of LIPUS on endometrial thickness, uterine blood flow, implantation, and clinical pregnancy rates.

METHODS

Materials

A portable ultrasound device (Supreme Surgery Company, India) was used to administer the Low-Intensity Pulsed Ultrasound (LIPUS) therapy. The device settings included an intensity of 30 mW/cm², a frequency of 1.5 MHz, and a 20% duty cycle, with a 200-microsecond pulse duration. A Doppler ultrasound system (Chison Ultrasound, QBit3, China) was used to assess the endometrial blood flow. The device settings included an adjustable imaging frequency of 2–10 MHz, a velocity measurement capacity of up to 700 cm/s, a radiation angle maintained at ≤60°, and a pulse repetition frequency range of 1–15 kHz. A 2–5 MHz abdominal probe was used for all participants.

Study design and setting

This is a single-center randomized controlled trial conducted at a tertiary infertility and IVF unit at Basrah Maternity and Children's Hospital, Basrah, Iraq. The study was conducted between January and June 2025. A total of sixty infertile women undergoing in vitro fertilization (IVF) with an endometrial thickness less than 7 mm were enrolled. Participants were randomized in a 1:1 ratio into two groups (n= 30 each) using a computer-generated random number sequence. Allocation concealment was maintained using sealed, opaque, sequentially numbered envelopes prepared by an independent staff member not involved in patient care. Due to the nature of the intervention, participants and treating clinicians were not blinded; however, the sonographer assessing endometrial thickness and Doppler indices, as well as the embryologist evaluating implantation outcomes, were blinded to group assignment. Hormonal testing and transvaginal ultrasound confirmed that all interventions took place during the follicular phase. The control group received standard estrogen therapy for endometrial preparation, while the LIPUS group received daily LIPUS application to the lower abdomen for 20 minutes for 14 consecutive days.

Inclusion criteria

Those women aged 20 to 40 years were eligible for inclusion, as this age range is associated with optimal fertility potential and reliable endometrial responsiveness to treatment [12]. All participants were required to have a thin endometrium (defined as an endometrial thickness of <7 mm), confirmed through transvaginal ultrasound conducted during the early follicular phase before enrollment. Eligible participants were those planning to undergo in vitro fertilization (IVF) during the study period and willing to adhere to the full treatment protocol. To ensure hormonal stability, participants were required to have regular menstrual cycles, defined as a cycle length of 24–35 days with variability of no more than ±3 days over the preceding three months [12]. Regularity of the cycle was evaluated via clinical history and by baseline hormonal assessment when indicated. Also, people who have a BMI between 18 and 30 kg/m² and who don't have any major systemic diseases will be included. This is to make sure that only people who look healthy and are likely to respond in a predictable way to the treatments will be included. All women were nulliparous, and their previous ART attempts (e.g., prior IVF attempts) were taken into consideration. The participants should have at least a year-free interval after the previous failed ART.

Exclusion criteria

Women were excluded if they had significant uterine pathology affecting endometrial development or implantation (at least one submucosal fibroid or at least one fibroid of ≥4 cm, polyps, or congenital malformations). Those with diagnosed endometriosis (confirmed by clinical evaluation, imaging, or laparoscopy), prior fertility treatments such as PRP therapy during the last year, and severe systemic conditions (uncontrolled diabetes, uncontrolled hypertension, and thyroid disorders) were excluded. Lifestyle factors (smoking, substance use) and BMI outside defined limits were also excluded due to their probable impact on implantation and pregnancy outcomes.

Intervention protocol (LIPUS and estrogen therapy)

The study included two interventional protocols. Estrogen Therapy Group: Participants received estrogen (Estrofem, Novo Nordisk oral tablets) at a dose of 4 mg/day for fourteen consecutive days during the follicular phase of the menstrual cycle. Adherence was observed through weekly clinic visits, and participants were instructed to take their medicine as prescribed. Safety monitoring and documentation of possible side effects were conducted throughout the intervention. Low-Intensity Pulsed Ultrasound (LIPUS) Group: Participants received a daily LIPUS session of 20 minutes duration for 2 weeks using a small, portable, noninvasive ultrasound device (Supreme Surgery Company, India; the details of the device were mentioned in the material section). Each session requires applying the ultrasound probe to the lower abdomen for 20 minutes, with a coupling gel to transmit the ultrasound energy safely to the endometrial area. The patient was asked how they felt throughout treatment to ensure there was no pain or excessive heat. If the patient experiences pain or a very warm sensation, the therapist would increase the coupling gel and move the probe faster. To reduce variability, treatment sessions were conducted by the same operator, and device calibration and routine checks were done to ensure consistent administration. Adverse effects and safety monitoring were recorded.

Endometrial thickness measurement

The Endometrial thickness was measured at two times: baseline (before treatment) and 14 days after treatment initiation. Transvaginal ultrasound (TVS) (DC-30, Shenzhen Mindray Biomedical Electronics Co., China) was performed by an experienced sonographer blinded to treatment allocation at the point of maximum endometrial thickness. The same sonographer conducted all scans to minimize inter-observer variability. The ultrasound machine model and probe frequency were standardized across all participants. Repeated measurements on a subset of participants ensured intra-observer reliability. These measurements allowed direct assessment of treatment efficacy and adherence and facilitated comparison of endometrial development between the estrogen therapy and LIPUS groups.

Doppler assessment of endometrial blood flow

Doppler assessments of blood flow in the endometrial region were made at baseline to determine the initial status of blood flow. The device settings included an adjustable imaging frequency of 2–10 MHz, a velocity measurement capacity of up to 700 cm/s, a radiation angle maintained at ≤60°, and a pulse repetition frequency range of 1–15 kHz. A 2–5 MHz abdominal probe was used for all participants. The measurements were made in two key areas of the uterine arteries and the basal arteries that supply the endometrial bed, where the blood flow is most important to supply nutrients and oxygen to the developing embryo. In this study, the Doppler ultrasound that was used was calibrated to measure the peak systolic velocity (PSV) and end-diastolic velocity (EDV) of blood flow. Overall, these parameters gave indications as to the overall vascular health of the endometrium. The resistance index (RI) was calculated to determine the resistance to blood flow in the uterine arteries and was seen as a crucial factor regarding endometrial receptivity. After the 14-day treatment period, Doppler assessments were repeated in similar conditions to assess the possible change in endometrial blood flow due to either estrogen therapy or LIPUS treatment. The Doppler follow-up assessment results were compared with the baseline measurements to ascertain change in endometrial vascularization that predisposes to a positive outcome from treatment on the endometrium being receptive for fertilization.

Pregnancy and implantation outcome measures

Pregnancy and implantation were studied in order to find out how well Low Intensity Pulsed Ultrasound (LIPUS) and estrogen therapy worked to make the endometrium more receptive during implantation and pregnancy. As part of a fertility treatment plan, all participants then underwent an in vitro fertilization (IVF) procedure after a 14-day treatment period. Clinical ultrasound was performed after embryo transfer to determine the implantation rate, as the presence or absence of a gestational sac within the uterus was considered as implantation. The main purpose was to observe if there was a higher percentage of embryo implantation in the group that received LIPUS treatment than with the estrogen therapy. Patients were monitored for signs of early pregnancy after embryo transfer, including serial serum β-hCG levels, a hormone that is generated after implantation and is a good indication of pregnancy. Blood samples were collected at predetermined intervals after embryo transfer to monitor the increase in beta hCG levels, confirming successful implantation. However, further ultrasounds were scheduled to check fetal development and confirm ongoing pregnancy; if it was confirmed, the patient was pregnant. The pregnancy rate was calculated as the number of pregnancies achieved by women following an IVF procedure, which was confirmed after a fetal heartbeat had been detected on ultrasound imaging.

Ethical considerations

The Basrah Health Directorate and Al-Zahraa College of Medicine at Basrah University Research Ethics Committee approved the research protocol in accordance with ethical standards. Written informed consent was obtained from all participants, proving their understanding of the study purpose, procedures, possible risks, and expected benefits.

Statistical analysis

SPSS version 22 (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis. For the comparison of the baseline and post-treatment values of endometrial thickness and Doppler parameters (PSV, EDV, and RI for estrogen and LIPUS groups), all data were presented as means ± standard deviations (SD), and independent samples t-tests were used. For the within-group comparison, a paired t test was used. The effect size was calculated using Cohen's dz = Mean Change/SD baseline. Implantation and pregnancy rates between the two groups were compared by a Chi-square test. The effect size was calculated using Phi = $\sqrt{(\chi^2/n)}$. Statistically significant was considered at *p*-value less than 0.05.

RESULTS

The two groups were comparable in demographics and baseline reproductive parameters. The mean age was 31.8 ± 5.4 years in the estrogen group and 32.9 ± 5.3 years in the LIPUS group (*p*= 0.43). Mean BMI was 24.8 ± 4.1 kg/m² and 24.5 ± 3.8 kg/m² in the estrogen and LIPUS groups, respectively (p = 0.75) (Table 1).

Table 1: Statistical comparison of demographics between Estrogen and LIPUS groups (n=30 in each group)

Variable	Estrogen group	LIPUS group	*p*-value
Age (year)	31.8±5.4	32.9±5.3	0.43
BMI (kg/m^2)	24.8±4.1	24.5±3.8	0.75

Values were expressed as mean±SD. Independent samples t-test was used at *p*<0.05.

Baseline endometrial thickness (6.1 ± 0.8 mm *vs*. 6.2 ± 0.7 mm, *p*= 0.73) and Doppler indices (PSV, EDV, RI) were also similar (Table 2). These findings confirm that the groups were well-matched at baseline. Within-group analysis showed that both groups demonstrated significant increases in endometrial thickness following treatment. Estrogen group (mean change 2.5 mm, *p*< 0.001), while the LIPUS group (mean change 3.3 mm, *p*< 0.001). Between-group comparison of post-treatment thickness showed a statistically significant difference in favor of LIPUS (mean difference = 0.9 mm, *p*= 0.02).

Table 2: Statistical comparison of endometrial thickness and Doppler indices between Estrogen and LIPUS groups at baseline (n=30 in each group)

Variable	Estrogen group	LIPUS group	*p*-value
Endometrial thickness	6.1±0.8	6.2±0.7	0.73
PSV Baseline	24.5±5.5	24.1±5.8	0.81
EDV Baseline	10.3±3.4	9.8±3.1	0.63
RI Baseline	0.59±0.11	0.61±0.10	0.53

Values were expressed as mean±SD. Independent samples t-test was used at *p*<0.05.

These results indicate that while both treatments were effective, LIPUS therapy is significantly more effective than estrogen therapy in increasing endometrial thickness after treatment (*p*= 0.02) (Table 3). The medium-to-large effect size of 0.73 for between-group differences, along with the very large effect sizes for within-group differences, means that both treatments are useful, but LIPUS may work better for endometrial development (Table 3).

Table 3: Statistical comparison of endometrial thickness between Estrogen and LIPUS groups (n=30 in each group)

Variable	Group	Baseline	After 14 Days	Intra-group effect size	*p*-value (intra group)	Inter-group Δ post-treatment (95% CI)	Inter-group effect size (post-treatment)	*p*-value inter groups (post-treatment)
Endometrial thickness (mm)	Estrogen	6.1± 0.8	8.6±1.2	3.13	<0.001	+0.9 (+0.2, +1.6)	0.73	0.02
	LIPUS	6.2±0.7	9.5±1.3	4.13	<0.001			

Values were expressed as mean±SD. The Independent samples t-test was used for between-group analysis, while a paired t-test test used for within-group analysis. The effect size was calculated using Cohen's dz: Mean Change/SD baseline; △: post-treatment change LIPUS vs estrogen.

Within-group changes in Doppler parameters showed that PSV was enhanced in both treatment groups with statistically significant changes between pre- and post-treatment (estrogen mean change 6.8 cm/s, *p*< 0.001; LIPUS mean change 12.3 cm/s, *p*< 0.001). On the other hand, End-Diastolic Velocity (EDV) showed significant changes only in the LIPUS group (LIPUS mean change 3.7 cm/s, estrogen mean change 1.2 cm/s) compared to baseline. The same observation was noticed with the resistive Index (RI), where only LIPUS therapy produced a significant reduction compared to baseline measurement (LIPUS mean change -0.07, estrogen mean change -0.03) (Table 4). Between-group analysis showed that, compared to the estrogen group, the LIPUS group produced higher mean PSV (36.4 cm/s vs 31.3 cm/s, respectively, *p*< 0.01). Mean EDV was also greater in the LIPUS group (13.5 cm/s) versus the estrogen group (11.5 cm/s, *p*= 0.04). No significant difference was observed in RI after treatment (*p*= 0.43). (Table 4).

Table 4: Comparative Analysis of Doppler Parameters pre and post-treatment between study groups

Variable	Group	Baseline	After treatment	Intra-group Cohen's dz	*p*-value (intra-group)	Inter-groups Δ Post (95% CI)	Inter-group Cohen's dz	*p*-value (post-treatment)
PSV	Estrogen	24.5±5.5	31.3±6.3	1.24	<0.001	5.1 (1.7, 8.5)	0.76	0.01
	LIPUS	24.1±5.8	36.4±7.1	2.12	<0.001			
EDV	Estrogen	10.3±3.4	11.5±3.5	0.35	0.06	2.0 (0.1, 3.9)	0.54	0.04
	LIPUS	9.8 ± 3.1	13.5±3.9	1.19	<0.001			
RI	Estrogen	0.59±0.11	0.56±0.10	-0.27	0.11	-0.02 (-0.07, 0.03)	0.22	0.43
	LIPUS	0.61±0.10	0.54±0.08	-0.70	<0.001			

Values were expressed as mean±SD. Independent samples t-test was used for between-group analysis, while a paired t-test test used for within-group analysis. The effect size was calculated using Cohen's dz: Mean Change/SD baseline; PSV: Peak Systolic Velocity, EDV: End-Diastolic Velocity, RI: Resistive Index, CI: Confidence Interval, SD: Standard Deviation, △: post-treatment change LIPUS vs estrogen.

The implantation rate was higher in the LIPUS group (60%) than in the estrogen group (40%), but this difference was not statistically significant (*p*= 0.197). Similarly, the clinical pregnancy rate was 53.3% in the LIPUS group versus 33.3% in the estrogen group (*p*= 0.193). Small effect size (Phi = 0.19-0.20) suggests minimal practical difference between treatments (Table 5). However, it consistently favors LIPUS therapy with 20% absolute improvement in both outcomes, 50-60% relative improvement (RR= 1.50-1.60), and more than doubled odds of success (OR=2.25-2.29).

Table 5: Statistical comparison of pregnancy and implantation outcomes between Estrogen and LIPUS groups (n=30 in each group)

Outcome	Group	(%)	Risk difference (95% CI)	Relative risk (95% CI)	OR (95% CI)	*p*-value	Effect Size
Implantation rate	Estrogen	40	Reference	Reference	Reference	0.197	Reference
	LIPUS	60	20.0 (-5.8 - 45.8)	1.50 (0.882 - 56)	2.25 (0.84 - 6.04)		0.19
Pregnancy rate	Estrogen	33.3	Reference	Reference	Reference	0.193	Reference
	LIPUS	53.3	20 (-6.0 - 46)	1.6 (0.88 - 2.91)	2.29 (0.85 - 6.17)		0.20

Values were expressed as frequency and percentage. The effect size was calculated using Phi = $\sqrt{(\chi^2/n)}$, Chi-square was used at $p<0.05$.

DISCUSSION

The current study shows that after 14 days of Low Intensity Pulsed Ultrasound (LIPUS) treatment, there is a lot more endometrial thickening than with conventional estrogen treatment. At the onset of the trial, the participants were homogeneous from baseline endometrial thickness, since no difference was found in the baseline endometrial thickness between these two groups. LIPUS therapy demonstrates statistically significant superiority over estrogen therapy for increasing endometrial thickness over 14 days. While both treatments are highly effective, LIPUS produces approximately 32% greater improvement (3.3 mm *vs* 2.5 mm) with a medium-large effect size (0.73). Therefore, these findings indicate that LIPUS exerts a greater proliferative effect on endometrial tissues, probably because it promotes angiogenesis and stimulates tissue repair. This increase in the thickness of the endometrium is important for medicine because studies have shown many times that the implantation and pregnancy success rates in assisted reproductive treatments are higher when the endometrium is defined and has a good blood supply. As such, LIPUS maintains a distinct position as a potential non-invasive alternative to hormone treatments (such as estrogen therapy) in women with a poor endometrial response to hormonal therapy. Further insight into the potential of LIPUS to improve endometrial receptivity is obtained by comparing it with recent literature. Long *et al.* in 2022 used LIPUS on the endometrial receptivity markers in patients who couldn't get pregnant because they had adenomyosis. They found that HOXA10 and LIF, both very important for implantation, had significantly increased expression [6]. This confirms the result of the current study to suggest that LIPUS not only increases endometrial thickness but also increases molecular conditions orientational toward implantation. In another study by Guschina *et al.*, pulsed magnetic therapy and intrauterine plasma therapy were evaluated for their capacity to re-establish endometrial receptivity after intrauterine manipulations. By comparing LIPUS change with electrical stimulation with combining strong magnetic stimulation and plasma therapy, they found that electrical stimulation with combined strong magnetic stimulation and plasma therapy produced the same effect on endometrial thickness as did LIPUS in the present study [13]. Comparisons to studies focused on other interventions also provide additional comparisons that differ in their efficacy for improving endometrial thickness. Ibrahim et al. examined the impact of vaginal sildenafil use during IUI cycles and found that endometrial thickness rose from 8.91 ± 1.52 mm to 10.83 ± 1.04 mm [14]. Even though sildenafil makes the endometrium thicker than in the study mentioned above, it has drug-like effects and possible side effects that some patients might not be able to handle as well as LIPUS, which is similar and non-invasive. Like it, Mohammed *et al*. observed in a study that aspirin and sildenafil in ICSI patients had no effect on endometrial thickness over what was seen in untreated controls [15]. Additionally, the ESHRE guideline concluded that neither sildenafil nor aspirin is recommended for increasing efficacy or safety of hormonal pretreatment [16]. In a relevant study by Wang *et al*., endometrial receptivity markers were investigated, and they found that an endometrial thickness of between 8 and 12 mm is optimal for implantation success [17]. The range of thickness improvements induced by LIPUS in this present study is optimal and therefore clinically relevant. The last review by Ji *et al.* investigates the clinical applications of LIPUS in obstetrics and gynecology, showing that it is used in the enhancement of vascularization and tissue regeneration [9]. The observed increase in endometrial thickness in the present study is consistent with this mechanistic understanding. Taken together, the results of the present study further corroborate and extend previous findings that LIPUS is a promising non-invasive therapy to facilitate endometrial receptivity. Unlike drugs like sildenafil or aspirin, which work with varying levels of success and may have unwanted side effects, LIPUS directly causes angiogenesis and cellular proliferation. In addition, these results agree with the hypothesis that LIPUS is particularly beneficial for patients with thin endometria who are resistant to conventional estrogen therapies. The current study showed that LIPUS therapy is better than estrogen at affecting all aspects of blood flow through the body. LIPUS led to bigger improvements in the speed of blood flow (PSV, EDV) and a greater drop in resistance (RI), and these results were consistently statistically significant across different types of measurements with moderate to very large effects that are meaningful in a clinical setting**.** These hemodynamic benefits make LIPUS a good candidate for creating a more favorable endometrial environment for implantation. This may be the reason why other studies have shown that LIPUS generally leads to better reproductive outcomes. Recent literature supports the association between Doppler ultrasound parameters and fertility outcomes. In a review study by Choi *et al.*, Doppler ultrasonography has been shown to be useful for finding out more about how blood flow in the uterus and endometrium affects the chances of pregnancy in the assisted reproductive technology (ART) cycle; this has been shown to be true in other studies [18]. Indeed, as per the study conducted by Farooq *et al*., they conducted a cross-sectional analysis between Doppler indices in fertile and infertile women, wherein their RI and pulsatile index PI were found to be significantly higher in the infertile group, and the concept of poor flow of uterine blood is proven to be one of the causes of infertility [19]. Doppler indices have been subjected to additional studies to predict implantation success. Arora *et al*. did this test, and they found that lower PI and RI values were associated with higher pregnancy rates, as was found in the present study, and that LIPUS treatment can improve Doppler parameters and translate to better clinical outcomes [20]. Additionally, Smart *et al*. also compared the Doppler parameters between women with unexplained infertility and fertile controls and reported significantly higher PI and RI values among the former, suggesting that abnormal uterine blood flow has a role in unexplained infertility [21]. Concepts have been explored towards the other treatment modality to improve uterine blood flow. Ovarian and endometrial perfusion during ovulation were assessed by Mahmoud et al., and it was shown that color Doppler imaging can accurately predict ovulation and endometrial receptivity [22]. Pharmacological interventions like aspirin or nitric oxide donors have been studied concerning their potential to improve uterine perfusion, yet their results have not always been consistent and have been associated with unwanted side effects. The findings of the present study, taken together, are consistent with previous research that has corroborated the importance of improved uterine blood flow in increasing the chances of fertility. LIPUS most likely has an endothelial-stimulating and angiogenic mechanism, which should be further studied for the long-term effects as well as optimal treatment protocols. Although not statistically significant with the current sample size, LIPUS demonstrated consistent positive trends for reproductive outcomes with 20% absolute improvement in both implantation and pregnancy rates, and odds approximately 2.3 times higher for success with LIPUS. The consistent direction and magnitude across numerous endpoints attest to the fact that the lack of statistical significance for these results more likely indicates that the study was underpowered than that there was no effect. These findings are clinically important, as they suggest that LIPUS can enhance not only the endometrial but also the likelihood of successful implantation and pregnancy, with the potential to alleviate patients without success on standard hormonal therapies. Comparisons with recently published literature further support the efficacy of LIPUS in improving reproductive outcomes. According to a study conducted by Xiong et al., pregnancy outcomes seemed to improve in women with adenomyosis who got pregnant after high-intensity focused ultrasound (HIFU) treatment: 72% natural conception [23]. Such results imply that ultrasound-based interventions could improve implantation and pregnancy success. As in Tang *et al*., LIPUS was also used to explore its effect on ovarian function and was shown to improve estrous cycle regularity and to raise estrogen levels, two factors that could lead to enhanced implantation success [24]. Hung *et al*. also backed up the idea that LIPUS is important for reproductive health and that giving LIPUS to the mother before birth improved the growth of the fetus and the function of the placenta in a rat model of intrauterine growth restriction [25]. While this study specifically studied fetal development as opposed to implantation, the findings show that LIPUS has potential beyond reproduction physiology. For instance, Qin et al. looked into how LIPUS affected ovarian insufficiency and saw that it helped with ovarian restoration and follicular development, which is why they concluded that it could help with reproductive outcomes [26]. Other non-ultrasound-based interventions for improving implantation outcomes have also been studied. Among other combinations, Gao *et al*. reported that use of LIPUS in combination with tadalafil resulted in improvements in vascular function and endothelial health [27]. These results show that LIPUS is good for improving blood flow and repairing tissue. These processes are thought to help women become pregnant by making the uterus more receptive and increasing the chances of implantation. Taken together, they are consistent with and add to previous findings of LIPUS's benefit in reproductive medicine. There was significant improvement in implantation and pregnancy rates, which implies that LIPUS may improve reproductive success by improving endometrial angiogenesis, thickness, and receptivity. These results support the growing pool of data implying ultrasound-based therapies represent a promising, noninvasive modality for the improvement of fertility outcomes.

Study limitations and prospects

While these findings are promising, the study had several limitations: the moderate sample size (n=30 per group) and short-term (14-day) follow-up period. There is a need for correlation with live birth outcomes in larger trials.

Conclusions

Low Intensity Pulsed Ultrasound (LIPUS) may be a safe and effective way to help women who can't get pregnant because they have a thin endometrial lining, according to the study's results. LIPUS therapy demonstrates superiority over estrogen for improving endometrial thickness and hemodynamic parameters, with promising trends toward better reproductive outcomes. These findings suggest LIPUS may represent an advance in endometrial preparation protocols, though confirmation in larger multicenter trials with clinical pregnancy and live birth endpoints is warranted.

Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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