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Original Research Article

Effect of Vaginal Isosorbide Mononitrate as an Adjuvant to Clomiphene Citrate on Pregnancy Rate in Women Undergoing Intrauterine Insemination: A Randomised Controlled Study

Suma B.[1], Renu Tanwar[2], Sudha Prasad[3]

[1,2,3]Department of Obstetrics and Gynaecology, IVF and Reproductive Biology Centre, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India

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Corresponding author: Dr. Suma B.

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Abstract

Background: Clomiphene citrate (CC), widely used for ovarian stimulation before intrauterine insemination (IUI), exerts anti-oestrogenic effects on the endometrium and may impair uterine perfusion. Nitric oxide donors such as isosorbide mononitrate (IMN) may improve uterine and subendometrial blood flow.

Objective: To evaluate the effect of vaginal IMN added to CC on clinical pregnancy, follicular response, endometrial thickness and uterine perfusion during IUI.

Methods: This open-label randomised controlled study was conducted at a tertiary IVF centre in New Delhi (December 2018 to December 2019). Sixty women aged 20-35 years with ovulatory cycles, patent tubes and normal partner semen analysis received CC 100 mg (days 3-7) plus vaginal IMN 10 mg daily from day 5 (n=30) or CC alone (n=30). Follicles, endometrial thickness, Applebaum zonal flow and uterine artery pulsatility and resistance indices were assessed on day 3 and trigger day. The primary outcome was clinical pregnancy.

Results: Groups were comparable except for hypothyroidism history (53.3% vs 23.3%, P=0.017). On trigger day, the IMN group had more left ovarian dominant follicles (1.00±0.83 vs 0.60±0.72, P=0.04), more zone 4 flow (53.3% vs 33.3%, P=0.12) and similar endometrial thickness (8.23±2.15 vs 8.05±1.86 mm, P=0.59). Left uterine artery resistance index fell significantly within the IMN group (0.63 to 0.42, P<0.01). Clinical pregnancy rates were 13.3% and 10.0% (relative risk 1.33, 95% CI 0.33-5.45; P=1.00). No ovarian hyperstimulation occurred; two women (6.7%) reported mild headache.

Conclusion: Adjuvant vaginal IMN was well tolerated and showed favourable but non-significant trends in endometrial perfusion and pregnancy rate. Adequately powered placebo-controlled trials are required.

Keywords: Clomiphene; Endometrium; Intrauterine insemination; Isosorbide mononitrate; Nitric oxide donors; Pregnancy rate; Uterine artery Doppler.

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Introduction

Infertility is defined as a disease characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse [1]. Beyond its biological dimension, infertility carries substantial psychological, social and economic consequences for affected couples. A systematic analysis of 277 demographic and reproductive health surveys estimated that the number of couples affected by infertility worldwide rose from 42.0 million in 1990 to 48.5 million in 2010, largely because of population growth, with the highest prevalence observed in South Asia, sub-Saharan Africa, North Africa and the Middle East [2]. Community-based data from India remain sparse, although a study of young sexually active women in Mysore reported a prevalence of primary infertility of 12.6% (95% confidence interval [CI] 10.5% to 15.0%) [3]. In the Indian social context, where childbearing is closely linked to marital and family expectations and childlessness is frequently stigmatised, couples tend to seek treatment early, and public-sector hospitals face a growing demand for fertility care that is effective, affordable and minimally invasive. Intrauterine insemination (IUI) is an assisted conception technique in which a processed semen sample is deposited in the upper uterine cavity around the time of ovulation, thereby bypassing the natural barriers to sperm ascent in the female reproductive tract [4]. By removing seminal plasma, prostaglandins and debris, and by concentrating motile spermatozoa close to the site of fertilisation, IUI increases the density of gametes

available at the ampulla. It is regarded as a cost-effective, noninvasive, first-line therapy for couples with functionally normal tubes and infertility attributable to cervical factors, anovulation, mild to moderate male factor, unexplained causes, immunological factors or ejaculatory dysfunction, with clinical pregnancy rates per cycle ranging from 10% to 20% [4]. Its usefulness is limited in endometriosis, severe male factor infertility, tubal disease and advanced maternal age. The principal prognostic indicators of IUI success include female age, duration of infertility, aetiology, the stimulation protocol, the number of preovulatory follicles on the day of human chorionic gonadotropin (hCG) administration, the timing of insemination and the processed total motile sperm count [4]. IUI may be performed in natural cycles, but ovarian stimulation generally improves pregnancy outcomes compared with natural cycles or timed intercourse, provided that multifollicular development is controlled to limit multiple pregnancy and ovarian hyperstimulation syndrome (OHSS).

Clomiphene citrate (CC) remains the most commonly used oral agent for ovarian stimulation in IUI programmes in resource-limited settings because it is inexpensive, orally administered, requires limited monitoring and carries a low risk of OHSS. CC is a nonsteroidal selective oestrogen receptor modulator that competitively binds hypothalamic oestrogen receptors, reduces oestrogen-mediated negative feedback and increases pituitary secretion of follicle-stimulating hormone and luteinising hormone, thereby promoting follicular recruitment and ovulation. A systematic review of randomised trials in ovulatory infertility found that CC combined with IUI achieved a higher cycle pregnancy rate than timed intercourse in natural cycles (odds ratio 4.6, 95% CI 1.9 to 11.3), although gonadotropins with IUI were superior to CC with IUI [5]. The principal drawback of CC is that its long half-life and persistent occupation of oestrogen receptors produce peripheral anti-oestrogenic effects at the cervix and endometrium. These effects manifest as poorer cervical mucus, a thinner endometrium and altered endometrial development, and they help to explain the well-recognised discrepancy between the high ovulation rates and the relatively modest pregnancy rates achieved with CC. In a meta-analysis of 33 randomised trials involving 4349 anovulatory women, CC was associated with a thinner mid-cycle endometrium than letrozole (weighted mean difference -1.39 mm) and with lower pregnancy and live birth rates [6]. Notably, the same meta-analysis showed that women treated with CC alone had a significantly thinner endometrium than those receiving CC combined with a nitric oxide (NO) donor (weighted mean difference -1.75 mm, 95% CI -2.08 to -1.41), together with lower ovulation and pregnancy rates [6].

Successful implantation requires a competent embryo and a receptive endometrium, and the latter depends on adequate endometrial growth, appropriate secretory transformation and a sufficient blood supply. Endometrial thickness is the most frequently used sonographic surrogate of receptivity, but its predictive value in IUI cycles is uncertain. A systematic review and meta-analysis of 23 studies involving 3846 women undergoing IUI with ovarian stimulation found no significant difference in preovulatory endometrial thickness between women who conceived and those who did not (mean difference 0.51 mm, 95% CI -0.05 to 1.07), while confirming that CC produced a thinner endometrium than gonadotropins [7]. This observation suggests that thickness alone does not capture the functional state of the endometrium, and attention has increasingly turned to uterine and subendometrial perfusion as additional determinants of receptivity. Doppler ultrasonography allows noninvasive assessment of uterine artery impedance through the pulsatility index (PI) and resistance index (RI), and of the depth to which vessels penetrate the endometrium. In a randomised study of 90 women undergoing stimulated IUI, subendometrial RI and PI were significantly lower and the endometrium significantly thicker in cycles that resulted in implantation, and the lowest implantation rate was observed with CC stimulation [8]. Applebaum described a practical grading system in which endometrial vascularity is classified into zones according to the depth of vessel penetration, from vessels confined to the surrounding myometrium (zone 1) to vessels reaching the endometrial cavity (zone 4), with deeper penetration regarded as favourable for implantation [9].

Nitric oxide is a short-lived free radical synthesised from L-arginine by the endothelial, neuronal and inducible isoforms of nitric oxide synthase. Within the vasculature, NO activates soluble guanylate cyclase in smooth muscle cells, increases intracellular cyclic guanosine monophosphate and induces vasodilation, while also inhibiting platelet aggregation and leucocyte adhesion [10]. NO has been recognised as a polyvalent regulator of the female reproductive system, participating in ovarian steroidogenesis, ovulation, tubal function, cervical ripening, uterine quiescence and placental perfusion [10]. In the human endometrium, endothelial nitric oxide synthase has been localised to the glandular epithelium and the microvascular endothelium, predominantly during the luteal phase, and experimental evidence indicates that NO contributes to endometrial receptivity, decidualisation and implantation [11]. Within the ovary, NO appears to influence follicular

development and selection through angiogenic effects, to modulate steroidogenesis and to participate in the ovulatory cascade and in the meiotic maturation of the oocyte, although these actions are concentration-dependent [12]. These physiological roles provide a biological rationale for the use of exogenous NO donors, or of agents that potentiate the NO pathway, to enhance uterine perfusion and endometrial development in women undergoing fertility treatment.

Early clinical evidence came from sildenafil citrate, a phosphodiesterase type 5 inhibitor that augments NO-mediated vasodilation by preventing the breakdown of cyclic guanosine monophosphate. In a preliminary report, vaginal sildenafil reduced uterine artery PI and improved endometrial development in women with a prior poor endometrial response undergoing in vitro fertilisation, and three of the four treated women conceived [13]. Organic nitrates act more directly as NO donors. Isosorbide mononitrate (IMN), an established antianginal agent, releases NO without requiring enzymatic activation by the endothelium, has high oral and vaginal bioavailability and a relatively long duration of action, and is familiar to obstetricians through its vaginal use for cervical ripening. When administered vaginally to women with unexplained recurrent miscarriage, IMN 20 mg significantly lowered uterine artery impedance and increased three-dimensional subendometrial vascularisation indices within two hours ($P<0.001$) [14]. The vaginal route offers the theoretical advantage of preferential delivery to the uterus while limiting systemic vasodilatory effects such as headache, flushing and hypotension.

The most direct evidence for IMN in the IUI setting comes from a randomised controlled pilot study by Abdel Razik and colleagues, in which 120 women with unexplained infertility undergoing CC stimulation and IUI were allocated to vaginal IMN 10 mg or placebo. Women in the IMN group achieved a significantly higher pregnancy rate per cycle, together with a thicker endometrium, lower uterine artery blood flow indices and higher endometrial vascular flow indices ($P<0.05$) [15]. Despite these encouraging findings, the evidence base remains small and is derived largely from a single population. Differences in ethnicity, body mass index, aetiology of infertility, baseline endometrial response to CC and the timing of CC administration may all modify the effect of NO donors, and data from Indian women are lacking. Moreover, the relationship between improvements in sonographic surrogates and actual pregnancy outcomes remains uncertain, given that endometrial thickness alone has not been shown to predict conception in stimulated IUI cycles [7]. Independent replication in different clinical settings is therefore required before IMN can be recommended as a routine adjuvant. Against this background, we hypothesised that adding vaginal IMN to CC stimulation would counteract the adverse endometrial and vascular effects of CC by improving uterine and subendometrial perfusion, and would thereby increase the clinical pregnancy rate in women undergoing IUI. We conducted a randomised controlled study at a public-sector tertiary care IVF centre in North India to evaluate the effect of vaginal IMN on clinical pregnancy rate, follicular response, endometrial thickness, endometrial zonal blood flow and uterine artery Doppler indices in CC-stimulated IUI cycles.

Aims and Objectives

The primary objective of this study was to evaluate the effect of vaginal isosorbide mononitrate, administered as an adjuvant to clomiphene citrate, on the clinical pregnancy rate in women undergoing intrauterine insemination, and to compare the pregnancy rates between women receiving clomiphene citrate with isosorbide mononitrate and those receiving clomiphene citrate alone.

The secondary objectives were to compare the two groups with respect to the number and size of dominant follicles on day 9 and on the day of ovulation trigger, endometrial thickness, endometrial zonal blood flow graded by the Applebaum classification, and the pulsatility and resistance indices of the right and left uterine arteries, and to document the adverse effects of isosorbide mononitrate therapy.

Materials and Methods

Study Design and Setting: This was a prospective, open-label, parallel-group randomised controlled study conducted at the IVF and Reproductive Biology Centre, Department of Obstetrics and Gynaecology, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India, a public-sector tertiary care teaching institution. Participants were recruited over a period of one year, from December 2018 to December 2019.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of Maulana Azad Medical College and associated Lok Nayak Hospital [approval reference number]. Every participant received a patient information sheet explaining the purpose, procedures, potential benefits and risks of the study, and written informed consent was obtained before enrolment. Participants were informed of their right to withdraw at any time without any effect on their subsequent treatment, confidentiality of their records was assured, and no charges were levied for study-related procedures. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Sample Size: The sample size was estimated from the pregnancy rates reported by Abdel Razik et al. [15], namely 23.3% in women receiving CC with IMN and 8.3% in women receiving CC alone. Assuming a type I error (α) of 5% and a power (1-β) of 80%, the estimated sample size was 68 women per group. Because of the limited time frame available for the study, a minimum of 30 women per group was set as a feasible target, and a total of 60 women (30 per group) who fulfilled the eligibility criteria were enrolled. The study was therefore not powered to detect the anticipated difference in the primary outcome, and its findings should be interpreted as exploratory.

Study Population and Eligibility Criteria: Women attending the IVF and Reproductive Biology Centre with infertility and planned for IUI were screened for eligibility. Infertility was defined as failure to achieve a clinical pregnancy after 12 months of regular unprotected intercourse [1]; it was classified as primary when the woman had never conceived and as secondary when she had conceived previously. Women were eligible for inclusion if they were aged 20 to 35 years, had regular ovulatory menstrual cycles, had bilateral tubal patency documented during the infertility work-up, and had a male partner whose semen analysis was normal according to the World Health Organization 2010 reference values [16]. Women with moderate to severe endometriosis and those with active genital tuberculosis were excluded.

Randomisation and Allocation: Eligible women were allocated to the study group or the control group by simple randomisation using sealed envelopes. Envelopes containing the treatment allocation were labelled, shuffled and placed in a container, and each participant drew one envelope after enrolment; the allocation contained in the envelope determined her group assignment. The control group did not receive a placebo, and neither participants nor treating clinicians were blinded to group allocation.

Baseline Evaluation: All couples underwent a complete infertility evaluation according to the departmental protocol. This included a detailed medical, menstrual, obstetric and sexual history, general and systemic examination, measurement of height and weight for calculation of body mass index (BMI), estimation of serum thyroid-stimulating hormone (TSH), assessment of tubal patency and semen analysis of the male partner.

A history of hypothyroidism and of pulmonary tuberculosis was recorded. BMI was categorised according to World Health Organization criteria as underweight (below 18.5 kg/m²), normal (18.5-24.99 kg/m²), overweight (25.0-29.99 kg/m²) or obese (30 kg/m² or above). On day 3 of the menstrual cycle, a baseline transvaginal ultrasound examination was performed to exclude ovarian cysts and to record the antral follicle count (AFC) in each ovary, the endometrial thickness, the endometrial zonal blood flow and the PI and RI of the right and left uterine arteries. All sonographic examinations were performed with a Medison SA 8000 EX ultrasound system equipped with a transvaginal probe with colour and power Doppler facilities.

Intervention: Women in the study group received oral CC 100 mg once daily from day 3 to day 7 of the menstrual cycle, together with IMN 10 mg as a vaginal tablet once daily from day 5 of the cycle. IMN was continued until menstruation occurred or pregnancy was diagnosed. Women in the control group received oral CC 100 mg once daily from day 3 to day 7 of the menstrual cycle without IMN. All other aspects of cycle management were identical in the two groups.

Follicular Monitoring and Sonographic Assessment: Follicular monitoring was performed by serial transvaginal ultrasound according to the departmental protocol. On day 9 of the cycle, the number of dominant follicles and their mean diameter in each ovary were recorded, and monitoring was continued until the leading follicle attained a mean diameter of 18 mm or more. On the day of ovulation trigger, transvaginal ultrasound was repeated to record the number and size of dominant follicles in each ovary, the endometrial thickness, the endometrial zonal blood flow and the PI and RI of both uterine arteries. Endometrial vascularity on power Doppler was graded according to the Applebaum classification [9] as zone 1 when vessels were seen only in the myometrium surrounding the endometrium, zone 2 when vessels penetrated the hyperechogenic outer margin of the endometrium, zone 3 when vessels reached the internal hypoechogenic zone of the endometrium, and zone 4 when vessels reached the endometrial cavity.

Ovulation Trigger, Semen Preparation and Insemination: Ovulation was triggered with an intramuscular injection of hCG 10,000 IU when the dominant follicle reached a mean diameter of 18 mm or more. Transvaginal ultrasound was performed 36 hours after hCG administration to confirm ovulation, as evidenced by collapse of the dominant follicle and the presence of free fluid in the pouch of Douglas, and IUI was performed thereafter. The semen sample was prepared by the swim-up technique.

Luteal Phase Support and Pregnancy Assessment: Luteal phase support was provided with vaginal micronised progesterone 200 mg twice daily for 14 days following insemination. A urine pregnancy test was performed 14 days after IUI, and serum beta-hCG was estimated in women with

a positive urine test. Transvaginal ultrasound was performed at 6 weeks of gestation to confirm the presence of an intrauterine gestational sac with fetal cardiac activity. Adverse effects, including headache and features of OHSS, were recorded throughout the treatment cycle.

Outcome Measures: The primary outcome was the clinical pregnancy rate, defined as the percentage of women with an intrauterine gestational sac showing fetal cardiac activity on transvaginal ultrasound at 6 weeks of gestation. Secondary outcomes were the number and size of dominant follicles on day 9 and on trigger day, endometrial thickness on day 3 and on trigger day, endometrial zonal blood flow on day 3 and on trigger day, the PI and RI of the right and left uterine arteries on day 3 and on trigger day, the urine pregnancy test result and adverse effects.

Statistical Analysis: Data were entered in Microsoft Excel and analysed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation (SD) and compared between the groups using the unpaired Student t-test or the Mann-Whitney U test, as appropriate for the distribution of the data. Within-group changes between day 3 and trigger day were assessed using paired-sample analysis. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or the Fisher exact test, as appropriate. For the primary outcome, the relative risk (RR) of clinical pregnancy and the absolute risk difference were calculated with their 95% CIs. A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Study Participants: A total of 60 women who fulfilled the eligibility criteria were enrolled and randomised, 30 to the CC plus IMN group (study group) and 30 to the CC alone group (control group). All randomised women completed the treatment cycle, underwent IUI and were included in the final analysis.

Baseline Characteristics: The baseline demographic and clinical characteristics of the two groups are presented in Table 1. The mean age was 27.07 ± 3.35 years in the study group and 28.70 ± 3.53 years in the control group (P=0.07). The largest proportion of women in both groups was aged 26 to 30 years (43.3% and 50.0%, respectively), and the distribution of age categories did not differ significantly (P=0.50). Primary infertility predominated in both groups, accounting for 66.7% (20/30) of the study group and 83.3% (25/30) of the control group (P=0.23). The mean duration of infertility was identical in the two groups (5.33 ± 2.07 versus 5.33 ± 1.93 years, P=0.99), and the distribution according to duration category was similar (P=0.69), with 40.0% of the study group and 36.7% of the control group reporting infertility of 2 to 4 years.

The mean BMI was 25.49 ± 4.01 kg/m² in the study group and 24.66 ± 3.97 kg/m² in the control group (P=0.45). A normal BMI was recorded in 40.0% and 46.7% of women, respectively, overweight in 40.0% of both groups, and obesity in 16.7% and 6.7%, with no significant difference in the overall BMI distribution (P=0.62).

Mean serum TSH was comparable (1.97 ± 0.77 versus 2.04 ± 0.86 mIU/L, P=0.73), indicating adequately controlled thyroid status in both arms. However, a history of hypothyroidism was significantly more frequent in the study group (53.3%, 16/30) than in the control group (23.3%, 7/30; P=0.017). A history of pulmonary tuberculosis was reported by 3.3% (1/30) and 10.0% (3/30) of women, respectively (P=0.61).

Table 1: Baseline demographic and clinical characteristics of the study population

Variable	CC + IMN group (n=30)	CC alone group (n=30)	P value
Age (years), mean ± SD	27.07 ± 3.35	28.70 ± 3.53	0.07
Age group, n (%)			0.50
21-25 years	10 (33.3)	6 (20.0)	
26-30 years	13 (43.3)	15 (50.0)	
31-35 years	7 (23.3)	9 (30.0)	
Type of infertility, n (%)			0.23
Primary	20 (66.7)	25 (83.3)	
Secondary	10 (33.3)	5 (16.7)	
Duration of infertility (years), mean ± SD	5.33 ± 2.07	5.33 ± 1.93	0.99
Duration of infertility, n (%)			0.69
2-4 years	12 (40.0)	11 (36.7)	
5-7 years	11 (36.7)	14 (46.7)	
8-10 years	7 (23.3)	5 (16.7)	
BMI (kg/m²), mean ± SD	25.49 ± 4.01	24.66 ± 3.97	0.45
BMI category, n (%)			0.62

Below 18.5 kg/m²	1 (3.3)	2 (6.7)	
18.5-24.99 kg/m²	12 (40.0)	14 (46.7)	
25.0-29.99 kg/m²	12 (40.0)	12 (40.0)	
30 kg/m² or above	5 (16.7)	2 (6.7)	
Serum TSH (mIU/L), mean ± SD	1.97 ± 0.77	2.04 ± 0.86	0.73
History of hypothyroidism, n (%)	16 (53.3)	7 (23.3)	0.017
History of pulmonary tuberculosis, n (%)	1 (3.3)	3 (10.0)	0.61

CC, clomiphene citrate; IMN, isosorbide mononitrate; SD, standard deviation; BMI, body mass index; TSH, thyroid-stimulating hormone. Continuous variables compared by unpaired t-test or Mann-Whitney U test; categorical variables by chi-square or Fisher exact test.

Antral Follicle count and Follicular Response: Ovarian parameters are summarised in Table 2. The mean day 3 AFC was numerically higher in the study group in both the right ovary (5.17 ± 1.84 versus 4.43 ± 1.33, P=0.13) and the left ovary (5.47 ± 2.27 versus 4.97 ± 1.24, P=0.73), although neither difference was statistically significant. On day 9, the mean number of dominant follicles in the right ovary was similar in the two groups (1.21 ± 0.99 versus 1.23 ± 0.89, P=0.81), whereas in the left ovary it was higher in the study group, with a difference of borderline significance (1.10 ± 0.80 versus 0.70 ± 0.75, P=0.05). On trigger day, the study group had significantly more dominant follicles in the left ovary than the control group (1.00 ± 0.83 versus 0.60 ± 0.72, P=0.04), while the number in the right ovary was lower in the study group without a significant difference (0.77 ± 0.77 versus 1.03 ± 0.85, P=0.22). Taken together, the mean total number of dominant follicles per woman on trigger day was 1.77 in the study group and 1.63 in the control group.

The diameter of dominant follicles did not differ significantly between the groups at either time point. On day 9, the mean follicular diameter was 12.22 ± 2.07 mm versus 12.81 ± 2.11 mm in the right ovary (P=0.19) and 12.87 ± 2.28 mm versus 12.91 ± 2.21 mm in the left ovary (P=0.97). On trigger day, the corresponding values were 20.36 ± 1.89 mm versus 21.03 ± 1.90 mm in the right ovary (P=0.18) and 20.00 ± 2.01 mm versus 19.58 ± 1.38 mm in the left ovary (P=0.60).

Table 2: Day 3 antral follicle count and follicular response in the two groups

Variable	CC + IMN group (n=30)	CC alone group (n=30)	P value
Day 3 antral follicle count, mean ± SD			
Right ovary	5.17 ± 1.84	4.43 ± 1.33	0.13
Left ovary	5.47 ± 2.27	4.97 ± 1.24	0.73
Number of dominant follicles on day 9, mean ± SD			
Right ovary	1.21 ± 0.99	1.23 ± 0.89	0.81
Left ovary	1.10 ± 0.80	0.70 ± 0.75	0.05
Number of dominant follicles on trigger day, mean ± SD			
Right ovary	0.77 ± 0.77	1.03 ± 0.85	0.22
Left ovary	1.00 ± 0.83	0.60 ± 0.72	0.04
Size of dominant follicles on day 9 (mm), mean ± SD			
Right ovary	12.22 ± 2.07	12.81 ± 2.11	0.19
Left ovary	12.87 ± 2.28	12.91 ± 2.21	0.97
Size of dominant follicles on trigger day (mm), mean ± SD			
Right ovary	20.36 ± 1.89	21.03 ± 1.90	0.18
Left ovary	20.00 ± 2.01	19.58 ± 1.38	0.60

CC, clomiphene citrate; IMN, isosorbide mononitrate; SD, standard deviation. Between-group comparisons by unpaired t-test or Mann-Whitney U test.

Endometrial Thickness and Endometrial Zonal Blood Flow: Endometrial parameters are shown in Table 3. The mean endometrial thickness on day 3 was almost identical in the two groups (4.44 ± 0.68 mm versus 4.43 ± 0.66 mm, P=0.97). By trigger day, endometrial thickness had increased significantly within both the study group (to 8.23 ± 2.15 mm, P<0.001) and the control group (to 8.05 ± 1.86 mm, P<0.001), corresponding to mean increments of 3.79 mm and 3.62 mm, respectively. The trigger-day endometrium was 0.18 mm thicker

in the study group, but this difference was not statistically significant (P=0.59).

On day 3, endometrial vascularity was confined to zone 1 in 96.7% (29/30) of women in each group, and zone 2 flow was seen in one woman (3.3%) in each group (P=1.00). On trigger day, no woman in either group had zone 1 or zone 2 flow. Zone 4 vascularity, representing vessels reaching the endometrial cavity, was observed in 53.3% (16/30) of the study group compared with 33.3% (10/30) of the control group, whereas zone 3 flow was seen in 46.7% (14/30) and 66.7% (20/30), respectively.

Although the proportion of women with the deepest vascular penetration was 20 percentage points higher in the IMN group, the difference did not reach statistical significance (P=0.12).

Table 3: Endometrial thickness and endometrial zonal blood flow (Applebaum zones)

Variable	CC + IMN group (n=30)	CC alone group (n=30)	P value
Endometrial thickness (mm), mean ± SD			
Day 3	4.44 ± 0.68	4.43 ± 0.66	0.97
Trigger day	8.23 ± 2.15	8.05 ± 1.86	0.59
P value within group (day 3 vs trigger day)	<0.001	<0.001	
Zonal blood flow on day 3, n (%)			1.00
Zone 1	29 (96.7)	29 (96.7)	
Zone 2	1 (3.3)	1 (3.3)	
Zonal blood flow on trigger day, n (%)			0.12
Zone 3	14 (46.7)	20 (66.7)	
Zone 4	16 (53.3)	10 (33.3)	

CC, clomiphene citrate; IMN, isosorbide mononitrate; SD, standard deviation. Zone 1, vessels in surrounding myometrium only; zone 2, vessels penetrating the hyperechogenic endometrial margin; zone 3, vessels reaching the inner hypoechogenic zone; zone 4, vessels reaching the endometrial cavity.

Uterine Artery Doppler Indices: Uterine artery Doppler findings are presented in Table 4. At baseline on day 3, the right uterine artery PI was significantly lower in the study group than in the control group (1.64 ± 0.49 versus 1.94 ± 0.46, P=0.01), whereas the right uterine artery RI (0.60 ± 0.29 versus 0.62 ± 0.36, P=0.83), left uterine artery PI (1.67 ± 0.58 versus 1.73 ± 0.56, P=0.74) and left uterine artery RI (0.63 ± 0.34 versus 0.61 ± 0.30, P=0.65) were comparable.

All four indices declined between day 3 and trigger day in both groups. In the study group, the right uterine artery PI decreased from 1.64 to 1.50 (P=0.15), the right RI from 0.60 to 0.51 (P=0.05), the left PI from 1.67 to 1.45 (P=0.08) and the left RI from 0.63 to 0.42 (P<0.01); the reduction in left uterine artery RI was the only statistically significant within-group change. In the control group, significant reductions were observed in all four indices: right PI from 1.94 to 1.67 (P=0.01), right RI from 0.62 to 0.41 (P<0.01), left PI from 1.73 to 1.48 (P<0.01) and left RI from 0.61 to 0.34 (P<0.01).

On trigger day, there were no significant between-group differences in right uterine artery PI (1.50 ± 0.55 versus 1.67 ± 0.45, P=0.24), right RI (0.51 ± 0.38 versus 0.41 ± 0.31, P=0.31), left PI (1.45 ± 0.58 versus 1.48 ± 0.48, P=0.67) or left RI (0.42 ± 0.33 versus 0.34 ± 0.33, P=0.25). Thus, the absolute PI values on trigger day were numerically lower in the study group, whereas the RI values were numerically lower in the control group.

Table 4: Uterine artery Doppler flow indices on day 3 and trigger day

Variable	CC + IMN group (n=30)	CC alone group (n=30)	P value
Right uterine artery PI, mean ± SD			
Day 3	1.64 ± 0.49	1.94 ± 0.46	0.01
Trigger day	1.50 ± 0.55	1.67 ± 0.45	0.24
P value within group	0.15	0.01	
Right uterine artery RI, mean ± SD			
Day 3	0.60 ± 0.29	0.62 ± 0.36	0.83
Trigger day	0.51 ± 0.38	0.41 ± 0.31	0.31
P value within group	0.05	<0.01	
Left uterine artery PI, mean ± SD			
Day 3	1.67 ± 0.58	1.73 ± 0.56	0.74
Trigger day	1.45 ± 0.58	1.48 ± 0.48	0.67
P value within group	0.08	<0.01	

Left uterine artery RI, mean ± SD			
Day 3	0.63 ± 0.34	0.61 ± 0.30	0.65
Trigger day	0.42 ± 0.33	0.34 ± 0.33	0.25
P value within group	<0.01	<0.01	

CC, clomiphene citrate; IMN, isosorbide mononitrate; PI, pulsatility index; RI, resistance index; SD, standard deviation. Within-group P values compare day 3 with trigger day.

Pregnancy and Safety Outcomes: Pregnancy and safety outcomes are summarised in Table 5. The urine pregnancy test was positive in 4 women (13.3%) in the study group and in 3 women (10.0%) in the control group (P=1.00).

All women with a positive urine pregnancy test were subsequently found to have an intrauterine gestational sac with fetal cardiac activity at 6 weeks of gestation, and no biochemical pregnancy was recorded in either group.

The clinical pregnancy rate was therefore 13.3% in the study group and 10.0% in the control group. This corresponded to an absolute risk difference of 3.3 percentage points (95% CI -12.9 to 19.6) and a relative risk of 1.33 (95% CI 0.33 to 5.45), and the difference was not statistically significant (P=1.00). No case of OHSS occurred in either group. Two women (6.7%) in the study group reported mild headache during IMN therapy, which responded to simple analgesics, and no adverse effects were reported in the control group (P=0.49).

Table 5: Pregnancy and safety outcomes

Variable	CC + IMN group (n=30)	CC alone group (n=30)	P value
Positive urine pregnancy test, n (%)	4 (13.3)	3 (10.0)	1.00
Biochemical pregnancy, n (%)	0 (0.0)	0 (0.0)	NA
Clinical pregnancy (fetal cardiac activity at 6 weeks), n (%)	4 (13.3)	3 (10.0)	1.00
Relative risk of clinical pregnancy (95% CI)	1.33 (0.33 to 5.45)	Reference	
Absolute risk difference, percentage points (95% CI)	3.3 (-12.9 to 19.6)	Reference	
Ovarian hyperstimulation syndrome, n (%)	0 (0.0)	0 (0.0)	NA
Mild headache, n (%)	2 (6.7)	0 (0.0)	0.49

CC, clomiphene citrate; IMN, isosorbide mononitrate; CI, confidence interval; NA, not applicable. Proportions compared by Fisher exact test.

Discussion

In this randomised controlled study of women undergoing CC-stimulated IUI, the addition of vaginal IMN was associated with a clinical pregnancy rate of 13.3% compared with 10.0% with CC alone, a relative increase of one third that was not statistically significant. IMN was also associated with significantly more dominant follicles in the left ovary on trigger day, a 20 percentage point higher proportion of zone 4 endometrial vascularity, a marginally thicker endometrium on trigger day and a significant within-group reduction in left uterine artery RI.

None of the between-group differences in endometrial thickness, zonal flow or trigger-day Doppler indices reached statistical significance, and the study was substantially underpowered for its primary outcome. Treatment was well tolerated, with mild headache in 6.7% of treated women and no OHSS.

Pregnancy Outcome: The direction of effect in the present study agrees with the randomised pilot trial by Abdel Razik et al., in which vaginal IMN 10 mg added to CC in women with unexplained infertility undergoing IUI increased the pregnancy rate to 23.3% compared with 8.3% with CC and placebo (P=0.04) [15]. The pregnancy rate in our control group (10.0%) was close to that of their placebo group, whereas the rate in our IMN group was lower than theirs. Several differences may account for this. Their larger sample of 120 women provided greater precision; they administered CC from day 5 to day 9 with a placebo, while our participants received CC from day 3 to day 7 in an open-label design; and the populations differed in ethnicity and possibly in baseline endometrial response. Our pregnancy rate with CC alone is consistent with other reports of CC-stimulated IUI. Seckin et al. observed clinical pregnancy rates per cycle of 8.5%, 10% and 9.2% across different leading follicle sizes in 563 CC and IUI cycles in women with polycystic ovary syndrome (P=0.86) [27], and Roy et al. reported that 28 pregnancies occurred in 318 CC cycles (8.8% per cycle) in an Indian population [26]. Hembram et al., who combined CC with human menopausal gonadotropin before IUI in unexplained infertility, reported a higher pregnancy rate of 23.3% [28], illustrating the influence of the stimulation protocol on outcome.

Evidence from agents acting on the same NO and cyclic guanosine monophosphate pathway provides a useful context. Aboelroose et al. randomised 80

women with unexplained infertility to CC with or without oral sildenafil and found significantly higher pregnancy rates (65% versus 40%, P=0.043) [17], and Mohammed et al., in a crossover trial of 595 women with polycystic ovary syndrome, reported clinical pregnancy rates of 36.6% versus 18.98% with sildenafil added to CC (P=0.001) [18]. In contrast, Sarhan et al. found that sildenafil added to CC in 130 women with unexplained infertility improved endometrial thickness but did not significantly increase pregnancy rates [19], consistent with our findings. At the level of pooled evidence, a meta-analysis by Li et al. reported a risk ratio for clinical pregnancy of 1.31 (95% CI 1.11 to 1.53) with sildenafil in women with a thin endometrium [20], and Baradwan et al. reported a risk ratio of 1.35 (95% CI 1.19 to 1.53) when sildenafil was combined with CC [22].

The relative risk of 1.33 observed in our study is strikingly similar to these pooled estimates, suggesting that the magnitude of effect is plausible but that our sample was far too small to estimate it with precision. Not all evidence is favourable, however. Marin et al. concluded that sildenafil improved endometrial thickness and pregnancy in timed intercourse cycles but was not effective in IUI and IVF cycles [21], and in a double-blind randomised trial of 138 IVF patients with prior implantation failure, transdermal nitroglycerin did not improve implantation or pregnancy rates [23].

Follicular Response: The significantly higher number of left ovarian dominant follicles on trigger day in the IMN group parallels the findings of Abdel Razik et al., who reported more mature follicles with IMN than with placebo (1.45 ± 0.6 versus 1.20 ± 0.5, P=0.01) [15]. A biological basis for such an effect exists, since NO participates in follicular development, angiogenesis around the growing follicle and the ovulatory process [12]. Nevertheless, this finding should be interpreted with caution. The number of dominant follicles in the right ovary was lower in the IMN group, the combined mean difference between the groups was small (1.77 versus 1.63), the day 3 AFC was numerically higher in the IMN group, and multiple secondary comparisons were performed. The mean number of dominant follicles in our study was comparable to that reported by Roy et al. with CC (1.92 ± 0.17) [26]. Follicle diameter on trigger day did not differ between groups in our study, and Seckin et al. showed that leading follicle size between 17 and more than 22 mm did not influence pregnancy rates in CC and IUI cycles [27], so differences in follicular size are unlikely to explain outcome differences.

Endometrial Thickness: Endometrial thickness increased significantly from day 3 to trigger day in both groups, but the between-group difference on trigger day was only 0.18 mm. This contrasts with Abdel Razik et al., who found a significantly thicker endometrium after IMN (11.12 ± 2.19 mm versus 10.32 ± 1.11 mm, P=0.01) [15], and with the meta-analysis by Gadalla et al., in which CC alone produced a thinner endometrium than CC combined with an NO donor (weighted mean difference -1.75 mm) [6]. Similar improvements have been reported with sildenafil added to CC, with endometrial thickness of 10.4 ± 1.4 mm versus 9.2 ± 1.9 mm (P=0.007) [17] and 9.6 ± 1.2 mm versus 8.7 ± 1.0 mm (P=0.003) [18], and a pooled weighted mean difference of 1.22 mm in women with thin endometrium [20]. One plausible explanation for the smaller effect in our study is that participants were not selected for a thin endometrium. The mean trigger-day thickness with CC alone was 8.05 mm, considerably greater than the 6.3 ± 1.1 mm reported with CC by Roy et al. [26], leaving less room for improvement. Takasaki et al. demonstrated that vasoactive therapy, including vaginal sildenafil, improved radial artery RI and endometrial thickness in 92% of women specifically selected for a thin endometrium and high uterine radial artery impedance [25], suggesting that the benefit of vasodilators may be concentrated in women with impaired endometrial perfusion. Importantly, the lack of a meaningful difference in thickness does not preclude an effect on receptivity, since the meta-analysis by Weiss et al. found no association between preovulatory endometrial thickness and pregnancy in stimulated IUI cycles [7].

Endometrial and Uterine Perfusion: The most notable perfusion finding in our study was the higher proportion of women with zone 4 endometrial vascularity in the IMN group (53.3% versus 33.3%). Although not statistically significant, this 20 percentage point difference is biologically consistent with the vasodilatory action of NO on the subendometrial microcirculation and with the higher endometrial flow index reported with IMN by Abdel Razik et al. (11.27 ± 2.18 versus 10.18 ± 2.78, P=0.02) [15]. Deeper endometrial vascular penetration is considered favourable for implantation [9], and Riad and Hak showed in stimulated IUI cycles that lower subendometrial RI and PI were associated with successful implantation, with CC stimulation yielding the lowest implantation rate [8]. Acute vaginal administration of IMN has also been shown to significantly increase subendometrial vascularisation indices in women with recurrent miscarriage (P<0.001) [14].

Uterine artery Doppler findings were less clear. The significant within-group decrease in left uterine artery RI in the IMN group, and the lower absolute PI values on trigger day, are in keeping with the reductions in uterine artery impedance reported with IMN (RI 0.77 ± 0.22 versus 0.84 ±

0.11, P=0.03) [15], with vaginal sildenafil [13] and with sildenafil in women with a thin endometrium (weighted mean difference in radial artery RI -0.12) [20].

However, all four indices also fell significantly in the control group, reflecting the physiological periovulatory decline in uterine artery impedance that accompanies rising oestradiol levels, and trigger-day RI values were numerically lower in controls. The significantly lower baseline right uterine artery PI in the IMN group further complicates interpretation of change scores. Contrasting evidence also exists: transdermal nitroglycerin did not change the uterine artery PI in IVF patients [23], and Lees et al. observed a paradoxical increase in uterine artery RI (0.93 to 1.00) and PI (3.77 to 4.99) after a nitric oxide donor in oligomenorrhoeic women with polycystic ovaries (P<0.05) [24], indicating that uterine vascular responses to NO donors vary with the underlying endocrine and vascular milieu. It should also be noted that the absolute RI values in our study were lower than those reported by Abdel Razik et al. [15], which may reflect differences in sampling technique and limits direct comparison. Main uterine artery indices reflect global uterine blood flow and may be less sensitive to local endometrial perfusion than zonal assessment, which may explain why a trend was apparent in zonal flow but not in trigger-day uterine artery indices.

Safety: Vaginal IMN at a dose of 10 mg daily was well tolerated. Mild headache occurred in two women (6.7%), no treatment was discontinued, and no case of OHSS was recorded. This compares favourably with a randomised study of vaginal IMN 40 mg for cervical ripening at term, in which headache and palpitations were significantly more frequent than with placebo and changes in maternal blood pressure and pulse rate were observed [29], and with trials of sildenafil added to CC, in which headache was reported by 20.0% [17] and 9.2% [19] of treated women. Dose selection is relevant not only for tolerability but also for efficacy, since experimental data show that high concentrations of NO donors inhibit embryo development and implantation in a dose-dependent manner [30]. The low vaginal dose used in our study therefore appears to offer a reasonable balance between local vascular effect and safety.

Strengths and limitations: The strengths of this study include its randomised design, a standardised stimulation, trigger, insemination and luteal support protocol applied identically in both groups, comprehensive assessment of both follicular and endometrial parameters with Doppler evaluation at two time points, and its conduct in a public-sector setting that reflects routine practice in India. Several limitations must be acknowledged. Most importantly, only 60 women were enrolled against an estimated requirement of 68 per group, so the study had low power and wide confidence intervals, and a clinically important benefit cannot be excluded. The design was open-label without a placebo, and sonographers were not blinded, introducing the possibility of performance and measurement bias. Simple randomisation in a small sample resulted in baseline imbalance in the history of hypothyroidism and in right uterine artery PI; although TSH levels were comparable and well controlled, residual confounding cannot be ruled out. Outcomes were assessed over a single cycle, and ongoing pregnancy, miscarriage and live birth were not reported. Multiple secondary comparisons increased the likelihood of chance findings, and the reproducibility of Doppler measurements was not formally assessed.

Implications for Practice and Research: IMN is inexpensive, widely available and simple to administer, which makes it an attractive candidate adjuvant in resource-limited IUI programmes. The consistency of our effect estimate with pooled data on NO-pathway agents supports further evaluation rather than routine use.

Future research should take the form of adequately powered, multicentre, double-blind, placebo-controlled trials with live birth as the primary outcome, and should examine whether benefit is concentrated in women with a thin endometrium or impaired endometrial perfusion, the optimal dose and timing of IMN relative to CC, and cumulative outcomes over several cycles.

Conclusion

In women with ovulatory cycles, patent tubes and normal partner semen parameters undergoing clomiphene citrate-stimulated intrauterine insemination, adjuvant vaginal isosorbide mononitrate 10 mg daily was safe and well tolerated. Its use was associated with a higher clinical pregnancy rate (13.3% versus 10.0%), a greater proportion of women with zone 4 endometrial vascularity on trigger day (53.3% versus 33.3%), a slightly thicker trigger-day endometrium and a significant within-group reduction in left uterine artery resistance index, together with more dominant follicles in the left ovary on trigger day.

However, apart from the difference in left ovarian dominant follicles, these differences did not reach statistical significance, and endometrial thickness and uterine artery indices improved significantly in both groups, reflecting the normal periovulatory changes of a stimulated cycle.

The observed relative risk for clinical pregnancy of 1.33 lies close to pooled estimates reported for agents acting through the nitric oxide pathway, but

the wide confidence interval reflects the limited sample size and precludes firm conclusions about efficacy. On the basis of the present evidence, isosorbide mononitrate cannot yet be recommended as a routine adjuvant to clomiphene citrate in IUI cycles. Its favourable safety profile, low cost and biologically plausible effect on endometrial perfusion justify adequately powered, blinded, placebo-controlled multicentre trials with live birth as the primary outcome, preferably targeting women with a thin endometrium or poor endometrial blood flow, in whom the benefit of vasodilator therapy is most likely to be realised.

Declarations

Ethics Approval and Consent to Participate: The study was approved by the Institutional Ethics Committee of Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi [approval reference number]. Written informed consent was obtained from all participants.

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Data Availability: The data supporting the findings of this study are available from the corresponding author on reasonable request.

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