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RESEARCH ARTICLE

INTRAUTERINE AUTOLOGOUS PLATELET-RICH PLASMA FOR THIN ENDOMETRIUM IN CLOMIPHENE CITRATE–INDUCED CYCLES: A PRE- AND POST-INTERVENTIONAL STUDY

Chanchal Banjare, Ruchi Kishore, Rajesh Singh and Piyush Bhargava

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Abstract

Background: Clomiphene citrate (CC) is first-line therapy for World Health Organization type II anovulation, but its anti-oestrogenic action often leaves the endometrium thin, underlying the gap between its high ovulation rates and far lower conception rates. Autologous platelet-rich plasma (PRP), rich in growth factors, has been proposed to rescue such cycles.

Objectives: To determine whether intrauterine PRP increases endometri al thickness in women with a persistently thin endometrium on CC, and to record the clinical pregnancy rate.

Methods: This pre- and post-interventional study was conducted in a tertiary teaching hospital in central India. Forty infertile women with endometrial thickness under 7 mm on the day of trigger were enrolled. CC 50 mg was given daily for five days from day 2, and 1 mL of autologous PRP was instilled intrauterine on days 8 and 10 of the subsequent induced cycle. Thickness was measured sonographically before and after intervention. Paired t-tests and the chi-square test were applied ($p < 0.05$).

Results: Mean age was 27.62 ± 3.54 years and 72.5% had primary infertility. Mean endometrial thickness raised from 5.10 ± 1.19 mm to 7.43 ± 0.73 mm, a gain of 2.33 mm ($p < 0.001$). The increase was significant within every follicle-stimulating hormone, anti-Müllerian hormone, thyroid, prolactin and body mass index subgroup. Gains were largest where the endometrium was thinnest, averaging 4.35 mm below 3 mm. Six women (15.0%) conceived. No adverse events occurred.

Conclusion: Intrauterine PRP produced a consistent, significant increase in endometrial thickness across all subgroups, greatest in the thinnest endometria. It was simple and well tolerated, but the modest pregnancy rate and uncontrolled design mean randomised comparison remains necessary.

Introduction:-

Infertility affects roughly one couple in eight worldwide, and disordered ovulation accounts for close to a fifth of these cases.[1] The great majority of anovulatory women have gonadotrophin concentrations within the reference

Corresponding Author:- Chanchal Banjare

range and are classified as World Health Organization type II, a group dominated by polycystic ovary syndrome and characterised clinically by oligomenorrhoea or amenorrhoea.[2,3] For more than six decades clomiphene citrate has been the drug of first resort in this population.[4] Acting as a selective oestrogen receptor modulator, it blocks hypothalamic oestrogen receptors, releases the pituitary from negative feedback and provokes the follicle-stimulating hormone surge that drives folliculogenesis.[5]

The difficulty is that ovulation and conception do not follow one another as closely as might be expected. Clomiphene induces ovulation in 60% to 85% of treated women, yet cumulative pregnancy rates after six cycles remain in the region of 10% to 20%.[6] This discordance has long been attributed to the very property that makes the drug effective centrally. Because clomiphene occupies oestrogen receptors indiscriminately, its action at the endometrium and cervix is antagonistic rather than agonistic, blunting proliferation of the functionalis and reducing uterine perfusion at precisely the point in the cycle when both are needed.[7]

Endometrial thickness has become the practical surrogate for receptivity in this setting. A minimum of 7 mm on the day of trigger is widely accepted as the threshold below which implantation becomes substantially less likely,[8] and thin endometrium has been reported in anywhere between 15% and half of clomiphene cycles depending on the population and the criteria applied.[9] The clinical consequence is a cycle that is technically successful — a dominant follicle, a documented ovulation — but reproductively futile.

A considerable number of adjuvants have been tried in an attempt to close this gap, among them supplementary oestrogen, low-dose aspirin, vaginal sildenafil, pentoxifylline and granulocyte colony-stimulating factor.[10] None has proved reliably effective, and a substantial minority of women remain refractory to all of them. This therapeutic impasse has directed attention towards regenerative approaches.

Autologous platelet-rich plasma is prepared by centrifuging the patient's own blood to concentrate the platelet fraction. Activated platelets release a cocktail of mediators — vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor and transforming growth factor among them — that together promote angiogenesis, cellular proliferation and matrix remodelling.[11,12] Because the preparation is derived from the patient, questions of immunogenicity and disease transmission largely fall away. The first report of intrauterine PRP for thin endometrium appeared in 2015,[13] and subsequent series and trials have described gains in thickness and, less consistently, in pregnancy rates.[14,15]

Most of this literature, however, concerns frozen-thawed embryo transfer and in vitro fertilisation, where the endometrium is prepared with exogenous hormones. Evidence drawn specifically from clomiphene-induced cycles, in which the mechanism of thinning is pharmacological antagonism rather than atrophy or scarring, remains comparatively sparse.[16,17]The present study was undertaken to address that gap, examining whether intrauterine PRP can restore endometrial thickness in women whose endometrium fails to develop adequately on clomiphene, and whether such restoration translates into pregnancy.

Materials and Methods:-

This pre- and post-interventional study was conducted in the Department of Obstetrics and Gynaecology of a tertiary teaching hospital in Raipur, Chhattisgarh, India. The protocol was approved by the Institutional Ethics Committee and written informed consent, explained in the participant's own language, was obtained before enrolment.

Infertile women attending the outpatient clinic who had been induced with clomiphene citrate and whose endometrial thickness measured less than 7 mm on the day of trigger were eligible. Women who declined consent were excluded. Because no comparable published series was available from which to derive an effect size, complete enumeration sampling was used and recruitment continued until 40 participants had been enrolled.

At enrolment, age, weight, body mass index, duration of marriage, presenting complaint, menstrual pattern and coexisting medical disorders were recorded. Serum thyroid-stimulating hormone, anti-Müllerian hormone, follicle-stimulating hormone and prolactin were measured, and the partner's semen analysed. Baseline ultrasonography documented endometrial thickness, antral follicle number and dominant follicle size.

Each participant received clomiphene citrate 50 mg daily for five days from day 2. In the subsequent induced cycle, 1 mL of autologous PRP, prepared by centrifugation of autologous venous blood in the institutional laboratory, was instilled into the uterine cavity through an insemination catheter under aseptic conditions on days 8 and 10.

Endometrial thickness was reassessed on day 8, on the day of trigger and two days after ovulation. Participants were followed until a positive urine pregnancy test, clinical evidence of pregnancy, or the seventh day after the missed period.

Data were compiled in Microsoft Excel 2019 and analysed in SPSS version 23.0. Categorical variables are presented as frequency and percentage, continuous variables as mean ± standard deviation. Paired t-tests were used for within-subject comparison of endometrial thickness and the chi-square test for categorical associations. A two-tailed p-value below 0.05 was taken as significant.

Results:-

Forty women completed the protocol. Their baseline demographic and clinical characteristics are summarised in Table 1. The cohort was young, with a mean age of 27.62 ± 3.54 years and a range of 22 to 38 years, and three-quarters were between 21 and 30 years old. Mean body weight was 54.72 ± 8.47 kg and two-thirds had a body mass index within the normal range. Three-quarters had been married for five years or less. Primary infertility predominated, and all but one woman menstruated regularly.

Table 1. Baseline demographic and clinical profile of participants (n = 40)

Characteristic	Category	n	%
Age (years)	21–30	30	75.0
	31–40	6	15.0
	Mean ± SD	27.62 ± 3.54	Range 22–38
Weight (kg)	41–60	33	82.5
	61–80	6	15.0
	> 80	1	2.5
	Mean ± SD	54.72 ± 8.47	Range 43–83
Body mass index	Normal	27	67.5
	Overweight	9	22.5
	Obese	4	10.0
Duration of marriage (years)	1–5	30	75.0
	6–10	9	22.5
	> 10	1	2.5
Type of infertility	Primary	29	72.5
	Secondary	11	27.5
Menstrual pattern	Regular	39	97.5
	Irregular	1	2.5
Coexisting disorder	Hypothyroidism	4	10.0
	Hyperprolactinaemia	2	5.0
	Polycystic ovary syndrome	1	2.5
	Sickle cell trait	1	2.5

The endocrine profile of the cohort is shown in Table 2. Ovarian reserve was broadly preserved: two-thirds had an anti-Müllerian hormone concentration between 1.5 and 3.5 ng/mL and only five women fell below 1.5 ng/mL. Follicle-stimulating hormone lay between 5 and 10 mIU/mL in just over two-thirds. Mild thyroid and prolactin abnormalities were present in a minority. The partner's semen analysis was normal in 38 of the 40 couples; the two abnormal samples, one showing pyospermia and one reduced motility, were treated before the study cycle. The mean antral follicle count was 8.37 ± 3.42.

Table 2. Baseline endocrine profile and partner semen analysis (n = 40)

Parameter	Category	n	%
Thyroid-stimulating hormone (mIU/L)	≤ 3	29	72.5
	> 3	11	27.5
	Mean ± SD	2.50 ± 1.41	Range 0.4–8.01
Anti-Müllerian hormone (ng/mL)	< 1.5	5	12.5

	1.5–3.5	26	65.0
	> 3.5	9	22.5
Follicle-stimulating hormone (mIU/mL)	< 5	13	32.5
	5–10	27	67.5
	Mean ± SD	5.80 ± 1.69	Range 2.25–8.9
Serum prolactin (ng/mL)	≤ 28	33	82.5
	> 28	7	17.5
Partner semen analysis	No abnormality	38	95.0
	Pyospermia	1	2.5
	Reduced motility	1	2.5

The primary outcome is presented in Table 3. Mean endometrial thickness rose from 5.10 ± 1.19 mm before treatment to 7.43 ± 0.73 mm afterwards, an absolute gain of 2.33 mm, and the difference was highly significant on paired analysis ($p < 0.001$). The narrowing of the standard deviation is as notable as the shift in the mean: the post-treatment distribution was appreciably more compact, indicating that the intervention brought outlying endometria towards a common range rather than simply adding a fixed increment to every participant. Stratification by baseline thickness makes this clearer. Women who began with an endometrium thinner than 3 mm gained an average of 4.35 mm, those in the 3 to 4.9 mm band gained 2.96 mm, and those already between 5 and 7 mm gained 1.85 mm. The response was therefore inversely proportional to the starting thickness, and after treatment every participant reached at least 5 mm.

Table 3. Endometrial thickness before and after PRP, overall and by baseline stratum (n = 40)

Baseline stratum	n (%)	ET before PRP (mm)	Mean ET after PRP (mm)	Mean gain (mm)	p
Overall cohort	40 (100.0)	5.10 ± 1.19	7.43 ± 0.73	2.33	< 0.001
< 3 mm	4 (10.0)	—	6.38	4.35	< 0.001
3–4.9 mm	10 (25.0)	—	7.19	2.96	
5–7 mm	26 (65.0)	—	7.68	1.85	

ET, endometrial thickness; PRP, platelet-rich plasma.

Table 4 shows the response within endocrine and anthropometric subgroups. The increase in endometrial thickness was statistically significant in every stratum examined. Neither ovarian reserve, as reflected by anti-Müllerian hormone, nor basal follicle-stimulating hormone, thyroid status, prolactin concentration or body mass index abolished the effect. Post-treatment thickness clustered tightly between 7.04 and 7.75 mm across all twelve subgroups despite pre-treatment means ranging from 4.33 to 5.75 mm, which again suggests convergence towards a ceiling rather than a uniform additive gain.

Table 4. Endometrial response by endocrine and anthropometric subgroup (n = 40)

Stratifying variable	Category	n (%)	ET before PRP (mm)	ET after PRP (mm)	p
Follicle-stimulating hormone (mIU/mL)	< 5	13 (32.5)	4.33 ± 1.64	7.27 ± 0.74	< 0.001
	5–10	27 (67.5)	5.40 ± 0.97	7.50 ± 0.73	< 0.001
Anti-Müllerian hormone (ng/mL)	< 1.5	5 (12.5)	4.38 ± 1.60	7.04 ± 1.19	0.0193
	1.5–3.5	26 (65.0)	5.21 ± 1.20	7.50 ± 0.65	< 0.001
	> 3.5	9 (22.5)	4.95 ± 1.47	7.43 ± 0.71	0.0007
Thyroid-stimulating hormone (mIU/L)	≤ 3	29 (72.5)	5.10 ± 1.23	7.75 ± 0.56	< 0.001
	> 3	11 (27.5)	5.03 ± 1.35	7.31 ± 0.76	< 0.001
Serum prolactin (ng/mL)	≤ 28	33	5.07 ± 1.31	7.41 ± 0.78	<

		(82.5)			0.001
	> 28	7 (17.5)	4.94 ± 1.39	7.50 ± 0.48	0.0020
Body mass index	Normal	27 (67.5)	4.87 ± 1.46	7.40 ± 0.78	< 0.001
	Overweight	9 (22.5)	5.27 ± 0.97	7.50 ± 0.49	< 0.001
	Obese	4 (10.0)	5.75 ± 0.23	7.47 ± 1.02	0.0400

ET, endometrial thickness; PRP, platelet-rich plasma.

Cycle outcome is given in Table 5. Six of the 40 women (15.0%) achieved a clinical pregnancy. No local or systemic adverse effect was recorded in any participant, and no procedure had to be abandoned.

Table 5. Cycle outcome following PRP instillation (n = 40)

Outcome	n	%
Clinical pregnancy achieved	6	15.0
Not conceived	34	85.0
Adverse events recorded	0	0.0

Discussion:-

The central observation is straightforward: in women whose endometrium failed to develop adequately on clomiphene citrate, two intrauterine instillations of autologous platelet-rich plasma were followed by a mean increase of 2.33 mm, from 5.10 mm to 7.43 mm, carrying the group mean across the 7 mm threshold conventionally regarded as compatible with implantation. The effect was highly significant and was reproduced in every subgroup examined.

The magnitude of this change sits within the range described elsewhere. Chang and colleagues, in the first published application, reported growth from approximately 5 mm to above 7 mm in refractory thin endometrium during in vitro fertilisation.[13] Zadehmodarres and co-workers observed a comparable increase in a pilot series,[18] and Tandulwadkar's group documented similar gains before frozen embryo transfer.[14] Randomised evidence is broadly supportive: Nazari and colleagues found significantly greater expansion with PRP than with standard preparation,[15] and a recent meta-analysis concluded that PRP increases both thickness and clinical pregnancy rates.[19]

What distinguishes this cohort is the context in which the endometrium was thin. Most published work concerns hormonally prepared cycles for embryo transfer, where thinning reflects atrophy, adhesions or previous instrumentation. Here the mechanism is pharmacological: clomiphene's occupancy of endometrial oestrogen receptors is a functional, self-limiting blockade rather than structural tissue loss.[20] A receptive substrate is therefore to be expected, and the near-uniform response observed is consistent with that. The two studies closest in design support this reading. Morad and colleagues, in a self-controlled trial of PRP during clomiphene therapy, reported a comparable baseline thickness and a similar direction of change,[16] and Özyurt and co-workers, comparing clomiphene plus PRP against clomiphene alone, found significantly greater endometrial expansion in the PRP arm.[17]

Two features of the data deserve emphasis. First, the response was inversely related to baseline thickness: women beginning below 3 mm gained 4.35 mm, while those already between 5 and 7 mm gained 1.85 mm. Second, and consistent with this, the post-treatment values converged into a narrow band between roughly 7.0 and 7.8 mm across all twelve subgroups, even though pre-treatment means differed by nearly a millimetre and a half. Taken together these observations suggest that PRP does not add a fixed increment but rather restores the endometrium towards its physiological potential, with the greatest apparent benefit where the deficit is largest. This has an obvious practical corollary — the women most likely to gain are those currently considered least salvageable — though regression to the mean cannot be excluded as a partial explanation in an uncontrolled design and the subgroup with the thinnest endometrium contained only four participants.

The absence of any modifying effect from ovarian reserve, thyroid status, prolactin or body mass index is also noteworthy. Obesity is known to impair the response to ovulation induction,[20] yet obese participants here reached a post-treatment thickness indistinguishable from that of normal-weight women. This suggests the endometrial action of PRP is largely independent of the systemic endocrine milieu — plausible, since the growth factors are delivered directly to the target tissue and act locally.[11,12]

The clinical pregnancy rate of 15.0% is the least encouraging finding and requires candid interpretation. It is lower than several published series, and it demonstrates that thickening the endometrium is not synonymous with restoring receptivity. Thickness is a convenient sonographic proxy, but implantation depends additionally on vascularity, glandular maturation, molecular receptivity and embryo quality, none of which was assessed here. A structurally adequate but functionally unreceptive endometrium remains entirely possible, and the gap between the near-universal morphological response and the modest reproductive one is a useful corrective to over-interpretation of thickness alone.

Several limitations constrain these conclusions. The study was single-armed, so the contribution of PRP cannot be separated from that of the second clomiphene cycle or from spontaneous cycle-to-cycle variation. The sample of 40 was modest and drawn from a single centre, and follow-up ended at clinical pregnancy, leaving live birth unrecorded. PRP was not standardised to a defined platelet concentration, limiting reproducibility across centres. Endometrial thickness was measured transabdominally, which is less precise than the transvaginal approach.

Notwithstanding these caveats, the procedure was simple, inexpensive, performed in the outpatient setting and free of adverse effects. For women who ovulate satisfactorily yet cannot conceive, and whose alternative is escalation to gonadotrophins with their cost and risk of multiple pregnancy, an autologous intervention of this kind is attractive. Adequately powered randomised trials with standardised preparation and live birth as the endpoint are the necessary next step.

Conclusion:-

Intrauterine instillation of autologous platelet-rich plasma produced a significant increase in endometrial thickness in women with a thin endometrium in clomiphene citrate–induced cycles, raising the group mean above the 7 mm threshold and benefiting every endocrine and anthropometric subgroup examined. The gain was greatest where the endometrium was thinnest. The intervention was safe, technically undemanding and well tolerated, but the modest clinical pregnancy rate indicates that improved thickness alone does not guarantee conception. Randomised controlled trials with standardised preparation protocols and live birth as the primary endpoint are needed before the technique can be recommended for routine use.

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