

Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: A pilot study

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Abstract

Aim: To evaluate differences in uteroplacental blood flow and pregnancy outcome in women with idiopathic recurrent spontaneous miscarriage (IRSM) following administration of micronized vaginal progesterone and oral dydrogesterone.

Methods: One hundred and thirty-three women (aged 23–40 years) who had had early miscarriages and spontaneous conception participated. Oral dydrogesterone (group A, $n = 51$) and micronized vaginal progesterone (group B, $n = 50$) were administered for luteal support and compared. Pregnant women without history of recurrent miscarriage served as controls (group C, $n = 32$). The outcome measures consisted of endometrial blood flow parameters by Doppler indices and ongoing pregnancy rate.

Results: Before progesterone supplementation, resistivity index (RI) and pulsatility index (PI) were found to be significantly higher in groups A and B as compared to controls. Although statistically not significant, end diastolic velocity (EDV) and systolic/diastolic (S/D) ratio was found to be superior in controls than IRSM women. Peak systolic velocity (PSV) was comparable between IRSM and non-IRSM groups. Following progesterone supplementation, groups A and B showed a highly significant reduction in RI, PI and an increase in EDV. A relative increase in the value of PSV was observed in group A as compared to group B. There was remarkable difference in S/D in both groups. Although not statistically significant, group C showed reduction in RI, PI, PSV, EDV and S/D ratio. Pregnancy salvage rates were higher in group A (92.0%) as compared to group B (82.3%).

Conclusion: Progesterone supplementation appears to lower vascular resistance in women with IRSM. Oral dydrogesterone appears to be equally effective in improving endometrial blood flow as compared with micronized progesterone.

Key words: dydrogesterone, endometrial blood flow, endometrial receptivity, idiopathic recurrent miscarriage, micronized vaginal progesterone, progesterone supplementation.

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Introduction

Recurrent spontaneous miscarriage is defined as three or more consecutive pregnancy losses within 20 weeks of gestation. The etiology of this disorder remains unsolved in nearly 50% of these cases.¹ An unresponsive endometrium, leading to abnormal implantation, is considered to be a key factor contributing to idiopathic recurrent spontaneous miscarriage (IRSM). Structural and functional modifications of the endometrial vasculature are essential for endometrial receptivity during the implantation window.²⁻⁴ Uterine perfusion is one of the major factors regulating uterine receptivity and is of great importance in achieving a normal pregnancy.⁵ Increased uterine artery vascular resistance and reduced uterine blood flow have been used as predictors of high-risk pregnancies, which also may be the likely causes of IRSM.⁶

In IRSM, uterine artery vascular resistance is increased, as reflected by increased pulsatility index (PI). Pulsed Doppler ultrasonography has provided the means for non-invasive evaluation of uterine impedance and can be used to identify impaired uterine perfusion in woman with recurrent pregnancy loss.⁷ It is well established that during pregnancy, progesterone (P)-induced nitric oxide (NO) contributes to improved vascularity by lowering uteroplacental vascular resistance. Dydrogesterone is a synthetic progestin and its chemical structure has a strong affinity for the P receptor (PR). The structure of dydrogesterone is similar to that of natural progesterone and is largely converted to its stable metabolite, 20- α -dihydrodydrogesterone.⁸ Differences in pharmaco-biological actions amongst different progestins suggest different types of signaling action after being bound to either progesterone (PR)-A or PR-B receptors.⁹

The objective of the present study is to evaluate differences, if any, in uteroplacental blood flow parameters and pregnancy outcome following administration of two types of progestins, micronized vaginal progesterone and oral dydrogesterone, in women with IRSM.

Methods

This prospective, randomized, single-blinded comparative study was carried out in the Institute of Reproductive Medicine, a tertiary infertility care unit at Kolkata, India. The study was approved by the institutional ethics committee and informed consent was obtained from all couples. A total of 133 women (aged 23–40 years) were included out of whom 101 women

had three or more consecutive miscarriages within the first trimester (up to 12 weeks of gestation) followed by spontaneous conception. The remaining 32 pregnant women without history of recurrent miscarriage served as controls. Only women who were euthyroid, normoprolactinemic and had not received any medication in the last 3 months were considered. The following tests were performed to confirm that there was no apparent cause of recurrent pregnancy loss: thyroid-stimulating hormone and antithyroid antibody tests, antiphospholipid antibodies test (anticardiolipin antibodies and lupus anticoagulants immunoglobulin G and M), TORCH (toxoplasmosis, rubella, cytomegalovirus and herpes) tests, paternal and maternal chromosomal analysis, hysterosalpingography, and hysteroscopy to rule out uterine defects, abnormal fasting level of homocysteine, exclusion of diabetes mellitus, and estimation of midluteal serum progesterone to exclude luteal phase defect.

Next, women with IRSM were randomly assigned into group A ($n = 50$), group B ($n = 51$) and group C ($n = 32$). The enrolled participants in group A and B were counseled, and informed consent was obtained before randomization, as per the institution's protocol. Sequentially numbered sealed envelopes were prepared and provided by the study coordinator, according to simple randomization. Single-blinding was achieved by keeping study investigators and sonologist unaware of the type of protocol used. A double-blind study protocol was not possible because the drug delivery methods in the two groups were different.

While women in group A received 10 mg oral dydrogesterone (Duphaston; Solvay Pharma India, Mumbai, India) twice daily, group B women were treated with 100 mg micronized vaginal progesterone (P) (Utrogestan; Solvay Pharma India) thrice daily. Ongoing clinical pregnancy, viable delivery and miscarriage rates were considered to be the primary outcome measures in both groups. Women without history of recurrent miscarriage in the control group ($n = 32$) did not receive any progesterone. Two women were initially included as negative controls and not given progesterone supplementation for recurrent miscarriage. However, they had to be excluded from the study because one of them developed spotting and had to be supplemented with progesterone from 8 weeks onwards. The second woman had spontaneous miscarriage at 9 weeks, before progesterone could be initiated.

The presence of a viable fetus on ultrasound scan, performed at 6 or 7 weeks after conception, is defined

as clinical pregnancy. At least one viable fetus at 28 weeks of gestation was termed as ongoing pregnancy. Data related to obstetric problems in the second and third trimester such as pre-eclamptic toxemia, antepartum hemorrhage and gestational diabetes were not included in the present study because the objective was to compare two types of progesterone in terms of their efficacy in the prevention of miscarriage recurrence and/or continuation of pregnancy. Further, baseline uterine artery Doppler indices including PI, resistance index (RI), peak systolic velocity (PSV), end diastolic velocity (EDV) and systolic to diastolic (S/D) ratio were measured while confirming pregnancy at 6–7 weeks of gestation. After 4 weeks, Doppler assessment was performed again and the indices estimated. Endometrial blood flow was assessed at 6 and 10 weeks of pregnancy. Oral dydrogesterone and micronized progesterone were continued up to 12 weeks in groups A and B, respectively.

Statistical analysis

All data were analyzed using commercially available software packages SPSS version 10.0 (SPSS, Chicago, IL, USA) and Ky-Plot version 2.0 b13. Pregnancy rates in the two groups were statistically compared using the χ^2 -test. All values are presented as mean \pm standard deviation or percentage, unless otherwise stated. Differences were considered to be significant at $P < 0.05$.

Results

Demographic profiles of pregnant women from all three groups are summarized in Table 1. On comparing the Doppler indices before progesterone supplementation, RI and PI were found to be significantly higher in the IRSM cases (groups A and B) as compared to the

non-IRSM (group C). Although EDV and S/D were found to be superior in non-IRSM than IRSM cases, the values were not statistically significant. PSV was observed to be comparable between IRSM and non-IRSM groups (Table 3).

Following progesterone supplementation of 4 weeks, both groups A and B showed a highly significant reduction in RI ($P < 0.0001$) and PI ($P < 0.0001$) after 4 weeks as compared with the baseline levels (Table 2). Similarly, both groups showed a significant increase in EDV. PSV increased significantly in group A ($P < 0.001$) after oral progesterone support. Though PSV increased in group B, the values were not statistically significant. Following progesterone supplementation, a significant decrease in S/D ratio was observed in both groups ($P < 0.001$). The number of take-home babies was 20 and 19 for groups A and B, respectively. Six miscarriages were recorded for group A and 11 for group B. The number of ongoing pregnancies were 24 for group A and 22 in group B. Pregnancy salvage rates were higher in group A (92.0%) as compared to group B (84.3%). Group C showed reduction in RI, PI, PSV, EDV and S/D ratio after 4 weeks of pregnancy, however, it was not statistically significant. There were no miscarriages recorded in the control group (Table 3).

Discussion

It is established that women with recurrent pregnancy loss have a relatively increased level of PI in the uterine artery.¹⁰⁻¹¹ To counteract this condition of inadequate vascularity to the developing embryo in women with IRSM, agents like progesterone are used to ameliorate uterine blood flow.¹¹ Additional physiological supportive functions of progesterone during pregnancy

Table 1 Demographic profile of women with recurrent spontaneous miscarriage (group A and group B) and without history of recurrent spontaneous miscarriage (group C)

Doppler indices	Oral dydrogesterone (group A)	Vaginal progesterone (group B)	Controls (group C)
Age	28.8 \pm 3.02	28.87 \pm 3.20	28.69 \pm 2.86
BMI	27.78 \pm 1.64	27.92 \pm 1.57	27.16 \pm 1.91
ET	8.78 \pm 1.58	8.80 \pm 1.52	9.07 \pm 1.70
S. estradiol	229.2 \pm 57.97	224.7 \pm 59.2	209.9 \pm 64.97
S. progesterone	18.18 \pm 3.67	17.88 \pm 3.51	19.33 \pm 3.07
No. of miscarriages	4	8	0
No. of ongoing pregnancies	26	24	32
No. of viable deliveries	20	19	0

BMI, body mass index; ET, endometrial thickness; S. estradiol, serum estradiol.

Table 2 Endometrial Doppler blood flow indices in women receiving oral dydrogesterone (group A), vaginal progesterone (group B) and non-IRSM (group C)

Doppler indices	Oral dydrogesterone (group A)		Vaginal progesterone (group B)		Non-IRSM (group C)	
	Baseline (at 7 weeks of pregnancy)	After 4 weeks (at 12 weeks of pregnancy)	Baseline (at 7 weeks of pregnancy)	After 4 weeks (at 12 weeks of pregnancy)	Baseline (at 7 weeks of pregnancy)	After 4 weeks (at 12 weeks of pregnancy)
RI	0.779 ± 0.14	0.638 ± 0.15	0.771 ± 0.11	0.625 ± 0.12	0.704 ± 0.12	0.669 ± 0.11
PI	1.705 ± 0.57	1.274 ± 0.47	1.670 ± 0.45	1.221 ± 0.40	1.448 ± 0.34	1.272 ± 0.36
PSV	32.436 ± 8.06	38.406 ± 12.26	32.900 ± 8.91	35.393 ± 7.75	33.24 ± 7.10	35.53 ± 9.65
S/D	4.047 ± 1.70	3.029 ± 0.76	4.300 ± 1.68	3.096 ± 1.15	3.68 ± 0.65	3.10 ± 0.82
EDV	8.906 ± 2.86	14.102 ± 6.57	8.917 ± 3.98	13.399 ± 6.54	9.39 ± 2.68	12.19 ± 4.94

Data presented as mean ± standard deviation. EDV, end diastolic velocity; IRSM, idiopathic recurrent spontaneous miscarriage; NS, not significant; PI, pulsatility index; PSV, peak systolic velocity; RI, resistivity index; S/D, systolic/diastolic.

Table 3 Comparison of endometrial Doppler blood flow indices before and after receiving oral dydrogesterone (group A), vaginal progesterone (group B) with non-IRSM (group C) women

Doppler indices	Baseline (at 7 weeks of pregnancy)		After 4 weeks (at 12 weeks of pregnancy)		P-value
	Group A (n = 50)	Group B (n = 51)	Group A (n = 50)	Group B (n = 51)	
RI	0.779 ± 0.14	0.771 ± 0.11	0.638 ± 0.15	0.625 ± 0.12	ab NS bc 0.005 ca NS
PI	1.705 ± 0.57	1.670 ± 0.45	1.274 ± 0.47	1.221 ± 0.40	ab NS bc 0.009 ca 0.012
PSV	32.436 ± 8.06	32.900 ± 8.91	38.406 ± 12.26	35.393 ± 7.75	ab NS bc NS ca NS
S/D	4.047 ± 1.70	4.300 ± 1.68	3.029 ± 0.76	3.096 ± 1.15	ab NS bc 0.02 ca NS
EDV	8.906 ± 2.86	8.917 ± 3.98	14.102 ± 6.57	13.399 ± 6.54	ab NS bc NS ca NS

EDV, end diastolic velocity; IRSM, idiopathic recurrent spontaneous miscarriage; NS, not significant; PI, pulsatility index; PSV, peak systolic velocity; RI, resistivity index; S/D, systolic/diastolic.

include myometrial quiescence and immunological modulation for endometrial receptivity, which further help in implantation and maintenance of pregnancy.

Progesterone upregulates endothelial nitric oxide synthase (eNOS) expression in uterine and spiral arteries necessary for implantation.¹² It is well agreed upon that NO helps in vasodilatation, decidua formation, endometrial remodeling during trophoblast invasion¹³ and also regulates endometrial functions such as receptivity, implantation and menstruation.^{14,15}

Prior to progesterone supplementation, we found RI and PI to be significantly higher in women with IRSM as compared to controls. However, following exogenous administration of progesterone for 4 weeks, improvement in endometrial blood flow in both the groups became apparent, with the Doppler indices comparable between the two groups. There are evidences suggesting that vascular effects of natural micronized progesterone and synthetic progesterone may not be similar.^{16,17} Although dydrogesterone has close structural analogies with natural progesterone, dydrogesterone and its metabolite, dihydrodydrogesterone (DHD) significantly differ from progesterone and other synthetic progesterone like medroxyprogesterone acetate in terms of molecular signaling in human endothelial cells.¹⁷ A study on endometrial blood flow comparing oral dydrogesterone with micronized vaginal progesterone administration in pregnant women with IRSM has not been reported so far. The present study was, therefore, undertaken with an objective to evaluate the vascular effects of dydrogesterone compared with micronized progesterone.

In this study, both the drugs were found to be effective in improving the endometrial blood flow parameters. While dydrogesterone was more effective in improving all Doppler indices including PI, RI, PSV, EDV and S/D ratio, micronized progesterone did not show any significant differences with respect to PSV. The difference in pharmacological action of these two types of progesterone may be explained due to differences in their signaling action after being bound to progesterone receptor (PR)-A or PR-B. Expression of eNOS and NO synthesis at the endothelial cell level essentially occurs through PR-A receptors.¹⁸ We, therefore, hypothesize that the increased efficacy of dydrogesterone could be due to its enhanced affinity to PR-A receptors. Dysregulated eNOS synthesis may be prevented by myometrial quiescence and immunomodulatory changes on treatment with progesterone, especially with dydrogesterone and DHD.¹⁹ In addition

to NO synthesis, vascular effects of dydrogesterone are also attributed to its antithrombotic action, such as decrease in the expression of atherogenic adhesion molecules like vascular cell adhesion molecule 1 and intercellular adhesion molecule 1.²⁰

Summarizing, considerable improvement in uteroplacental blood flow parameters of pregnant women with IRSM is evident with progesterone supplementation. The concern regarding the efficacy of oral dydrogesterone compared to vaginal micronized progesterone is addressed. Oral dydrogesterone was found to be as effective as the commonly used vaginal gel. This finding opens up an opportunity for women with IRSM to opt for oral dydrogesterone owing to its ease of use, high tolerability and fewer side-effects. The vaginal route is not very well accepted by all patients because of side-effects such as vaginal irritation and discharge. In fact, in India, the oral route is preferred by most of the women because they find this route of administration more convenient. We propose that larger studies be undertaken to confirm the efficacy of oral dydrogesterone because, if found appropriate, its mode of administration would make it the drug of choice amongst quite a large number of women. Assessment of eNOS and NO expression in IRSM women following oral dydrogesterone administration is also suggested to validate the drug's mechanism of action.

Disclosure

No conflicts of interest are disclosed and no financial support was received.

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