Gynecology & Obstetrics
ISSN: 2161-0932

Pellicer-Iborra et al., Gynecol Obstet 2017, 7:9
DOI: 10.4172/2161-0932.1000451

Research Article OMICS International

Three-Dimensional Angiogenic Evaluation of the Effect of Mifepristone in Early Gestation: Pilot Study

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Received date: August 29, 2017**; Accepted date:** September 13, 2017; **Published date:** September 20, 2017

Abstract

Mifepristone (RU486) it is known as an effective abortifacient and postcoital contraceptive method, whose mechanism is not yet known. We carried on a pilot study with the aim of determining the effect that Mifepristone could have in utero-placental vascular compartment during the first trimester of pregnancy compared with placebo. This is a randomized, double-blind, placebo-controlled research. We randomly assigned to two groups patients requesting pregnancy termination with a gestational age between 9th and 11st weeks: Group A receiving placebo and Group B receiving RU. With transvaginal ultrasound tridimensional probe we measured at an initial time (t1) and then 4 hours after administration of Mifepristone or placebo (t2) Doppler parameters: uterine arteries mean Resistance Index, spiral arteries Resistance Index, intervillous flow, umbilical Resistance Index and tridimensional vascular settings and the placental volume. We observed how Mifepristone shows an immediate selective hemodynamic effect in trophoblastic tissue in the first hours of administration. A significant decrease in spiral arteries pulsatility index was demonstrated, without modifying uterine maternal and fetal territories or the other studied parameters. Angiopower 3D evaluation of the interface maternal fetal is complex and encourages to carry further investigations carry further investigations.

Keywords: Mifepristone; Earlypregnancy; 3d powerdoppler; Contraception trophoblast

Introduction

Mifepristone (RU486) was the first of Progesterone antagonists in which anti progesterone activity was shown to be an effective abortifacient and postcoital contraceptive method. The selective progesterone receptor modulators have been daily used in the treatment of endometriosis, uterine myomas and for meningioma treatment, however its uses will increase soon due to the potential clinical applications of these compounds [1,2].

RU486 is a local vasodilator inducing endometrial haemorrhage and in vitro it has seen that creates a haemorrhagic and fibrinolytic milieu around endometrial vessels and modifing the expression of blood vessel function regulators which are expressed in general stroma and glandular tissues [3-5]. Their administration leads to early changes in prostaglandin (PG) levels in perivascular cells of chorion villi that may result in an increase of spontaneous uterine activity and enhanced sensitivity to the PG analogues, this is the main reason to administer together mifepristone and prostaglandins with an interval between them [2-4]. This effect seems to occur through stimulating the release of cervical nitric oxide and prostaglandin E (PGE) [9]. The Food Drug Agency approved initially higher doses [2]. Additional the clinical evidence based regimens use low doses of mifepristone (200 mg) and have similar efficacy with a shorter timing between mifepristone and misoprostol dosing to allow women more flexibility and the FDA released the new label for mifepristone recommending the 200-mg dose based on this vast history of clinical efficacy [6,7].

Otherwise oral administration of Mifepristone achieves the maximum plasmatic level in two or three hours and cross placenta easily but the clinical effect does not seem to be depending so much on the dose, as it depends more in terms of an individual progesterone receptors susceptibility to the substance [2]. Multiple investigators based on their clinical experience have evaluated medical abortion regimens with a shorter interval between drugs reducing time between dosages and increasing acceptability [2,3]. In our protocol we administer RU486 about 24 hours before than Misoprostol.

The written above supports the theory that Mifespristone may have some effect on placental flow, however it has not been tested in vivo enough to know the precise mechanism and the action temporally of its vascular effects on decidual and trophoblastic territories [2].

Transvaginal ultrasonography is commonly used for follow-up examination after medical abortion, primarily because it provides a definitive assessment of whether or not the products of conception have been expelled but about on the ultrasound follow-up of medicines there are few studies on.

Nowadays the advantages in ultrasound allow an angio-power system mode (Doppler energy) and the possibility of quantifying the blood vessels density through the study of three-dimensional volume in studied region (Angiopower 3D) [8]. Today these advantages permit to quantify the blood supply in intervillous space, this could be useful to demonstrate a vasodilator effect on this vascular space.

We conducted a pilot study with the aim observe the blood supply in intervillous space and utero-placental vascular compartment with tridimensional ultrasound after unique administration of Mifepristone during the first trimester of pregnancy.

Methods

This is a double-blind placebo-controlled study performed in the Unit of Legal Voluntary Pregnancy Terminations (LVPT), carried out in Doctor Peset University Hospital of Valencia, Spain, for twelve months. Patients requesting LVPT with a gestational age between the 9th and 11th weeks were randomly assigned to control Group A (n=15), receiving 5 mg folate acid as a placebo, or treatment Group B (n=15) receiving 200 mg of RU 486. An ultrasound examination was performed in each patient at the initial time t1 and then 4 hours after administration of Mifepristone or placebo t2. A transvaginal ultrasound scan was performed to all subjects by one investigator (B.P.I.) using a Voluson Expert 730TM (GE Medical Systems, Zipf, Austria) and a four-dimensional 5-9 M Hz transvaginal probe. And we measured the parameters described below and are shown partially in Figures 1A-1D.

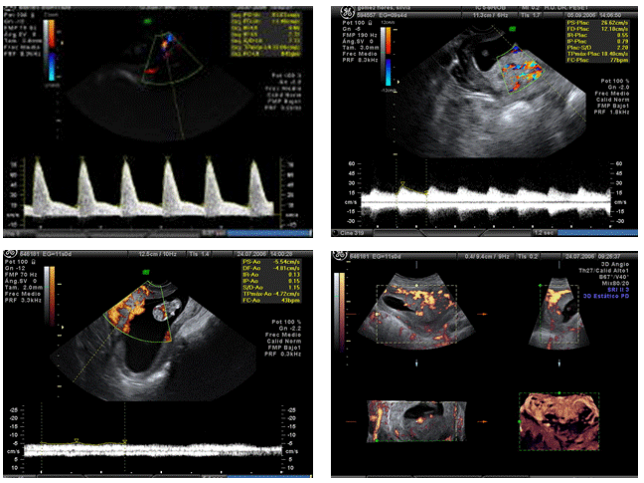

Figure 1: Pictures from a patient scan with waveforms of uterine (A) and spiral (B) arteries and intervillous flow (C). Placental volume acquisition with 3D angio-power (D).

The mean of bilateral uterine arteries Resistance Index was calculated (RI uterine) (Figure 1A). The spiral arteries were identified in the junction of endometrium and myometrium located in the central part of the uteroplacental interface and the mean of three sampled measures was obtained as spiral arteries Resistance Index value (RI spiral) (Figure 1B).

The intervillous circulation showed a continuous venous-like blood flow inside the placental tissue. It was studied in three different areas located in the thickness of central maternal decidua. The amplitude was measured by using angio-power pulse to obtain the maximum velocity of this intervillous flow (IV Flow) (Figure 1C).

For placental volume (Plac Vol) the patient was requested to stop breathing and a uterus volume was acquired, being the sampling volume angle set to 45°. Any images affected by movement (maternal, fetal or transducer) were discharged and the procedure was repeated within 5 min. The vascular territory of the decidua-myometrium interface was not included inside the volume analysis (Figure 1D).

Umbilical Resistance Index (RI umbilical artery) was achieved in an umbilical free cord loop near fetus abdominal wall.

In every examination, power Doppler setting was standardized using a customized first trimester preset. Thermal index (TI) was ≤ 1.0 and exposure time was kept as short as possible. These settings remained unmodified for all stored volume datasets.

Patients were excluded if they had a previous history of preeclampsia or bleeding, treatments with any type of drug with vascular effects, cardiovascular disease. The study was approved by the Hospital Trust's Ethics Committee. A written consent to Doppler exploration was obtained in each subject prior to the enrolment in the study. Volume datasets were analysed offline using Virtual Organ Computer-aided Analysis (VOCAL™) software, as previously described Merce et al. We calculated three indexes representing vascularity: vascularity index (VI), flow index (FI) and density index (VFI). Out machine analysis was performed by the same investigator (B.P.I). Intra-class Correlation Coefficient of vascularization measurements were at least 0.94 for intra-observer and 0.59 for inter-acquisition reproducibility. Statistical study and data analysis of Doppler measurements based on the percentage change in median values taken before and after pill administration were performed by using STATA computer program with the Student test.

Results

At the beginning of the investigation both studied groups were similar and comparable in gestational age, with CRL between 26-41mm. In terms of all the studied parameters both groups remained equal.

The value of spiral RI when comparing separately the RU group, after the Mifepristone administration, was significantly diminished ($p<0.037$) (Figure 2).

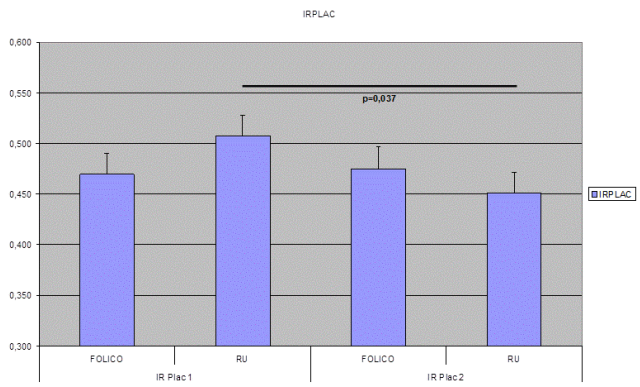

Figure 2: Spiral arteries Resistance Index value (RI spiral) in both gropus before and after treatment or placebo.

All other variables analyzed in the study showed no significant changes between the groups. The value of uterine RI didn't show any differences intra or intergroup between t1 and t2 in placebo (p: 0.143) and RU group (p: 0.484).

The intervillous space maximum peak flow didn't show a significant modification after RU administration (p: 0.258). The value of umbilical RI showed no differences intra or intergroup between t1 and t2 in placebo (p: 0.690) and RU group (p: 0.343).

Neither the placental volume didn't show any differences either intra or intergroup in terms of percentage of volume variation between t1 and t2 in placebo group (p: 0.198) or after RU administration (p: 0.749).

And the statistical analysis didn´t show any differences in the studied volume datasets. The three indexes representing vascularity failed in demonstrating any differences in both groups after placebo or RU administration: VI placebo group (p: 0.358), VI RU group (p: 0.808); FI placebo group (p: 0.016), FI RU group (p: 0.084); VFI placebo group (p: 0.120), VFI RU group (p: 0.284).

Discussion

There are just a few studies focused on Mifepristone effect in pregnant uterus vascularization. We have observed how Mifepristone shows selective hemodynamic effect in trophoblastic tissue in the first hours of administration. A significant decrease in spiral arteries resistance index was demonstrated, without modifying uterine maternal territory.

A similar study with pregnant women showed a significant decreased of spiral resistance index [9]. This latest study, also showed uterine resitance index decrease as well as others authors classically had described using Mifepristone for reduce myoma volume [10]. It should be noticed that hemodynamic assessment in both studies was performed at least at 24 hours after the administration of the drug then it could be a late consequence. Nevertheless, we have not seen any alteration in intervillous space, neither in placental volume. We expected some modification because it has been described an edema, microhematoma and a venous dilatation in the stromal compartment in endometrial tissue under RU effect [11-13]. However, these studies were carried out in non-pregnant women and it could be possible that the effect would be different during gestation.

Our study showed that the value of 3D power Doppler histogram in vascularization evaluation and analysis was limited. For example, we found a small hematoma localized detachment of the gestational sac in the decidua capsularis as previously others authors have described. This hemorrhage has seen an obstacle in our study since it was not easy to reduce artifacts or standardize the examination.

Vascularity indexes measeured in our study have been valuable and reproducible in first trimester intervillous and uteroplacental. However we consider that maternalfetal interface angiopower 3D evaluation is complex and therefore more studies are needed in the future in this field.

In our research the number of studied women and the gestational age variation would be considered as a limitation in our results. After being randomized, our data encourage us to carry further investigations in the effect of other molecules over the placental formation stage.

Conclusion

The results showed that the immediate effects of mifepristone measured with Doppler parameters seem to exert its effect locally on trophoblastic blood flow rather than on uterine artery or fetal territory which may be relevant for shortening the time of administration of prostaglandins.

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