# Enhancement of endometrial receptivity: ultrasound evaluation parameters in infertile Iraqi women treated with Acetyl salicylic acid and Sildenafil citrate and their effect on ICSI cycle outcome

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**Abstract**
Receptivity of endometrium in majority of women normally occur through the middle of luteal phase, guided especially by consequences of effect of steroid hormones, E2 and P. Receptivity refers to the endometrium's capacity to support typical implantation, and optimal receptivity results in typical implantation procedures that provide the groundwork for a healthy pregnancy. During the reproductive years of a normal female, the uterus undergoes ultrasonographically detectable alterations characterized by cyclical changes in the echo pattern of the endometrium. From the first day of the menstrual cycle till the midcycle, the normal endometrium progressively thickens and develops sonographically detectable strata. This appearance can be described as layered, trilaminar or 5-line. Intracytoplasmic sperm injection (ICSI) procedure "entails the deposition of a single spermatozoon directly into the cytoplasm of the oocyte, thus bypassing the zonapellucida and the oolemma PP". It is assumed that ICSI can improve the fertilization rate and lead to higher pregnancy and live birth rates (LBRs) than Conventional IVF (CI) as the number of oocyte retrieved decreases. The role of Acetyl Salicylic acid (Aspirin) in women with infertility is controversial and the evidence is inconsistent. sildenafil citrate has the ability to enhance the blood flow of the uterus, hence, permit the proliferation of endometrium under influence of estrogen. Patients, Materials and Methods The study was done on 90 infertile females who were undergoing "intracytoplasmic sperm injection" (ICSI). The patients categorized into three groups randomly. Patients in Group I (n = 30) received low dose aspirin (80 mg) during controlled ovarian stimulation till day of HCG, while those in Group II (n = 30) received sildenafil as 25 mg four times daily vaginally from day of stopping of cycle to day of HCG, and group three were regarded as control group (n = 30) who received no treatment. Initial ultrasound scanning performed transvaginally at cycle day 2. The endometrial thickness and morphology were evaluated at the longitudinal axis of the uterus. ICSI procedure refers to the deposition of a single sperm directly into the cytoplasm of the oocyte by passing the zona pellucida and the oolemma. Results: There was no significant difference in mean age, mean BMI, the frequency distribution of women according to type of infertility and the frequency distribution of women according to cause of infertility among aspirin treated group, sildenafil treated group and placebo group. There was no significant difference in mean endometrial thickness and mean dose of gonadotropin. Positive pregnancy test was reported in 12 (40.0 %) of women in aspirin group, 10 (33.3 %) of women in sildenafil group and 6 (20.0 %) of women in placebo group. There was also no significant difference in mean sub-endometrial V1\V2 (systolic / diastolic) and Endometrial Vascular Zones. With respect to Endometrial Vascular Zones, there was significant variation in favor of sildenafil and aspirin groups. Pregnancy outcome was significantly and positively correlated to endometrial thickness (r = 0.245; p = 0.021) indicating that the greater thickness of endometrium is correlated to better pregnancy outcome.
Keywords: endometrial receptivity, Aspirin, sildenafil, ICSI cycle.

## 1. Introduction

The first phases of the complicated process of embryo implantation, which involves both the embryo and the mother's endometrium, take place over a period of around 4 to 6 days in the middle of the luteal phase. Receptivity refers to the endometrium's capacity to support typical implantation, and optimal receptivity results in typical implantation procedures that provide the groundwork for a healthy pregnancy.

Receptivity of endometrium in majority of women normally occur through the middle of luteal phase, guided especially by consequences of effect of steroid hormones, E2 and P. (Huang et al., 2015). ndometrial receptivity can be briefed as the maturation process of which the epithelial lining of the uterus that allow the embryonic trophectoderm to attach and to penetrate the endometrial stroma and the underlining tissues of the uterus. In fact, this

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process is not as recognized as a threshold event that is based on''all or none'', it is a culmination of several factors that work together to achieve a successful implantation. This has been observed clinically where the degree of unsuccessful implantation was found to be dependent on factors connected to endometrial-related subfertility in patients. In fact, various degrees of uterine receptivity could produce various forms of pregnancy-related disorders such as, infertility due to failure of implantation, abortion due to incomplete implantation, and pre-eclampsia in cases with abnormal form of implantation. It is worth mentioning that failure of implantation is not fully understood process. However, it was found to be correlated with events related to endocrine profile, contracting diseases, limited development of endometrium, uterine fibroids, and other immune-related damaging conditions (Lessey and Young, 2019).

To completely entangle the limitation in understanding receptivity failure, it is essential therefore to examine all the possible factors that contribute to normal receptivity. Special attention should be given to inflammatory process that govern most of cases with unexplained endometrial receptivity which has been found to affect the progesterone resistance by the uterine endometrium. Ultrasound (TVS) important investigations include assessment of the anatomy of the pelvic organs and monitoring the development and evolution of ovarian follicles (Kondagari et al., 2022). In fact, late progress in manufacturing advanced ultrasound devices facilitated the mission of exploring oviducts, and tubal patency. This device can also provide information regarding pelvic anatomy including uterus and ovaries.

the uterine endometrium undergoes several cyclic changes in coordination with the ovarian cycle throughout female reproductive years, and these changes can be detectable by utilizing ultrasonography.. From the first day of the menstrual cycle till the midcycle, the normal endometrium progressively thickens and develops sonographically detectable strata. This appearance can be described as layered, trilaminar or 5-line (term of preference)( Zhao et al., 2014).

During the first half of the ovarian cycle, endometrium increases in thickness increasingly in response to estrogen. These changes can be observed by ultrasound as layered of endometrium of trilaminar or5-line (term of preference). Post the ovulation time, the endometrium thickness digresses due to changes in the sub glandular layer of the uterus. The endometrium is developing under the influence of estrogen and progesterone throughout the ovarian cycle, and these changes can be seen by an ultrasound which have always been associated with the detected concentration of hormones. In fact, transvaginal ultrasound is widely applied in conditions related with thickness of the endometrium, vascularity of the tissue layer, and the uterine receptivity. As an overall estimation of the uterine receptivity by utilizing ultrasound was found to be correlated with the morphology and thickness endometrium, and with end-diastolic blood flow which presented effective evaluation of uterine receptivity (Malhotra et al., 2017). The endometrium suffers transformational changes following each ovarian cycles, these changes include higher blood flow to the area, higher mitotic activity of cells of the uterine stroma and the epithelial lining, and higher oxygen uptake and diffusion inside the uterine lumen with signs of inflammatory edema.

## Intracytoplasmic sperm injection (ICSI)

The procedure includes sperm injection inside the oocyte by utilizing a special devise capable on holding and injecting the gametes by passing the zona layers and the oocyte's plasma membrane (Simopoulou et al., 2016). This method is considered superior to the conventional IVF due to number of reasons such as achieving higher ferritization and pregnancy rates with ICSI, also live birth rates (LBRs) is irrespective to different semen parameters as most of these abnormal parameters can be bypassed by injecting the sperm directly (Guo etal.,2018; and Luna et al., 2011). The technique also can be applied in infertility conditions related with unexplained infertility, high women age, fertilization failure, PGD, oocyte in vitro maturation, and in condition where the oocyte has been cryopreserved (Gianaroli et al., 2012).

The role of Acetyl Salicylic acid (Aspirin) in women with infertility is controversial and the evidence is inconsistent Aspirin's significance in helping infertile women conceive is debatable, and the research is still in its infancy hood. Aspirin has been shown in certain studies to be advantageous for women undergoing assisted conception.whilst others have not. One of aspirin's alleged advantages is an improvement in uterine and ovarian blood flow; and inhibition of platelet cyclooxygenase, which prevents thrombosis in the placental blood supply by preventing thromboxane production. By increasing leukotriene synthesis, it may also be a powerful stimulator of interleukin-3 (IL-3) in modest dosages (proteins associated with pregnancy success). However, aspirin usage before conception has been linked in retrospective investigations to higher miscarriage rates. Aspirin medication is frequently used to assist ICSI cycles in addition to conventional IVF since it is hypothesized that aspirin increases endometrial thickness, which is expected to boost implantation rates (Siristatidis et al., 2016).

Sildenafil citrate was used world widely as a medication to improve erectile dysfunction in male. The enzymatic inhibitory effect of it on phosphodiesterase type 5 enzyme is claimed to potentiate the nitric oxide effectivity on smooth muscle and vasodilatation. In the same way, sildenafil citrate has the ability to enhance the blood flow of the uterus, hence, permit the proliferation of

endometrium under influence of estrogen. However, sildenafil citrate could be used in women whom suffer from thin endometrium to improve its growth and capability for conception.

## 2. Patients, Materials and Methods

The study was done on 90 infertile females who were undergoing "intracytoplasmic sperm injection" (ICSI) at the infertility center of "High Institute of Infertility Diagnosis and Assisted Reproductive Technologies. The age range of 18 to 42 years and an infertility duration ranging from 2 years to 15 years. Women with both primary and secondary types of infertility were included. Some women have experienced IVF/ICSI cycles before while others have not. Full history was obtained from infertile couples, according to preformed questionnaire. Infertile women were completely examined, including general and gynecological examination and body mass index (BMI). Fertility investigation were also accomplished including baseline hormonal evaluation at early follicular phase (day 1or 2 of menstrual cycle). Trans-vaginal ultrasound, hysterosalpingography and Hycosy were performed to evaluate uterine cavity and assure tubal patency and / or laparoscopy for evaluation of tubal patency and exclusion of pelvic pathology. Seminal fluid analysis (SFA) was performed for male partners.

The patients categorized into three groups randomly. Patients in Group I (n = 30) received low dose aspirin (80 mg) during controlled ovarian stimulation till day of HCG, while those in Group II (n = 30) received sildenafil as 25 mg four times daily vaginally from day of stopping of cycle to day of HCG, and group three were regarded as control group (n = 30) who received no treatment.

### Ultrasound examination

#### Initial ultrasound scanning performed transvaginally at cycle day 2 for

Assessment of the ovarian morphology and pathology (like PCO and ovarian cyst) as well as AFC.

Evaluation of both ovaries accessibility which refer to achievement of transvaginal oocyte retrieval without undue hardship.

Assessment of uterine abnormalities, such as congenital uterine anomalies, uterine leiomyoma, adenomyosis and endometrial polyp as well as evaluation of endometrial thickness.

Screening of remainder of the pelvis to rule out other pathologies.

The endometrial thickness and morphology were evaluated at the longitudinal axis of the uterus. The maximum thickness of the endometrium, including both layers, was measured . Endometrium morphology was reported as hyperechoic , isoechoic, or triple line. Power Doppler of the thickest part of the endometrium was used to evaluate the vascular distribution , with the different colored zones graded as defined previously. Zone I referred to vascularization in the subendometrial region. Zone II denoted vascularization in the outer hyperechoic zone, and Zone III referred to vascularization in the inner hypoechoic zone. Zone IV defined vascularization reaching the endometrial cavity. Patients with zoneIII–IV were classified as having a well-vascularized endometrium (WVE).

### Intracytoplasmic sperm injection procedure

ICSI procedure refers to the deposition of a single sperm directly into the cytoplasm of the oocyte by passing the zona pellucida and the oolemma" (Simopoulou *et al.*, 2016). MII stage oocytes that did not display the visible morphological signs of degeneration used for insemination. The whole procedure was following Javed and Michael, 2012 methods.

### Ovarian stimulation protocol

In the current study the flexible GnRH antagonist protocol was utilized. It comprised ovarian stimulation with recombinant FSH (r-FSH) harboring 75 IU of FSH /vial by regular subcutaneous injection with doses depended on the BMI, age of women, previous response to ovulation induction and AFC. The r-FSH started on the second day of the menstrual cycle with or without human menopausal gonadotropin (hMG) 75 IU of urinary FSH and LH /ampule, based on the requirement intramuscularly were given. Trans-vaginal ultrasound performed on the fifth day of stimulation and consequent scan had been done every two to three days as required. GnRH antagonist injections (Cetrorelix 0.25 mg)" were initiated as soon as the leading follicles reached a diameter of 13-14 mm with multiple dose regimen, in which Cetrorelix 0.25 mg was given daily until the trigger day when at least two to three leading follicles reached a mean 18 mm diameter (Copperman, and Benadiva 2013). The follicular growth monitored by E2 level and trans-vaginal ultrasound until the day of trigger. Each patient underwent serial Ultrasonographic examinations during the controlled ovarian hyperstimulation (COH) protocol, starting from day 6 to 7 of the cycle and continued every ulternate days till human chorionic gonadotropin (rhCG ) was administrated.

## 3. The Results

Demographic characteristics of infertile women participating in the present study are shown in table 1. There was no significant difference in mean age, mean BMI, the frequency distribution of women according to type of infertility and the frequency distribution of women according to cause of infertility among aspirin treated group, sildenafil treated group and placebo group ($p > 0.05$).

| Table -1: Demographic characteristics of infertile women participating in the present study | | | | |
|---|---|---|---|---|
| Characteristic | Aspirin group n = 30 | Sildenafil group n = 30 | Placebo group n = 30 | P |
| Age (years) | | | | |
| Mean ±SD | 31.97 ±4.50 | 31.23 ±5.35 | 29.47 ±4.10 | 0.110 O NS |
| Range | 26 -40 | 24 -41 | 22 -40 | |
| ≤35, *n* (%) | 23 (76.7 %) | 22 (73.3 %) | 28 (93.3 %) | 0.106 C NS |
| >35, *n* (%) | 7 (23.3 %) | 8 (26.7 %) | 2 (6.7 %) | |
| BMI (kg/m²) | | | | |
| Mean ±SD | 27.68 ±3.74 | 26.84 ±3.33 | 25.84 ±2.88 | 107 O NS |
| Range | 18.7 -34 | 20.2 -32 | 20.3 -30.8 | |
| Normal weight, *n* (%) | 9 (30.0 %) | 9 (30.0 %) | 10 (33.3 %) | 0.394 C NS |
| Over weight, *n* (%) | 16 (53.3 %) | 15 (50.0 %) | 19 (63.3 %) | |
| Obese, *n* (%) | 5 (16.7 %) | 6 (20.0 %) | 1 (3.3 %) | |
| Type of infertility | | | | |
| Primary, *n* (%) | 25 (83.3 %) | 28 (93.3 %) | 27 (90.0 %) | 0.455 C NS |
| Secondary, *n* (%) | 5 (16.7 %) | 2 (6.7 %) | 3 (10.0 %) | |
| Causes of infertility | | | | |
| Male, *n* (%) | 13 (43.3 %) | 12 (40.0 %) | 16 (53.3 %) | 0.208 C NS |
| Female, *n* (%) | 11 (36.7 %) | 16 (53.3 %) | 8 (26.7 %) | |
| Combined, *n* (%) | 2 (6.7 %) | 2 (6.7 %) | 4 (13.3 %) | |
| Unexplained, *n* (%) | 4 (13.3 %) | 0 (0.0 %) | 2 (6.7 %) | |

Comparison of endometrial thickness and gonadotropins dose of infertile women participating in the present study among study groups is shown in table 2. There was no significant difference in mean endometrial thickness and mean dose of gonadotropin (p > 0.05) among study groups.

| Table-2: Comparison of endometrial thickness and gonadotropins dose of infertile women among study groups | | | | |
|---|---|---|---|---|
| Characteristic | Aspirin group n = 30 | Sildenafil group n = 30 | Placebo group n = 30 | p |
| Endometrial thickness | | | | |
| Mean ±SD | 8.51 ±1.06 | 8.98 ±1.34 | 9.11 ±1.73 | 0.226 O NS |
| Range | 6.5 -9.6 | 7 -11 | 7 -14.4 | |
| Dose of gonadotropin | | | | |
| Mean ±SD | 1615.00 ±335.83 | 1997.50 ±839.83 | 1892.50 ±634.16 | 0.061 O NS |
| Range | 1350 -2250 | 1125 -3850 | 1350 -3750 | |
| n: number of cases; SD: standard deviation; O: one way ANOVA; C: chi-square test; NS: not significant | | | | |

## Embryo characteristic of infertile women participating in the present study

Comparison of embryo characteristic of infertile women participating in the present study is shown in table 3. There was no significant difference in grade 1 and grade 3 embryo counts and in count of transferred embryos (p > 0.05). However, the count of grade 2 embryos was highest in aspirin group followed by sildenafil group and then by placebo group and the difference was significant (p = 0.026).

| Table -3: Embryo characteristic of infertile women participating in the present study | | | | |
|---|---|---|---|---|
| Characteristic | Aspirin group n = 30 | Sildenafil group n = 30 | Placebo group n = 30 | p |
| Grade1embryo | | | | |
| Median (IQR) | 2 (2) | 2 (2.25) | 3 (2.25) | 0.572 K NS |
| Range | 0 -10 | 0 -6 | 0 -8 | |
| Grade2embryo | | | | |
| Median (IQR) | 2 (2.25) | 1 (2.25) | 1 (2) | 0.026 K * |
| Range | 0 -10 | 0 -6 | 0 -3 | |
| Grade3embryo | | | | |
| Median (IQR) | 0 (0) | 0 (0) | 0 (0) | 0.903 K NS |
| Range | 0 -5 | 0 -3 | 0 -4 | |
| Number of transferred embryos | | | | |
| Median (IQR) | 3 (2) | 2.5 (2) | 3 (1) | 0.755 K NS |
| Range | 2 -4 | 2 -4 | 1 -4 | |
| n: number of cases; IQR: inter-quartile range; K: Kruskal Wallis test; NS: not significant; *: significant at p ≤ 0.05 | | | | |

## Comparison of primary outcome (pregnancy test) among study groups

Comparison of primary outcome (pregnancy test) among study groups is shown in table 4 Positive pregnancy test was reported in 12 (40.0 %) of women in aspirin group, 10 (33.3 %) of women in sildenafil group and 6 (20.0 %) of women in placebo group, but the difference was insignificant from statistical perspective.

Table-4: Comparison of primary outcome (pregnancy test) among study groups

| Characteristic | Aspirin group n = 30 | Sildenafil group n = 30 | Placebo group n = 30 | P |
|---|---|---|---|---|
| Pregnancy test | | | | |
| Positive, n (%) | 12 (40.0 %) | 10 (33.3 %) | 6 (20.0 %) | 0.234 C NS |
| Negative, n (%) | 18 (60.0 %) | 20 (66.7 %) | 24 (80.0 %) | |
| n: number of cases; C: chi-square test; NS: not significant | | | | |

Comparison of secondary outcomes among study groups is shown in table 5. With respect to sub-endometrial resistive index (RI), there was no significant difference among study groups ($p$ = 0.453). There was also no significant difference in mean sub-endometrial V1\V2 (systolic / diastolic) and Endometrial Vascular Zones ($p > 0.05$). With respect to Endometrial Vascular Zones, there was significant variation in favor of sildenafil and aspirin groups ($p$ = 0.037).

Table-5: Comparison of secondary outcomes among study groups.

| Characteristic | Aspirin group *n* = 30 | Sildenafil group *n* = 30 | Placebo group *n* = 30 | *p* |
|---|---|---|---|---|
| Sub-endometrial RI | | | | |
| Mean ±SD | 0.47 ±0.23 | 0.48 ±0.15 | 0.49 ±0.16 | 0.453 O NS |
| Range | 0.29 -0.97 | 0.2 -0.84 | 0.2 -0.84 | |
| Sub-endometrial V1\V2 | | | | |
| Mean ±SD | 2.98 ±1.80 | 2.76 ±1.42 | 2.26 ±1.17 | 0.164 O NS |
| Range | 0.41 -6.17 | 1.54 -6.17 | 0.41 -6.17 | |
| Endometrial Vascular Zones | | | | |
| 1, *n* (%) | 0 0.0 %) | 0 (0.0 %) | 2 (6.7 %) | 0.037 C * |
| 2, *n* (%) | 10 (33.3 %) | 11 (36.7 %) | 16 (53.3 %) | |
| 3, *n* (%) | 20 (66.7 %) | 19 (63.3 %) | 12 (40.0 %) | |
| n: number of cases; SD: standard deviation; O: one way ANOVA; C: chi-square test; NS: not significant; *: significant at p ≤ 0.05 | | | | |

Correlation of pregnancy test to stimulation characteristics of all enrolled infertile women is shown in table 6. Pregnancy outcome was significantly and positively correlated to endometrial thickness (r = 0.245; p = 0.021) indicating that the greater thickness of endometrium is correlated to better pregnancy outcome. Moreover, pregnancy outcome was significantly and positively correlated to dose of gonadotropin (r = 0.253; p = 0.016).

Table-6: Correlation of pregnancy test to stimulation characteristics of all enrolled infertile women

| Characteristic | Pregnancy test | |
|---|---|---|
| | r | p |
| Endometrial thickness | 0.245 | 0.021 * |
| Dose of gonadotropin | 0.253 | 0.016 * |
| r: correlation coefficient; *: significant at p ≤ 0.05 | | |

## 4. Discussion

In the present study, there was no significant difference in mean endometrial thickness and mean dose of gonadotropin among study groups. The lack of significant difference in mean endometrial to low dose aspirin. Therefore, the role of aspirin in improving endometrial thickness is controversial and in order to reach a consensus, further experimental and clinical research work is needed.

thickness revealed that the use of aspirin and sildenafil did not succeed in improving this corner stone parameter in association with ART outcome.

In one recent Iraqi study, aspirin in low dose was shown to endometrial thickness in intervention group in comparison with placebo group (Jamel and Abid-Alkareem, 2022). In the study of (Zhang et al., 2022), there was no significant difference in endometrial thickness after treatment (P = 0.302) and our results are in agreement with these findings. However, in contrast to our finding, another study showed that low-dose aspirin significantly enhanced endometrial thickness in patients undergoing ART (Kaaja et al., 1993). In a randomized controlled clinical trial carried out by Davar et al in 2020 "The endometrial thickness was lower in patients who received aspirin in comparison to the control group. There were statistically significant differences between the two groups (p = 0.018)". In addition, the study of Zhang et al (2022b), no significant improvement in endometrial thickness was observed. In one meta-analysis done by Wang et al in 2017, there was no significant improvement in endometrial thickness with respect

In our study, sildenafil was also unable to improve endometrial thickness significantly. In accordance with our findings Moini et al in 2020 showed that

vagianl sildenafil did not improve endometrial thickness significantly. Check et al in 2004 also reported no significant progress in endometrial thickness following administration which is also consistent with our observation. The results of previous studies have shown that sildenafil citrate (vaginal or oral alone or with oestradiol) is significantly effective in improving endometrial thickness (Paulus et al., 2002; Takasaki et al., 2010; Al-Assadi et al., 2012).

Studies have shown that sildenafil widens the vasculature by its effects on the smooth muscles of the arteries (Jerzak et al., 2010; Ballard et al., 1998). Sildenafil citrate is an inhibitor-5-phosphodiestrase type that, by preventing the effect of cGMP, exacerbates the effect of NO on the smooth muscle of the arteries (Ballard et al., 1998, Boolell et al., 1996). According to the results of some studies, the use of sildenafil during the proliferative phase of the cycle improves uterine blood flow and endometrial growth, (Sher and Fisch, 2002, Sher and Fisch, 2000). In the present study, endometrial blood flow improved following the use of Aspirin and sildenafil as evidence by improvement in endometrial vascular zone; however, we observed no significant improvement in endometrial thickness, thus we can suggest that endometrial thickness is determined by other factors other than blood flow that need further research in order to be explained for example age of the mother and hormonal characteristics.

In our study, the best rate of positive pregnancy test was reported in 12 in aspirin group followed by sildenafil and lastly by placebo group, but the difference was insignificant from statistical perspective.

In one previous randomized controlled clinical trial carried out by Davar et al in 2020, Chemical and clinical pregnancy rates and abortion rate was similar in the two groups (aspirin versus no treatment) and there was no statistically significant difference. In the contrary to our findings Madani et al in 2019 reported that the administration of aspirin in ICSI cycles improved the implantation, clinical pregnancy, and live birthrates. Hsieh and colleagues in 2000 showed higher clinical pregnancy rate following aspirin administration, but they select women with thin endometrium.

Conforming to our study, a meta-analysis (Khairy et al., 2007) and reports by Cochrane reviews (Siristatidis et al., 2012, Siristatidis et al., 2016) also establish that there was no improvement in pregnancy rates with the use of low-dose aspirin. Jeromeh demonstrated that the clinical pregnancy rate was lower in the aspirin group compared with control group (11.1% vs 33.3% respectively) for, and the implantation rates were 2.9 and 10.9%, respectively. In this study, low-dose aspirin administration did not cause positive effect on pregnancy rates in FET cycles (Check et al., 1998). Gelbaya and co-workers suggested that in FET cycles, there was no significant difference in pregnancy rate between untreated women with normal uterine perfusion and those that uterine perfusion was improved after aspirin administration. This result is similar with our study (Gelbaya et al., 2007).

In our study, sildenafil fails to improve RI. With respect to sub-endometrial resistive index, Moini et al in 2020 and Taher et al in 2020 found no significant variation in RI following the use of sildenafil. On the contrary, Takasaki et al in 2010 and Yahia et al in 2019 have shown that sildenafil can improve RI.

In our study, aspirin was unable to improve RI. Previous studies evaluated the effect of low dose aspirin on uterine artery resistive index in women with pre-eclmpsia and the results were conflicting. In the study of Atarod et al in 2015 there was no significant difference in mean RI between the group that received low dose aspirin therapy and the control group. In the study of (Zimmermanna et al., 1997), the conclusion was that "Low-dose aspirin treatment does not affect the resistance index in the uterine". However, Adibrata et al in 2018 have shown that the use of aspirin can reduce uterine artery RI significantly. With respect to recurrent pregnancy loss, Zhang et al in 2022 showed that low dose aspirin reduced RI significantly in women with recurrent pregnancy loss. Therefore, the results of aspirin administration, based on our results and previous reports, are conflicting and further research work is still needed to explore the exact way by which aspirin increases pregnancy rate in some women and not in all women undergoing ICSI. The previous claim that the improvement in endometrial blood flow and or ovarian follicle vascularity following aspirin administration would ensure better pregnancy outcome appears partly misleading and there must be other unknown confounders that need to be adjusted in such case control trials in order to reach better consensus about aspirin used in ART.

In the current study, pregnancy outcome was significantly and positively correlated to endometrial thickness indicating that the greater thickness of endometrium is correlated to better pregnancy outcome. The higher pregnancy rate in association with greater endometrial thickness has been confirmed previously and the claim was attributed to better implantation rate in association with increased endometrial thickness (Xu et al., 2022).

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