Sildenafil and Infertility Treatments

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One of the adjuvants that showed potential beneficial effects on endometrial thickening in women undergoing infertility treatments is sildenafil citrate, a 5-phosphodiesterase inhibitor widely used for male erectile dysfunction. The Sildenafil pharmacological effect of Sildenafil is based on the prevention of cGMP breakdown thereby increasing smooth muscle relaxation and vasodilation. At the endometrium level, Sildenafil may increase uterine artery flow and exert a positive effect on endometrial growth in response to estrogenic stimulation. Moreover, it may improve endometrial tolerance to the embryo through decreasing local natural killer cell activity and favoring the accomplishment of proper embryo implantation.

Keywords: Sildenafil ; endometrial thickness ; timed intercourse ; intrauterine insemination ; in vitro fertilization

1. Introduction

Despite advances in assisted reproductive technologies (ARTs), the cumulative success rate of the procedures remains suboptimal, with an estimated overall pregnancy rate of around 30% [1]. According to several studies, one of the major limiting factors for the success of ART might be represented by impaired endometrial receptivity (ER) [2].

Despite all efforts to validate specific and effective markers to find an optimal window of implantation for embryo transfer [3], endometrial thickness (ETh) is still considered the best surrogate measurement and a crucial factor for implantation. Accordingly, several studies reported a direct correlation between low ETh (<7 mm) and low success rates of ARTs—and medically assisted reproduction—(MAR) procedures, including intrauterine insemination (IUI) and in vitro fertilization (IVF) with fresh embryo transfer (fresh-ET) or frozen embryo transfer (frozen-ET) [4][5][6].

During the last decades, several strategies (including hormonal and non-hormonal adjuvants) have been tested with the purpose of increasing ETh in women undergoing infertility treatments, with conflicting results [7][8][9][10][11][12][13][14][15][16][17].

One of the adjuvants that showed potential beneficial effects on endometrial thickening in women undergoing infertility treatments is sildenafil citrate, a 5-phosphodiesterase inhibitor widely used for male erectile dysfunction [18]. The Sildenafil pharmacological effect of Sildenafil is based on the prevention of cGMP breakdown thereby increasing smooth muscle relaxation and vasodilation [18]. At the endometrium level, Sildenafil may increase uterine artery flow and exert a positive effect on endometrial growth in response to estrogenic stimulation [19]. Moreover, it may improve endometrial tolerance to the embryo through decreasing local natural killer cell activity and favoring the accomplishment of proper embryo implantation [20]. Mechanisms of action of Sildenafil on the endometrium are not fully understood. Due to its supposed action of favoring implantation both through the increase in endometrial thickness [19] and through the immune action [20], this type of add-therapy has been studied on different types of infertile women, both those with a thin endometrium and those without an apparent endometrial problem. In fact, implantation does not occur in about 1/3 of transfers of euploid blastocyst in women without an apparent endometrial abnormality [21].

Based on these principles, randomized controlled trials investigated the efficacy of oral or vaginal Sildenafil administration in women undergoing infertility treatments. Thus, the aim of this present systematic review and meta-analysis was to summarize the current evidence on the effectiveness of Sildenafil administration for improving ETh and the success of ARTs and MAR procedures.

2. Sildenafil Supplementation for Women Undergoing Infertility Treatments

2.1. General Considerations

Despite the improvement in ARTs, the live birth rate is still low even if top-quality embryos are obtained [22]. A great issue is the obtaining of a receptive endometrium [23][24]. Despite new technologies that allow the detection of the implantation

window through an endometrial biopsy performed during the previous menstrual cycle [25][26], the widely used method in the clinical practice to establish if an endometrium is suitable for implantation is the transvaginal ultrasound evaluation of ETh [27][28][29].

The underlying cause of the thin endometrium must be sought and resolved before attempting another cycle for achieving pregnancy. Hysteroscopy is usually the gold standard as a second-line diagnostic investigation [30][31][32], and Asherman's syndrome is the first pathological condition that must be excluded [33]. Another underlying underdiagnosed condition that has recently been re-examined might be chronic endometritis that can be suspected with diagnostic hysteroscopy and confirmed with endometrial biopsy [34][35][36][37].

Despite these second-line investigations, many times the underlying cause cannot be identified. Although sometimes the endometrium might be receptive even if a thinner value is used as a cut-off [24], an association has been demonstrated between low endometrial thickness, ART failure and adverse pregnancy outcomes related to an abnormal placentation such as hypertension, preeclampsia, intrauterine growth defects [38][39][40].

For these reasons, many efforts have been made in order to obtain a thicker endometrium with different strategies involving hormonal approaches (estradiol administration adjustment, hCG administration during the follicular phase, GnRH agonist administration during the luteal phase), the intrauterine infusion of growth factors such as the granulocyte colony-stimulating factor and platelet-rich plasma and the usage of factors that act on endometrium vascularity [41]. For this latter approach, low dose aspirin has been used and also phosphodiesterase inhibitors [41]. Among phosphodiesterase inhibitors, there are non-specific inhibitors such as pentoxifylline and selective ones such as phosphodiesterase type 5 inhibitor (Tadalafil and Sildenafil) [42][43]. However, despite different approaches that might be available, a lack of solid evidence in the published literature limits their clinical applicability.

In particular, the usage of selective phosphodiesterase type 5 inhibitors seems a promising strategy supported by a valid biological rationale. Indeed, Sildenafil causes vasodilatation preventing cGMP breakdown and increasing relaxation of the smooth muscle [12][44]. This effect is widely used in males for erectile dysfunction [45]. With a similar mechanism, Sildenafil might increase uterine artery flow with subsequent enhanced endometrial vascularization and improved endometrial growth under estrogenic influence [19][44].

2.2. Main Findings

In this meta-analysis, we tested the effect of Sildenafil as an add-therapy during the TI or IUI cycle and during IVF and fresh-ET or frozen-ET on ETh and the pregnancy rate. We found that Sildenafil supplementation significantly improves ETh when administered during a timed intercourse or IUI cycles; on the contrary, it does not seem to take a significant advantage when administered during fresh-ET or frozen-ET. In both groups, there was a bad consistency (I2 86% and 97%, respectively). Similarly, analyzing TI or IUI cycles, we found that the intervention was associated with a higher CPR and ChPR (low inconsistency, I2 = 0%). In fresh-ET or frozen-ET groups, there was a higher rate of ChPR in Sildenafil co-treatment women.

A subgroup analysis for the evaluation of the way of Sildenafil administration was possible only for the IVF Fresh-ET/Frozen-ET groups. Even if only one study evaluated the oral administration of Sildenafil in these groups [46], vaginal administration seems to be more effective, but further studies are needed to confirm these results.

A subgroup analysis revealed that also timing of administration had a significant effect. In fact, only the delayed starting of Sildenafil administration during the TI and IUI cycles led to a thicker endometrium and to a higher biochemical pregnancy rate.

2.3. Interpretation

Based on our results, it would seem that ETh, CPR and ChPR are higher with the use of Sildenafil in women undergoing TI and IUI. In particular, a subgroup analysis evidenced that the delayed start of Sildenafil administration might significantly increase the chances of obtaining a thicker endometrium and pregnancy. Further studies are needed to reveal whether the way of Sildenafil administration has a significant effect on endometrial thickness and the pregnancy rate.

Considering women undergoing TI/IUI [19][47][48][49][50], in all except one trial [51], Sildenafil was orally administered. In this group, a significant improvement was highlighted for Eth, CPR and ChPR. Vaginal administration did not show significant advantages. This way of administration was evaluated in a single trial [51], but this trial compared Sildenafil to estrogen, while the other subgroup studies compared Sildenafil to no intervention.

Regarding the improvement of Eth in women undergoing MAR treated with Sildenafil, it is known that this molecule improves artery blood flow through the prevention of cGMP breakdown [18]. This leads to an increase in smooth muscle relaxation and vasodilation. The possible explanation of the impact of the Sildenafil on the endometrium is that this molecule exerts a positive effect on endometrial growth increasing endometrial vascularization through the described method. This mechanism acts in synergy with estrogens that secrete angiogenic factors to enhance revascularization [52] [53]. This improvement in endometrial growth through an increased vascularization led to an improvement in the CPR and ChPR.

Better outcomes in terms of the CPR and ChPR were reported when Sildenafil supplementation was started 7–8 days from ovarian stimulation.

Physiologically, endometrial vascularization increases during the endometrial proliferative phase that generally last from the 7th day of the menstrual cycle under the influence of estrogens through the action of different angiogenic factors [52][53] [54]. As natural killer cells release cytokines that are involved in embryo implantation failure through nitric oxide action, it may be beneficial to limit Sildenafil administration only when spiral arteries have already formed to avoid a high concentration of nitric oxide [55]. In fact, if the assumption of Sildenafil administration is to increase the endometrial vascularity, the delayed administration of this molecule adapts better to the physiology of the endometrial cycle, acting in concert with the increase in estrogen.

Considering women undergoing fresh or frozen-ET [12][46][56][57][44][58], vaginal Sildenafil represented the most common way of administration, and only one trial administered oral Sildenafil [46]. In this group, a significant improvement in ETh was not highlighted in patients treated with Sildenafil. Nevertheless, in treated women, a higher pregnancy rate was present. The only trail that considered oral administration in women undergoing the described ART techniques [46] showed a significant improvement in ETh but not in the pregnancy rate. However, considering women undergoing fresh- or frozen-ET, only the ChPR improvement was reported and not the CPR.

Regarding the non-improvement of Eth in women undergoing ART treated with Sildenafil, different explanations can be provided for patients undergoing fresh-ET and for patients undergoing frozen-ET. Women undergoing controlled ovarian stimulation achieve an increase in peak serum estradiol levels up to 10–12 times higher [59]. Since estradiol acts on the growth of the endometrium, the maximum effect on endometrial thickness can be obtained with only the high concentration of estrogen due to ovarian stimulation.

Instead, all women evaluated in the frozen-ET groups underwent an endometrial preparation with an artificial cycle. The dynamics of action of the estrogens administered in the artificial cycles of endometrial preparation on the endometrium are not fully known. It is possible that in this type of treatment, the synergy is present in MAR treatments in which Sildenafil acts in concert with estrogen to increase endometrial vascularization and therefore increase its thickness is lost.

Improvement in the ChPR was reported when the fresh-ET and frozen-ET groups were analyzed together. However, there was no significant improvement when the two groups were analyzed separately. The lack of improvement in the analysis of the frozen-ET group alone may be due to the number of limited studies available. In frozen-ET, the supplementation of Sildenafil might be useful to reach the maximum effect on endometrial vascularization, while maybe this is not possible in women undergoing fresh-ET who have higher levels of estrogens. Further studies are necessary to prove this hypothesis.

In summary, a biological explanation of the apparently different efficacies of Sildenafil among women undergoing TI and IUI compared to women undergoing IVF and fresh or frozen-ET might lie on the different levels of estrogen that are achieved during the different types of treatments [60][61]. In fact, as previously reported, estrogen treatment is an option for achieving a thicker endometrium, and high levels of endogenous estradiol might act as a cotreatment. This aspect may explain the non-significant results in endometrium thickness obtained in women undergoing transfer after treatments that required higher estradiol levels. Moreover, in our meta-analysis, the pregnancy rate resulted higher in Sildenafil treated women (p = 0.05), probably due to higher vascularization and, therefore, higher receptivity.

Regarding the route of administration, further studies are needed to evaluate the efficacy of the vaginal route of administration of sildenafil in women undergoing ART. This route of administration could ensure a higher endometrial concentration of sildenafil. In fact, vaginal absorption occurs through the vaginal mucosa which is highly vascularized, and it does not depend on food intake and avoids hepatic metabolism.

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