Sildenafil citrate therapy for IUGR and its effect on umbilical artery Doppler
Abdel A.G.E.-D.T. El-Darwisha, Mahmoud A. Badawy, Sally M.G. Farghaly

Background
Intrauterine growth restriction (IUGR) occurs when there is deficiency of gas exchange and nutrient delivery to the fetus not allowing it to thrive in utero. This happens because of maternal diseases that decrease oxygen-carrying capacity (e.g. cyanotic heart disease, smoking, and hemoglobinopathy) or by maternal vascular diseases causing a dysfunctional oxygen delivery system or idiopathic causes. Sildenafil (phosphodiesterase-5) inhibitor consists of the citrate salt of sildenafil; it is a selective and specific inhibitor of cyclic guanosine monophosphate. It is primarily used for sexual dysfunction, antidepressant-associated sexual dysfunction, pulmonary hypertension, altitude thickness, and Raynaud's phenomenon. Herein, the trial is used for improving uteroplacental perfusion by enhancing vasodilatation of myometrial small artery, decreasing peripheral resistance, and boosting flow within the uteroplacental bed.

Aim
The aim was to evaluate efficacy and role of sildenafil citrate on the blood flow of uteroplacental circulation and fetal growth in pregnancies accompanied by fetal growth restriction because of dysfunctional oxygen delivery system guided by umbilical Doppler ultrasound.

Patients and methods
Our study was a prospective double-blind, randomized, controlled trial. The patients were recruited from women with IUGR attending the emergency ward and outpatient clinic at Sohag teaching Hospital. The study comparing three groups of 150 women. Each group consisted of 50 women. One group received 20 mg of sildenafil citrate orally twice/day, the second received a dose of 40 mg every 12 h vaginally, whereas the last one received a placebo, as a control group.

Results
After treatment, improvement of Doppler in the form of S/D, resistance index, and pulsatility index showed highly significant difference between the two sildenafil groups compared with the control one.

Conclusion
Sildenafil therapy may offer a new breakthrough in treatment of IUGR-complicated pregnancies, with improvement of the perinatal outcomes.

Keywords:
fetal growth restriction, small for gestational age, umbilical artery Doppler, sildenafil citrate therapy

Introduction
Fetal growth restriction [also called intrauterine growth restriction ([IUGR]) is the expression used to depict a fetus that has not reached its growth potential owing to genetic or environmental factors. IUGR occurs as a result of impaired gas exchange and/or if the nutrients delivered to the fetus are not sufficient to allow it to normally thrive in utero. This process can occur owing to any maternal disease leading to decreased oxygen-carrying capacity (e.g. smoking, cyanotic heart disease, or hemoglobinopathy), or by disorders in the oxygen delivery system secondary to maternal vascular diseases [1].

An estimated fetal weight at or below the 10th percentile is used for most purposes to set apart fetuses at risk. However, it should be understood that this cannot be considered as a definitive cutoff for uteroplacental insufficiency. A definite number of fetuses at or below the 10th percentile may be constitutionally small [2].

Moreover, regarding follow-up growth of fetus, one of the easiest and most common method is measuring the distance from the mother's fundus to the pubic bone. After the 20th week of pregnancy,
the measure of this distance in centimeters usually coincides with the number of weeks of pregnancy [3].

We used sildenafil to overcome the problem of increased resistance to blood flow in placental bed and thereby improving the growth of the fetus.

Aim
The aim of this study was to evaluate the role of efficacy and tolerability of sildenafil citrate on the blood flow of uteroplacental circulation and fetal growth in pregnancies accompanied by fetal growth restriction because of dysfunctional oxygen delivery system guided by umbilical Doppler ultrasound.

Patients and methods
Study design
This was a prospective double-blind, randomized, controlled trial.

Study place and time
This study was conducted in the period from July 2017 to December 2018. The patients were recruited from women experiencing IUGR attending the emergency ward and outpatient at Sohag Teaching Hospital.

Ethical considerations
(1) The study protocol was approved by the Local Ethical Committee, Sohag Faculty of Medicine, Sohag University.
(2) An informed written consent was taken from all of the pregnant women included in the study.

Patients
Our study included 150 pregnant women. All cases were subjected to the following inclusion and exclusion criteria.

Inclusion criteria
(1) Age: 20–35 years.
(2) Regular menstrual history prior pregnancy.
(3) Singleton pregnancy.
(4) Gestational age (GA) starting 24–36 weeks.
(5) IUGR owing to decreased uteroplacental blood flow because of maternal causes.
(6) Fetal well-being.

Exclusion criteria
(1) Pregnancy before 23 weeks.
(2) Maternal cardiovascular morbidity, diabetes, and hypertension.
(3) Iatrogenic IUGR.
(4) Smoking and/or alcohol or drug abuse.
(5) Allergy to sildenafil citrate.
(6) Known or suspected fetal anomaly.
(7) Constitutionally small fetus.

Methods
The study population was divided into three equal groups, each of them contained 50 women:

(1) The first group received 40 mg of sildenafil citrate orally twice.
(2) The second group received sildenafil citrate in a dose of 20 mg every 12 h vaginally.
(3) The third group received a placebo and is considered as the control group.

All cases were subjected to the following after obtaining their consent:

(1) Full history taking, including past, medical, obstetric, and menstrual history.
(2) General and abdominal examination.
(3) Investigations included the following:
   (a) Laboratory: full urine, blood count analysis, liver and kidney function, and glucose tolerance test.
   (b) Ultrasonic measurement to estimate GA, fetal weight, amniotic fluid index, biophysical profile, and placental features (location, thickness, and grading), as well as for ultrasound markers of chromosomal abnormalities.
   (c) Umbilical Doppler was done before starting the drug and repeated it after one week, then used for weekly follow-up.

Technique of Doppler
Positioning of the patients: for obstetric Doppler examinations, the patients assumed a supine, slightly left lateral tilted position, and a wedge was placed under the right flank. It was important to avoid the supine hypotension syndrome, as it has been associated with alterations in Doppler indices of uterine and umbilical vessels.

(1) The umbilical artery: the umbilical artery in the cord was recognized by the characteristic shape of the velocity waveform on the oscilloscope (and sound) and the ability to simultaneous display flow in the umbilical vein in the opposite direction.
(2) As waveforms obtained near the placental end of the cord reflect downstream resistance and show higher end-diastolic flow velocity than waveforms...
obtained near the abdominal cord insertion [4], in the present study to optimize reproducibility, the umbilical artery Doppler was interrogated at the abdominal cord insertion in all cases.

(3) The umbilical cord was visualized in cross-section in a free loop and magnified to the maximum possible extent. In most cases, the cord appeared as two arteries and one vein.

(4) At least two measurements were made of the cross-sectional area of the artery, if necessary by using different cross-sections of the cord. The ellipse function allowed a directly derived internal cross-sectional area to be obtained for each vessel. Measurements were made in accordance with the manufacturer’s guidelines for this [5] as follows:
(a) Cord vessels were visualized longitudinally in the absence of fetal movements or breathing. In all cases, the angle of insonation was less than 60.
(b) Care was taken to avoid contamination of the waveform with other signals, either above or below the baseline, and only waveforms with a high signal to noise ratio was accepted. The sample volume was adjusted to insonate the whole width of the vessel.
(c) At least three consecutive arterial waveforms were obtained.
(d) Calipers were placed to allow time-averaged velocity measurements to be made with angle correction.

Measurements

(1) Placental and fetal Doppler parameters before and a week after sildenafil administration were taken.
(2) Doppler velocimetry: pulsatility index (PI) or resistance index (RI) of the umbilical artery was performed twice, immediately before giving sildenafil dose and after a week of therapy. We took measurements twice for each vessel, and then the mean value was recorded.
(3) Blood flow was acquired through using a triplex system (two-dimensional image, color Doppler, and pulsatile Doppler) with color mapping.
(4) Scans with a minimum of six uniform waves were analyzed. The volume size of the sample was set according to the vessel diameter to be studied and the angle of insonation was as close to 0° as possible. We froze the image after obtaining a good signal and then automatically measured the Doppler flow velocimetry parameters by the equipment’s software.
(5) Velocimetry of the umbilical artery was accomplished at the midpoint between the placental and abdominal insertions of the vessel.

Outcomes

(1) The primary outcome was the effect of sildenafil in improving Doppler indices and resultant effect on fetal growth.
(2) The secondary outcome was the difference between oral sildenafil in a dose of 20mg and vaginal sildenafil in a dose of 40mg every 12h.

Statistical analysis

(1) For statistical data analysis in the study, we used the Statistical Package for the Social Sciences (IBM-SPSS), version 24 IBM (IBM, Chicago, Illinois, USA) (May 2016).
(2) Analysis of variance test was used to compare means between more than two groups.
(3) Data were expressed as mean, SD, number, and percentage. Number and percentage were used to describe qualitative data, whereas mean and SD were used as descriptive value for quantitative data.
(4) Student *t*-test was used to compare the means among the three groups. Mann–Whitney test was used instead of Student *t*-test in case of nonparametric data.
(5) The level of significance (*P* value) was demonstrated as follows:
(a) Significance *P* less than 0.05.
(b) No significance *P* greater than 0.05.
(c) High significance *P* less than 0.001.

Results

Regarding GA among the three groups, our study shows that the GA as recorded by history of last menstrual cycle was ∼27–27.5 weeks, with nonsignificant difference among the three groups. The GA as estimated by physical examination was lower by ∼1.5–2 weeks among the three groups, with nonsignificant difference among the three groups.

GA by ultrasound showed growth restriction, with a mean GA of only 25.3, 25.1, and 24.6 weeks among groups 1, 2, and 3, respectively. Although the GA was more retarded by ultrasound among the control group compared with the other two groups, the difference was also not statistically significant among the groups before treatment neither in GA by date or by ultrasound.

This was reflected in the nonsignificant difference among the three groups regarding the fetal weight, which had a mean of 950, 924, and 887 g in groups 1, 2, and 3, respectively.
The comparison among groups 1, 2, and 3 regarding demographic and history data showed nonsignificant differences, as shown in Table 1.

The comparison among groups 1, 2, and 3 regarding examination of vital signs showed nonsignificant differences, as shown in Table 2.

The comparison among groups 1, 2, and 3 regarding GA (weeks) as assessed by history, symphysis fundal height, ultrasound, and fetal weight (g) showed highly significant differences, as shown in Table 3.

Table 4 shows that comparison between pretreatment and post-treatment Doppler findings in group I showed that there were high significant differences between all of S/D, RI, and PI in both pretreatment and post-treatment measurements.

Table 5 shows that comparison between pretreatment and post-treatment Doppler findings in group II showed that there were highly significant differences between all of S/D, RI, and PI in both pretreatment and posttreatment measurements.

Table 6 shows that comparison between pretreatment and post-treatment Doppler findings in group III showed that there were no significant differences between all of S/D, RI, and PI in both pretreatment and post-treatment measurements.

<table>
<thead>
<tr>
<th>Table 1 Demographic and history data of the study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Items</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gestational age</td>
</tr>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>Abortion</td>
</tr>
<tr>
<td>Previous CS</td>
</tr>
<tr>
<td>Previous gynecological operations</td>
</tr>
<tr>
<td>Menstrual regularity</td>
</tr>
<tr>
<td>Past history of similar conditions</td>
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<tr>
<td>Family history of similar conditions</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Values are represented as mean±SD and n (%). CS, cesarean section; DM, diabetes mellitus. PV no statistically significant difference between groups.

<table>
<thead>
<tr>
<th>Table 2 Examination of vital signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Items</td>
</tr>
<tr>
<td>Pulse</td>
</tr>
<tr>
<td>Systolic BP</td>
</tr>
<tr>
<td>Diastolic BP</td>
</tr>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Respiratory rate</td>
</tr>
</tbody>
</table>

Values are represented as mean±SD. BP, blood pressure. PV no statistically significant difference between groups.

<table>
<thead>
<tr>
<th>Table 3 Gestational age (weeks) among the three groups as assessed by history, symphysis fundal, height, ultrasound, and fetal weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Items</td>
</tr>
<tr>
<td>Gestational age by history</td>
</tr>
<tr>
<td>Gestational age by examination</td>
</tr>
<tr>
<td>Gestational age by ultrasound</td>
</tr>
<tr>
<td>History vs SFH &lt;0.001</td>
</tr>
<tr>
<td>PV</td>
</tr>
<tr>
<td>Fetal weight (g)</td>
</tr>
</tbody>
</table>

*Values are represented as mean±SD. P value among groups (P>0.05). SFH, symphysis fundal height.

<table>
<thead>
<tr>
<th>Table 4 Comparison between pre and posttreatment Doppler findings in group I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
</tr>
<tr>
<td>S/D</td>
</tr>
<tr>
<td>RI</td>
</tr>
<tr>
<td>PI</td>
</tr>
</tbody>
</table>

Values are represented as mean±SD. PI, pulsatility index; RI, resistance index.
Using analysis of variance test, Table 7 shows that on comparison between pretreatment and post-treatment Doppler findings (S/D, RI, and PI) in the three groups, there were no significant differences between all of S/D, RI, and PI in pretreatment findings, whereas there are highly significant differences in post-treatment findings.

**Discussion**
In a study of Sharp *et al.* [6], 75 women were enrolled before 26 weeks and 0 days’ gestation and 60 women between 26 weeks and 0 days’ gestation and 29 weeks and 6 days’ gestation.

Comparison of groups 1 and 2 regarding GA and fetal weight showed nonsignificant differences. Comparison of groups 1 and 3 regarding GA and fetal weight showed nonsignificant differences. Comparison of groups 2 and 3 regarding GA and fetal weight showed nonsignificant differences, and comparing the mean GA by history versus by examination, or by history versus by ultrasound showed highly significant differences, which means that there was significant growth retardation among the three groups.

On the contrary, after the end of the treatment course, the control group figures did not change markedly compared with the values of the two case groups. This was reflected in the highly significant differences among the three groups after treatment.

Comparison of groups 1 and 2 in our study regarding Doppler findings showed that there were nonsignificant differences between the two groups before the start of sildenafil treatment. However, after treatment, both RI and PI showed significant difference between the two groups. Comparison of groups 1 and 3 regarding Doppler findings showed that there were nonsignificant differences between the two groups before the start of sildenafil treatment. However, after treatment, all of S/D, RI, and PI showed highly significant difference between the two groups.

Sharp *et al.* [6] expected a valuable influence on placental function if sildenafil treatment was given efficiently, as suggested by uteroplacental and fetal Doppler studies and also by the study of angiogenic biomarkers, even in the absence of a definite beneficial clinical outcome. They observed high ratio of babies

### Table 5 Comparison between pre and posttreatment Doppler findings in group II

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/D</td>
<td>3.6±0.42</td>
<td>2.88±0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RI</td>
<td>1.23±0.19</td>
<td>0.96±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI</td>
<td>0.94±0.15</td>
<td>0.60±0.10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are represented as mean±SD. PI, pulsatility index; RI, resistance index.

### Table 6 Comparison between pre and posttreatment Doppler findings in group III

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/D</td>
<td>3.65±0.52</td>
<td>3.46±0.51</td>
<td>NS</td>
</tr>
<tr>
<td>RI</td>
<td>1.28±0.19</td>
<td>1.21±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>PI</td>
<td>0.98±0.16</td>
<td>0.89±0.13</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are represented as mean±SD. PI, pulsatility index; RI, resistance index.

### Table 7 Doppler examination among the three groups

<table>
<thead>
<tr>
<th>Items</th>
<th>Group 1: 40 mg sildenafil</th>
<th>Group 2: 20 mg sildenafil</th>
<th>Group 3: control</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
</tr>
<tr>
<td>S/D</td>
<td>3.51±0.46</td>
<td>3.6±0.42</td>
<td>3.65±0.52</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>1.22±0.15</td>
<td>1.23±0.19</td>
<td>1.28±0.19</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.93±0.13</td>
<td>0.94±0.15</td>
<td>0.98±0.16</td>
<td></td>
</tr>
<tr>
<td>Post treatment</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
<td>I vs II&lt;:glyph name=&quot;dbnd&quot;/&gt;:NS I vs III&amp;9552;NS II vs III&amp;9552;NS</td>
</tr>
<tr>
<td>S/D</td>
<td>3.02±0.44</td>
<td>2.88±0.35</td>
<td>3.46±0.51</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>1.05±0.15</td>
<td>0.96±0.16</td>
<td>1.21±0.19</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.68±0.11</td>
<td>0.60±0.10</td>
<td>0.89±0.13</td>
<td></td>
</tr>
</tbody>
</table>

Values are represented as mean±SD. PI, pulsatility index; RI, resistance index. *Analysis of variance test was used.
having ductus venosus with deteriorated Doppler findings after sildenafil treatment. However, they found no such adverse effect from sildenafil on the blood flow in uterine, umbilical, or middle cerebral arteries. They could not offer a reasonable pathophysiological explanation for the possible adverse effect of sildenafil on the fetal blood flow in their group. The cases recruited by Sharp et al. [6] had IUGR before 26 weeks’ gestation with severely compromised umbilical circulation with absent or reversed end-diastolic flow and showed an overall mortality of 45%.

In comparison, the average GA at randomization in the study by Dastjerdi et al. [7] was 35 weeks. They did not report the ratio of babies with absent or reversed umbilical artery flow but, provided the reported gestation. Dastjerdi et al. [7] and El-Sayed et al. [8] reported that only 20% (11 out of the 54 babies included in their study) developed absent or reversed end-diastolic umbilical artery blood flow at some level after randomization, whereas in the study by Trapani et al. [9], reversed umbilical artery blood flow was actually one of their exclusion criteria.

However, none of these studies reported any perinatal deaths or long-term follow-up data. This means that it is too early to presume that this documented improvement in uteroplacental perfusion in less severe IUGR at later GA would improve survival or lead to better long-term clinical fetal outcomes.

These findings were not compatible with Miller et al. [10] who found in an experimental animal study that sildenafil decreased uterine blood flow, and this was associated with big deterioration in fetal well-being. They explained their findings by the action of sildenafil on maternal systemic circulation, altering it and resulting in blood flow ‘steal’ from the uteroplacental circulation to the systemic vascular circulation, which has lowered its resistance owing to widespread systemic vasodilatation. These findings of Miller et al. in the animal study could not be confirmed in human.

There are also many case reports that report success on treating IUGR with sildenafil. In 2014, a patient with impaired umbilical artery flow and IUGR was treated with 50 mg sildenafil three times daily owing to the uteroplacental insufficiency. This case showed an improvement in Doppler measurements for three weeks until delivery was hastened because of reversed end-diastolic flow. Yet, the baby survived and was discharged from intensive are after 80 days. Another review reported significant improvement in Doppler after prescription of sildenafil in a dose of 25 mg twice a day vaginally until the 36th week of gestation, with resultant healthy child delivered [11–13].

**Conclusion and recommendation**

We have given the data referring that sildenafil therapy may offer a new choice to improve perinatal outcomes for women whose pregnancies are complicated by IUGR. However, these data are not sufficiently strong to guide decision making about the use of sildenafil citrate in pregnancies complicated by IUGR.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**