The use of low dose sildenafil citrate in cases of intrauterine growth restriction

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Abstract

Introduction: Intrauterine growth restriction (IUGR) is defined as a birth weight less than the 10th percentile for gestational age. It has a prevalence of the 5–8% in the general population. It represents the second cause of perinatal mortality, after prematurity. Sildenafil citrate is a phosphodiesterase5 (PDE-5) inhibitor, delaying the breakdown of cyclic guanosine monophosphate (cGMP) and enhancing nitric oxide (NO)-dependent vasodilatation. Sildenafil citrate is increasingly used for pulmonary hypertension in pregnancy, and is also emerging as a potential candidate for the treatment of intra-uterine growth retardation and for premature labour.

Aim of work: The aim of this work was to evaluate the effect of the use of low dose sildenafil citrate in cases of IUGR.

Patients and methodology: This study involved 30 patients who presented to Shatby Maternity University Hospital from August- December 2016, they were 26-32 weeks with singleton spontaneous pregnancy, who were diagnosed as intrauterine growth restriction by any of the following criteria:

1. Lag of two weeks or more between the current biometric measures and the documented pregnancy dating in the first trimester.

2. Estimated fetal weight less than the 10th percentile for gestational age.

Cases were subjected to full history taking, general and obstetric examination, laboratory investigations including blood grouping, Rh typing, complete blood count (CBC), blood urea, serum creatinine, liver function tests and complete urine analysis. Ultrasonographic examination was done including Serial fetal biometry (BPD, HC, AC, HC/AC ratio, FL, EFW) to monitor fetal growth and assessment of biophysical profile weekly. Doppler ultrasound: Doppler study of fetal blood vessels including umbilical artery (UA), middle cerebral arteries (MCA) and ductus venosus (DV) weekly. Who are divided into two groups: study group (n=15); women who received 20 mg sildenafil citrate oral tablets for 6 weeks, control group (n=15); women who received placebo. Follow-up was done for 4-6 weeks.

Results: Cases of both groups were matched in age, gestational age, gravidity, parity, blood pressure, weight, body mass index, estimated fetal weight, amniotic fluid index [AFI]. Comparing both groups regarding weekly increase of abdominal circumference [AC] and AFI after treatment; there was no statistically significant difference. Comparing both groups regarding umbilical artery systolic:diastolic ratio, pulsatility index [PI]; there was significant improvement in these indices in the study groups, however there was no statistically significant difference between both groups regarding gestational age at birth [mean 35 weeks versus 34 weeks] nor birth weight mean 1553 gm versus 1439 gm.

Conclusion: The administration of oral sildenafil tablets 20 mg twice a day for 6 weeks improved Doppler indices in umbilical artery and cerebroplacental ratio, yet it had no effect on gestational age at birth nor birth weight.

Introduction

Intrauterine growth restriction (IUGR) is defined as a birth weight less than the 10th percentile for gestational age. With a prevalence of the 5–8% in the general population, IUGR can complicate 10% to 15% of all pregnancies [1,2]. IUGR represents the second cause of perinatal mortality, after prematurity, and it is related to an increased risk of perinatal complication as hypoxemia, low Apgar scores, and cord blood acidemia, with possible negative effects for neonatal outcome [3,4].

IUGR is a wide-ranging pregnancy problem with a number of possible mechanisms leading to reduced fetal growth [5]. Frequently the etiology of IUGR is unknown; however in several cases it is possible to identify fetal (infection, malformation, and chromosomal aberration), placental (chorioangioma, infarction, circumvallated placenta, confined placental mosaicism, obliterator vasculopathy of the placental bed, etc.), maternal (chronic hypertension, pre-gestational diabetes, cardiovascular disease, substance abuse, autoimmune conditions, etc.), and external factors that modulate the normal fetal growth, by acting on a genetically predetermined potential growth [6-8].

Hemodynamic changes involve maternal uterine, fetal umbilical, and middle cerebral arteries and precordial veins for cardiac effects of placental dysfunction [9,10]. The circulatory adaptation consists in an increased umbilical artery and decreased middle cerebral artery blood-flow resistance [11].

Despite the significant risks associated with IUGR-affected pregnancies, there remains no treatment. The only option currently available to clinicians is early delivery of the baby which is itself associated with increased morbidity and/or mortality [12].

Furthermore, there are still no drugs developed specifically for obstetric conditions currently in clinical trials. This has led to the

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assessment of drugs currently used in clinical practice for other
diseases, to be assessed on a re-purpose basis as potential therapeutics
in the treatment of IUGR [13].

Sildenafil citrate is a phosphodiesterase5 inhibitor, delaying the
breakdown of cyclic guanosine monophosphate (cGMP) and
enhancing nitric oxide (NO)-dependent vasodilatation. Sildenafil
citrate is increasingly used for pulmonary hypertension in pregnancy,
and is also emerging as a potential candidate for the treatment of intra-
uterine growth retardation and for premature labour [14]. Sildenafil
has also been proposed as a potential therapeutic strategy to maintain
placental function in pre-eclampsia [15].

Recent studies have demonstrated that sildenafil citrate significantly
enhances vasodilation of myometrial small arteries and is also
associated with fetal weight gain which offers a potential therapeutic
possibility for IUGR [16].

Aim of the work
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dildenafil citrate in cases of IUGR.

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University Hospital from August- December 2016, they were 26-32
weeks with singleton spontaneous pregnancy, who were diagnosed as
intrauterine growth restriction by any of the following criteria:
1. Lag of two weeks or more between the current biometric measures
and the documented pregnancy dating in the first trimester.
2. Estimated fetal weight less than the 10th percentile for gestational age.

Cases were subjected to full history taking, general and obstetric
examination, laboratory investigations including blood grouping, Rh
typing, complete blood count (CBC), blood urea, serum creatinine,
liver function tests and complete urine analysis. Ultrasonographic
examination was done including Serial fetal biometry (BPD, HC, AC, 
HC/AC ratio, FL, EFW) to monitor fetal growth and assessment of
biophysical profile weekly.

Doppler ultrasound: Doppler study of fetal blood vessels
including umbilical artery (UA), middle cerebral arteries (MCA) and
ductus venosus (DV) weekly using Voluson P8 ultrasound machine [GE].

Who are divided into two groups: study group (n=15); women
who received 20 mg sildenafil citrate oral tablets for 6 weeks, control
group (n=15); women who received placebo. Follow-up was done for
4-6 weeks.

Statistical analysis of the data
Data were fed to the computer using IBM SPSS software package
version 20.0. Qualitative data were described using number and
percent. Comparison between different groups regarding categorical
variables was tested using Chi-square test. When more than 20% of
the cells have expected count less than 5, correction for chi-square was
conducted using Fisher’s Exact test. The distributions of quantitative
variables were tested for normality using Shapiro-Wilk test and 
D’Agostino test, also Histogram and QQ plot were used for vision test.
If it reveals normal data distribution, parametric tests were applied. If
the data were abnormally distributed, non-parametric tests were used.
Quantitative data were described using mean and standard deviation
for normally distributed data while abnormally distributed data was
expressed using median, minimum and maximum. For normally
distributed data, comparison between two independent population
were done using independent t-test.

For abnormally distributed data, Correlations between two
quantitative variables were assessed using Spearman coefficient.
Multivariate logistic regression was used. Significance test results are
quoted as two-tailed probabilities. Significance of the obtained results
was judged at the 5% level.

Results
Cases of study and control groups were matched in age [29.07 ±
5.39 versus 27.73 ± 5.55 years] , gestational age [28.13 ± 2.07 versus
28.80 ± 2.11 weeks], gravidity [3.33 ± 1.40 versus 3.53 ± 1.85], parity
[1.07 ± 1.22 versus 1.53 ± 1.64] abortion [1.27 ± 1.39 versus 1.0 ± 1.47],
blood pressure [systolic 127.33 ± 11.0 versus 120.67 ± 13.87, diastolic
78.67 ± 11.25 versus 80.0 ± 8.45 mmHg], weight [81.07 ± 14.42 versus
88.0 ± 9.61 kg], body mass index [30.32 ± 4.99 versus 33.49 ± 3.67],
estimated fetal weight [689.73 ± 207.35 versus 777.0 ± 316.50 gm] ,
amniotic fluid index [5.50 ± 3.08 versus 6.93 ± 3.79].

Comparing study and control groups regards changes in umbilical
artery S/D ratio, PI, middle cerebral artery and cerebroplacental ratio,
there was significant difference showing improvement of placental
perfusion in the study group compared to the control group; as shown
in tables 1-8.

Discussion
Intrauterine growth restriction (IUGR) is defined as a fetus who
is at or below the 10th percentile in weight for its gestational age as
adopted by the ACOG and the RCOG [1,2].

Table 1. Showing S/D ratio in study and control groups before and after therapy, showing
statistically significant decrease in the ratio in study group compared to control group after
therapy.

<table>
<thead>
<tr>
<th>UA S/D</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>2.30 – 3.90</td>
<td>2.50 – 4.20</td>
<td>0.022</td>
<td>0.982</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>3.0 ± 0.48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>2.30 – 3.70</td>
<td>2.60 – 3.70</td>
<td>1.031</td>
<td>0.314</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>3.14 ± 0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.322</td>
<td>0.047*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Showing umbilical artery PI in study and control groups before and after therapy
showing statistically significant decrease in PI in study group compared to control group after
therapy.

<table>
<thead>
<tr>
<th>UA PI</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>0.93 – 1.32</td>
<td>0.90 – 1.30</td>
<td>0.472</td>
<td>0.640</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.04 ± 0.13</td>
<td>1.06 ± 0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>0.89 – 1.30</td>
<td>0.90 – 1.40</td>
<td>2.297*</td>
<td>0.031*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.04 ± 0.15</td>
<td>1.17 ± 0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.917</td>
<td>0.026*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Comparing study and control groups regarding changes in umbilical artery PI and middle
cerebral artery PI before and after therapy, showing statistically significant decrease in PI in
study group compared to control group after therapy.

<table>
<thead>
<tr>
<th>UA PI</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>0.89 – 1.30</td>
<td>0.90 – 1.40</td>
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<td>0.031*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.04 ± 0.15</td>
<td>1.17 ± 0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.917</td>
<td>0.026*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Our results show significant statistical difference between umbilical artery (UA) indices in sildenafil treated cases and control. Mean umbilical artery systolic/diastolic ratio (UA S/D) significantly decreased in the Sildenafil group as compared to the placebo group at the end of trial (P = 0.047). Also, mean umbilical artery pulsatility index (UA PI) significantly decreased in the Sildenafil group in comparison with the placebo group (P = 0.026).

### Table 3. Showing middle cerebral artery PI before and after therapy; showing statistically significant difference.

<table>
<thead>
<tr>
<th>MCA PI</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>1.30 – 1.90</td>
<td>1.30 – 2.50</td>
<td>1.238</td>
<td>0.226</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.62 ± 0.19</td>
<td>1.87 ± 0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>1.80 – 2.40</td>
<td>1.88 – 2.40</td>
<td>2.817</td>
<td>0.009*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>2.10 ± 0.20</td>
<td>2.02 ± 0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.065</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p and t values for Student t-test for comparing between the two groups; *p* value for Paired t-test for comparing between before and after in each group; *: Statistically significant at p ≤ 0.05

### Table 4. Showing improvement in cerebroplacental ratio in study group compared to control group after therapy.

<table>
<thead>
<tr>
<th>CPR</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>1.46 – 2.58</td>
<td>1.38 – 2.67</td>
<td>0.358</td>
<td>0.723</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.97 ± 0.30</td>
<td>2.01 ± 0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>1.49 – 2.66</td>
<td>1.81 – 2.0</td>
<td>4.020*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.94 ± 0.34</td>
<td>1.42 ± 0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.689</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p and t values for Student t-test for comparing between the two groups; *p* value for Paired t-test for comparing between before and after in each group; *: Statistically significant at p ≤ 0.05

### Table 5. Comparing both groups regarding gestational age at delivery; there was no statistically significant difference between both groups.

<table>
<thead>
<tr>
<th>GA at delivery (weeks)</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>Test of sig.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. – Max.</td>
<td>30.0 – 38.0</td>
<td>32.0 – 37.0</td>
<td>t=0.711</td>
<td>0.483</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>35.47 ± 2.47</td>
<td>34.87 ± 2.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ², p: χ² and p values for Chi square test for comparing between the two groups; t, p: t and p values for Student t-test for comparing between the two groups.

### Table 6. Regarding rate of increase in Abdominal circumference in both groups after therapy, there was no statistically significant difference.

<table>
<thead>
<tr>
<th>AC/W (mm)</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>Test of sig.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. – Max.</td>
<td>0.60 – 0.90</td>
<td>0.50 – 0.99</td>
<td>t=0.815</td>
<td>0.422</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>0.75 ± 0.10</td>
<td>0.71 ± 0.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MW, p: p values for Mann Whitney test for comparing between the two groups; t, p: t and p values for Student t-test for comparing between the two groups.

### Table 7. Regarding rate of increase of estimated fetal weight per week in both study and control groups, there was no statistically significant difference.

<table>
<thead>
<tr>
<th>EFW/W (g)</th>
<th>Cases (n=15)</th>
<th>Control (n=15)</th>
<th>Test of sig.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. – Max.</td>
<td>62.50 – 121.50</td>
<td>65.0 – 115.0</td>
<td>t=1.724</td>
<td>0.096</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>98.77 ± 20.98</td>
<td>87.20 ± 15.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regarding MCA Doppler study our results show significant statistical difference between MCA PI between cases and control, mean MCA PI significantly higher in sildenafil group in comparison with placebo group P = 0.001. Also, cerebroplacental ratio significantly decreased at the end of study in control group compared to cases group (p = 0.001).

Results suggest that sildenafil improved uteroplacental circulation among sildenafil treated group. However, there was no significant statistical difference between the rate of increase in AC per week or EFW per week between case and control group. Also, there was no significant statistical difference between measurements of AFI between cases and control group at the end of the study.

Von Dadelszen et al. [17] tested the potential for sildenafil to improve fetal growth in an open-label pilot study. Ten women with pregnancies affected by severe early-onset FGR, where the chance of intact fetal survival was felt to be less than 50%, accepted the option of taking 25 mg sildenafil TDS. Outcomes were compared with those from matched contemporaneous sildenafil-naive pregnancies (n=17).

Sildenafil treatment was associated with increased post-treatment fetal growth velocity in the AC [9/10 (treated) vs7/17 (control); odds ratio, 12.9; 95% CI, 1.3, 126]. However, it is unclear if the higher levels of termination and permissive stillbirth in the sildenafil-naive group reflect poorer prognosis or altered management.

E. Ferreira et al. [18] performed a retrospective and descriptive case series of all hospitalized pregnant women who received sildenafil for severe IUGR. Study included 19 hospitalized pregnant women who received sildenafil for severe IUGR. Sildenafil was started at an average of 25 weeks +3 days (median: 25, [20+1, 30+6]) in average dosage of 20 mg orally 3 times/day until delivery. Before sildenafil, estimated average fetal weight was 558g [237, 1208] and increased to an average of 807g (median: 820, [320, 1360]) at delivery and with an average fetal weight was 558g [237, 1208] and increased to an average of 807g (median: 820, [320, 1360]) at delivery and with an average
velocity waveforms of the uterine (UtA), umbilical (UA) and fetal middle cerebral (MCA) arteries in pregnancies with intrauterine growth restriction (IUGR).

This was a prospective study of 35 singleton pregnancies (gestational age, 24–31 weeks) with IUGR and abnormal UtA and UA Doppler waveforms. They compared maternal arterial blood pressure and Z-scores of the pulsatility index (PI) of UtA, UA and fetal MCA before and after application of a transdermal GTN patch (average dose, 0.4 mg/h), oral sildenafil citrate (50 mg) or placebo.

There was a significant decrease in UtA-PI after application of GTN (21.0%) and sildenafil citrate (20.4%). A significant reduction in UA-PI was also observed for both GTN (19.1%) and sildenafil citrate (18.2%). There was no difference in UtA- and UA-PI when the GTN and sildenafil groups were compared. No changes in Doppler velocimetry were observed in the placebo group and no significant change in MCA-PI was observed in any group. Maternal arterial blood pressure decreased with administration of both GTN and sildenafil citrate in those with pre-eclampsia. No effect was noted on birthweight in both groups.

Dastjerdi et al. also performed a randomized double-blinded and placebo-controlled trial, forty one pregnant women with documented intrauterine growth retardation at 24–37 weeks of gestation who were evaluated for the effect of the single dose of Sildenafil citrate on uteroplacental circulation as determined by Doppler ultrasound study of the umbilical and middle cerebral arteries.

Sildenafil group fetuses demonstrated a significant decrease in systolic/diastolic ratios and pulsatility index for the umbilical artery and a significant increase in middle cerebral artery pulsatility index (MCA PI). They concluded that sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction. It could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR). Again, this agrees with our work.

Also, Lin et al. [21] reported a decrease in uterine artery pulsatility and resolution of uterine artery notching following administration of sildenafil citrate to a case of IUGR diagnosed at 26 weeks of gestations. Contradictory to our findings, they also observed increase in EFW without maternal or neonatal adverse outcomes.

Despite a few negatives studies, sildenafil citrate has shown promise in vitro as well as in animal studies in the treatment of both IUGR and pre-eclampsia. Wareing et al. [22] conducted a study where small artery dissected from myometrial biopsies obtained at cesarean section from normal pregnant women (n=27) or women whose pregnancies were complicated by FGR (n=12) were mounted on wire myographs. Vessels were constricted (with arginine vasopressin or U46619) and relaxed (with bradykinin) before and after incubation in myographs. Velocities of the uterine artery were measured before and after incubation in myographs. Vessels were constricted (with arginine vasopressin or U46619) and relaxed (with bradykinin) before and after incubation in myographs. Vessels were constricted (with arginine vasopressin or U46619) and relaxed (with bradykinin) before and after incubation in myographs.

Further studies with larger sample size are needed to fully verify the efficacy of sildenafil citrate in the management of IUGR.

Conflict of interest
Authors declare that there is no conflict of interest regarding publication of this article.

References

Conclusion
The administration of oral sildenafil tablets 20 mg twice a day for 6 weeks improved Doppler indices in umbilical artery and cerebroplacental ratio, yet it had no effect on gestational age at birth nor birth weight.