The effect of sildenafil on amniotic fluid volume in cases of borderline oligohydramnios in uncomplicated pregnancies: a randomized clinical trial.

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Research Article

Keywords: Amniotic fluid volume, sildenafil, pregnancy outcomes, oligohydramnios, borderline amniotic fluid index, umbilical cord pH, cardiotocography (CTG)

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Abstract

Introduction:
Low amniotic fluid volume and oligohydramnios is important issue during pregnancy and is associated with an increase in fetal and neonatal mortality and morbidity. Finding a solution to it can improve fetal and neonatal outcomes.

Objective:
The purpose of the present study was to evaluate the effect of sildenafil on oligohydramnios in uncomplicated pregnancies.

Methods:
A placebo-controlled randomized clinical trial was performed on women with oligohydramnios and gestational age of 30 to 37 weeks and singleton pregnancy. The eligible women were randomly assigned into two groups. In the intervention group, 25 mg oral sildenafil was prescribed every 8 hours in conjunction with intravenous hydration therapy with 2 liters isotonic solution (normal saline) infused within 4 hours and in the control group, placebo and hydration therapy similar to the intervention group was prescribed. Amniotic fluid volume was re-evaluated 24 hours after treatment. If at least a 20% increase in amniotic fluid volume was detected by ultrasound, the woman was discharged; otherwise, the above regimen was repeated again for the next 24 hours.

Discharged patients continued to take sildenafil or placebo at the same dose and consumption of 2 liters of oral fluids per day up to 37 weeks or delivery each happened earlier. Fetal monitoring was performed using non stress test (NST) twice a week, biophysical profile, and amniotic fluid volume measurement once a week. Amniotic fluid volume and pregnancy and neonatal outcomes were compared in the two groups.

Results:
One hundred ninety women finished the study. There was no statistically significant difference between the two groups in terms of maternal age, body mass index (BMI), parity, live birth rate, gestational age before the intervention, amniotic fluid index, and the type of pregnancy; spontaneous or using assisted reproductive technology (ART). In undelivered women, after the intervention, the amniotic fluid index was significantly higher in the case group than the control group. The number of women, whose pregnancies continued after the third week of intervention, were higher in the sildenafil group.

At the end of the sixth week after intervention, 40 women (42.1%) in the case group continued their pregnancies versus 5 women (5.3%) in the control group (P = 0.001). Cesarean section rate, neonatal intensive care unit (NICU) admission, abnormal cardiocograph, umbilical cord pH less than 7.2, and Apgar score of less than 7 in 5 minutes, were less in the intervention group than the control group. While
the mean gestational age at birth and birth weight was higher in the intervention group than the control group. There was no perinatal death in both groups.

Abnormal cardiotocography (CTG) (AOR= 6.3, CI95% 2.4-15.1, P< 0.001), cesarean section rate (AOR= 4.2, CI95% 2.1-8.9, P< 0.001), birth weight of less than 2500 gram (AOR= 3.3, CI95% 1.6-6.9, P= 0.001), gestational age at birth of less than 37 weeks (AOR= 3.2, CI95% 1.5-6.9, P= 0.009 ), Apgar score of less than 7 in 5 minutes (AOR= 2.6, CI95% 1.1-6.4, P=0.037), umbilical cord pH of less than 7.2 (AOR= 2.5, CI95% 1.9-6.9, P=0.064), and NICU admission (AOR= 2.5, CI95% 1.1-5.9, P=0.032) were more in the control group.

The most common maternal complication in patients was headache (15.8 vs. 7.4%) and headache (12.6 vs. 5.3%) which was more in the intervention group than the control group, but not statistically significant.

Conclusion:

In pregnant women with oligohydramnios, sildenafil may be associated with better pregnancy outcomes.

Introduction:

Oligohydramnios is an important issue during pregnancy and is associated with an increase in fetal and neonatal mortality and morbidity (1). Cord compression, NICU admission, cesarean delivery due to fetal distress, meconium aspiration syndrome, fetal growth restriction, preterm birth, and even fetal death have been reported in cases of oligohydramnios in different studies (1, 2, 3 ). AFI of 5 cm or less is defined as oligohydramnios (3) and borderline amniotic fluid index (AFI) or borderline (marginal) oligohydramnios has been defined as $5.1 \leq AFI \leq 8.0$ cm (4, 5). Borderline oligohydramnios has been reported in some studies (3, 6, 7, 8) as a risk factor for fetal wellbeing. However, the other studies did not propose such poor outcomes (4, 5, 9, and 10). Correct and timely diagnosis of oligohydramnios and borderline oligohydramnios is associated with better outcomes in patients (4, 5).

Different methods have been proposed for treating oligohydramnios, among which non-invasive methods like hydration are more practical and more acceptable methods. Sildenafil citrate has been proposed as one of these medical treatments (11, 12, 13). Sildenafil inhibits phosphodiesterase type 5 (PDE5), which is an enzyme in the walls of blood vessels. PDE5 inhibitors (like sildenafil) block the PDE5 enzyme and this inhibition relaxes the blood vessels and increases blood flow as a result (13). Sildenafil is also currently used to treat pulmonary arterial hypertension (14, 15). Using sildenafil leads to loosening the arterial wall, increasing uterine blood flow, and, uteroplacental perfusion as a consequence (11, 12). However, there are not enough studies on the effect of sildenafil on oligohydramnios. The purpose of the present study was to evaluate the effect of sildenafil on the amount of amniotic fluid volume in cases of borderline oligohydramnios.

Materials And Methods:
This clinical trial was performed in Akbarabadi Training Hospital in Tehran, Iran on pregnant women with the diagnosis of borderline oligohydramnios. Inclusion criteria were singleton pregnancy, gestational age between 30 to 37 weeks, and diagnosis of borderline oligohydramnios (mean amniotic fluid index between 5–8 cm, measured by transabdominal ultrasound in the third trimester of pregnancy. Patients with fetal growth restriction, abnormal fetal Doppler, fetal anomaly, fetal distress, any systemic maternal disorders like chronic hypertension, pre-pregnancy diabetes; beginning of labor, rupture of the membranes, using prostaglandin synthetase inhibitors, any maternal cardiac, pulmonary, and kidney disorders, in which using bolus fluid is not safe, were excluded the study. Written informed consent was obtained from all participants before entering the study. Ethics Committee of Iran University of Medical Sciences confirmed conducting the study (IR.IUMS ID IR.IUMS.REC 1396.31246). The study was registered in the Iran Registry of Clinical Trials (IRCT) (IRCT ID IRCT20091023002624N21). Recruitment started in December 2017. 230 women were assessed for eligibility and 210 eligible women were assigned into the two groups (Fig. 1). One of the colleagues who was not aware of the study using block randomization performed randomization. Eligible women were randomly assigned into two groups (using sealed, sequentially distributed envelopes to which the letters A and B had been allocated: the letter A was assigned to the case group and the letter B was decided for the placebo group). The women and investigator were not aware of the study groups. In addition, a statistician who was not aware of the groups of the study performed statistical analysis. In the intervention group, 25 mg oral sildenafil was prescribed every 8 hours in conjunction with intravenous hydration therapy (2 liters isotonic solution (normal saline) infused within 4 hours) and in the control group, placebo and hydration therapy was prescribed similar to the intervention group. Betamethasone was administered for pregnancies with a gestational age of fewer than 34 weeks. The amniotic fluid index was re-evaluated 24 hours after the intervention. The women were discharged if at least a 20% increase in amniotic fluid was detected by ultrasound; otherwise, the above regimen was repeated again for the next 24 hours. Discharged women continued to take sildenafil or placebo with the same dosages and consumption of 2 liters of oral fluids per day up to 37 weeks or delivery, each happened earlier. Fetal wellbeing was monitored by using NST, twice a week, and performing biophysical profile and amniotic fluid volume measurement once a week. Amniotic fluid level and pregnancy and neonatal outcomes were compared in the two groups. The main outcome of the study was increasing in the amniotic fluid index (AFI). The other outcomes were pregnancy and neonatal outcomes including the interval between intervention to delivery, gestational age at birth, birth weight, umbilical artery pH, Apgar score, and neonatal intensive care unit admission. Data were statistically analyzed using STATA software version 14(Texas 77845 USA). The significance level was considered less and equal to 0.05. Quantitative data were displayed as mean and standard deviation and qualitative data were displayed as numbers and percentages. Quantitative variables between the two groups were statistically analyzed using t-test or Mann-Whitney test and qualitative data were analyzed using Chi-square or Fisher test. Logistic regression test and odds ratio with 95% confidence interval was used to evaluate the consequences.

Results:
One hundred ninety women finished the study. There was no statistically significant difference between the two groups in terms of maternal age, body mass index (BMI), parity, live birth rate, gestational age before the intervention, amniotic fluid index, and the type of pregnancy (spontaneous or using ART) (Table 1). In undelivered women, after the intervention, the amniotic fluid index was significantly higher in the case group than the control group (Table 2). The number of women, whose pregnancies continued after the third week of intervention, were higher in the sildenafil group (Table 3).

### Table 1
Comparison of baseline characteristics between the two groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control group, n = 95</th>
<th>Intervention group, n = 95</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (year), mean ± SD</td>
<td>28.2 ± 7.4 (18–43)</td>
<td>26.7 ± 7.1 (18–42)</td>
<td>0.179</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>25.1 ± 1.9 (22–30)</td>
<td>24.8 ± 1.7 (22–28)</td>
<td>0.368†</td>
</tr>
<tr>
<td>Parity, mean ± SD</td>
<td>2.1 ± 1.5 (0–2)</td>
<td>2.0 ± 1.5 (0–2)</td>
<td>0.615†</td>
</tr>
<tr>
<td>Gestational age (week), mean ± SD</td>
<td>32.9 ± 1.6 (30-35.5)</td>
<td>33.1 ± 1.7 (30-35.5)</td>
<td>0.401†</td>
</tr>
<tr>
<td>AFI (cm), mean ± SD</td>
<td>5.4 ± 0.4 (5-6.5)</td>
<td>5.3 ± 0.4 (5-6.9)</td>
<td>0.422‡‡</td>
</tr>
<tr>
<td>Spontaneous pregnancy, N (%)</td>
<td>83 (87.4)</td>
<td>80 (84.2)</td>
<td>0.533*</td>
</tr>
</tbody>
</table>

Note: SD: standard deviation, AFI: amniotic fluid index, †: Mann-Whitney, *: chi², ‡‡: t-test

### Table 2
Amniotic fluid index in the two groups after treatment.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control group, n = 95</th>
<th>Intervention group, n = 95</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI Week 1 Mean ± SD</td>
<td>5.7 ± 0.9</td>
<td>6.2 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFI Week 2 Mean ± SD</td>
<td>5.5 ± 1.1</td>
<td>7.0 ± 1.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFI Week 3 Mean ± SD</td>
<td>5.4 ± 1.1</td>
<td>7.4 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFI Week 4 Mean ± SD</td>
<td>5.8 ± 1.1</td>
<td>9.4 ± 2.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFI Week 5 Mean ± SD</td>
<td>6.6 ± 1.9</td>
<td>10.1 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFI Week 6 Mean ± SD</td>
<td>5.5 ± 0.4</td>
<td>10.9 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Table 3
Number of undelivered women in the two groups.

<table>
<thead>
<tr>
<th>Undelivered, N (%)</th>
<th>Control group, n = 95</th>
<th>Intervention group, n = 95</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>92 (97.9)</td>
<td>95 (100.0)</td>
<td>0.497</td>
</tr>
<tr>
<td>Week 2</td>
<td>92 (96.8)</td>
<td>95 (100.0)</td>
<td>0.264</td>
</tr>
<tr>
<td>Week 3</td>
<td>76 (80.0)</td>
<td>95 (100.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>26 (27.4)</td>
<td>88 (92.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 5</td>
<td>8 (8.4)</td>
<td>72 (75.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 6</td>
<td>5 (5.3)</td>
<td>40 (42.1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

At the end of the sixth week after intervention, 40 women (42.1%) in the case group continued their pregnancies versus 5 women (5.3%) in the control group (P = 0.001) (Table 3). Cesarean section rate, NICU admission, abnormal cardiotocography, umbilical cord pH less than 7.2, and Apgar score of less than 7 in 5 minutes, were less in the intervention group than the control group (Table 4). While the mean gestational age at birth and birth weight was higher in the intervention group than the control group. There was no perinatal death in both groups.
Table 4
Comparison of maternal and neonatal outcomes in two groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control group, n = 95</th>
<th>Intervention group, n = 95</th>
<th>OR(95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean section, N (%)</td>
<td>58 (61.1)</td>
<td>27 (28.4)</td>
<td>3.9(2.15–7.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hemorrhage before delivery, N (%)</td>
<td>2 (2.1)</td>
<td>1 (1.1)</td>
<td>2.1(0.2–22.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abnormal cardiotocography, N (%)</td>
<td>34 (35.8)</td>
<td>11 (11.6)</td>
<td>4.2(2.0-9.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apgar Score min 5 &lt; 7, N (%)</td>
<td>30 (31.6)</td>
<td>13 (13.7)</td>
<td>2.9(1.4-6.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Abnormal Doppler, N (%)</td>
<td>5 (5.3)</td>
<td>0</td>
<td>-</td>
<td>0.06</td>
</tr>
<tr>
<td>PH &lt; 7.2, N (%)</td>
<td>20 (21.0)</td>
<td>9 (9.5)</td>
<td>2.5 (1.1–5.9)</td>
<td>0.026</td>
</tr>
<tr>
<td>NICU admission, N (%)</td>
<td>31 (32.6)</td>
<td>15 (15.8)</td>
<td>2.6(1.3–5.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Birth Weight &lt; 2500gr, N (%)</td>
<td>57 (60.0)</td>
<td>34 (35.8)</td>
<td>2.7(1.5–4.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gestational age &lt; 37 week, N (%)</td>
<td>61 (64.2)</td>
<td>34 (35.8)</td>
<td>3.2 (1.8–5.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abnormal cardiotocography (CTG) (AOR = 6.3, CI95% 2.4–15.1, P < 0.001), cesarean section rate (AOR = 4.2, CI95% 2.1–8.9, P < 0.001), birth weight of less than 2500 gram (AOR = 3.3, CI95% 1.6–6.9, P = 0.001), gestational age at birth of less than 37 weeks (AOR = 3.2, CI95% 1.5–6.9, P = 0.009 ), Apgar score of less than 7 in 5 minute (AOR = 2.6, CI95% 1.1–6.4, P = 0.037), umbilical cord pH of less than 7.2 (AOR = 2.5, CI95% 1.9–6.9, P = 0.064), and NICU admission (AOR = 2.5, CI95% 1.1–5.9, P = 0.032) were more in the control group. The most common maternal complication in patients was headache (15.8 vs. 7.4%) and headache (12.6 vs. 5.3%) which in the intervention group was more than the control group, but not statistically significant.

Discussion:

The aim of the present study was to evaluate the effect of sildenafil on amniotic fluid volume in cases of borderline oligohydramnios and pregnancy outcome. The results of the study showed that sildenafil is associated with an increase in the amniotic fluid volume and better pregnancy outcomes.

Amniotic fluid volume has an important role in the safety of the fetal environment (16) and its measurement is an important part of fetal and prenatal surveillance (17). Low volume of amniotic fluid...
including borderline oligohydramnios is an important issue during pregnancy and is associated with an increase in fetal and neonatal mortality and morbidity and poor pregnancy outcome (4, 6, 18, and 19). Finding a way to increase the amount of amniotic fluid volume can improve pregnancy, fetal and neonatal outcomes (19). Amnioinfusion is an option for increasing amniotic fluid volume; however, it is an invasive procedure and has some probable risks. Using non-invasive methods (if effective) without hospitalization can be accompanied by fewer complications and more patient comfort and convenience. In some cases, the women need etiology-specific management of oligohydramnios like in cases of the ruptured membrane. However, there are some cases of the low volume of amniotic fluid where no specific cause is known. In these cases, increasing the amniotic fluid volume can improve the pregnancy outcome (1, 19, 20). Various modalities have been suggested for patients with oligohydramnios, including maternal hydration. Maternal hydration, particularly in cases of isolated oligohydramnios in the third trimester, can be effective in this way (1, 19, 20, 21, and 22). Hydration can increase the amniotic fluid volume both in women with oligohydramnios and normal amniotic fluid volume as well (22). It has been reported that a combination of intravenous hydration (for a duration of 1 day) and oral hydration (for a duration of at least 14 days) had better results (22). The effects of maternal hydration on amniotic fluid volume are temporary; therefore, oral hydration should continue until delivery (23). There is currently no known approved medication for increasing the amniotic fluid volume and treating oligohydramnios (including borderline oligohydramnios) (19).

Prescription of L-arginine which is an amino acid and endogenous precursor of nitric oxide (NO) and other amino acids (24, 25, 26, 27), antioxidant supplements (28), and recently sildenafil (11, 12, 13), have been proposed in some studies for increasing the amniotic fluid volume and improving perinatal outcomes.

Sildenafil increases the effects of nitric oxide (NO) which leads to arterial vasodilatation and therefore, can increase the uteroplacental perfusion as a consequence (11, 12). This mechanism may increase the amniotic fluid volume and improve fetal growth and pregnancy outcome. The previous studies have used sildenafil in cases of intrauterine fetal growth restriction and reported successful outcomes (29, 30, and 31). In addition, a multicenter study (32) showed that sildenafil therapy could cause a significant improvement in perinatal outcome in women with oligohydramnios only, fetal growth restriction (FGR) only, and a combination of oligohydramnios and FGR. The results of these studies are in agreement with the present study and the other studies (6, 11, and 31). Vasodilation produced by sildenafil can improve blood supply to the placenta and uterine vasculature, which can lead to an increase in fetal renal blood flow, and consequently amniotic fluid (31, 32, and 33).

In the present study, there were no significant side effects in women receiving sildenafil. Conducted studies have also shown that this treatment is safe (34).

There are still many unanswered questions about the efficacy of sildenafil on oligohydramnios, and this study is a preliminary study on this subject. Further research is essential to build on the study's results and future studies are required to reach robust conclusions on this matter.
Declarations:

Conflicts of interests:

All authors declare no conflict of interest.

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Ethics approval:

Institutional review board approval and institutional ethics committee approval was obtained.

Ethics committee reference number: IR.IUMS.REC 1396.31246

Authors' Contribution:

Maryam Kashanian: The conception and design of the study, data interpretation, writing of the paper.

Nooshin Eshraghi: Data collection.

Saeedeh Moslemi: Data analysis, Data collection

Narges Sheikhansari: Data interpretation, writing, and revising.

References:


Figure 1
The Consort Flowchart

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