

Comparison Between The Effect Of Sildenafil Citrate And Routine Tocolytic Agents In A Prevention Of Preterm Labor

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Abstract

Background: Labor is the occurrence of regular contractions lead to opening up of the cervix. This normally occurs at between 37 and 42 weeks of pregnancy. Its occurrence before 37 weeks known as preterm labor. The aim of the present study is to assess the chance of term delivery in patients using vaginal sildenafil prophylactically vs using routine tocolytic agents therapeutically.

Methods: The study conducted on 60 pregnant women with gestational age 24- 34 weeks. they were randomly divided into two groups: Group I included 30 cases received Sildenafil citrate (50 mg once at night vaginally) from 24 week to 34 week gestation plus routine therapy for preterm labor. Group II included 30 cases who treated only with β_2 -adrenergic-receptor agonists/ Isoxsuprine (duvadilan) 10 mg/btd on presence of contraction and calcium channel blocker. An assessment of uterine contraction done clinically by abdominal examination, vaginal examination for cervical dilatation and by CTG that evaluated uterine contraction severity and fetal wellbeing.

Results: The results of the present study showed that there was no significant difference ($p>0.05$) in age, parity, number of preterm labor, abortions, and presence or absence of uterine pathology. Post-partum hemorrhage not recorded in 73% of control group and 50% of study group. The live birth rate was higher in the control group with higher congenital anomaly and intrauterine growth retardation of the newborns but also statistically not significant. **Conclusions:** Examine the health Using of vaginal sildenafil citrate is an effective option for prevention of threatened preterm labor than therapeutic tocolytics that used routinely.

Keyword: Sildenafil citrate, Pre-term delivery, Tocolytic therapy, nitrates

Introduction:

Preterm labor define as the labor that occurs between 24 to 37 weeks gestation ⁽¹⁾. Preterm labors grouped to early or late preterm. Early preterm labor happens before 33 weeks of gestation, and late preterm happens between 34 to 36 weeks of gestation ⁽²⁾. Three factors affected with labor: cervical variations, persistent contractions of uterus and initiation of the decidua besides membranes. Perinatal mortality, neonatal mortality and morbidity contrariwise related with gestational age, complications include “periventricular leukomalacia, necrotizing enterocolitis, respiratory distress syndrome, jaundice and kernicterus, neonatal infections, and long hospitalization” ⁽³⁾. Multiple pregnancies related with high preterm delivery rate, the rate of preterm delivery varies significantly between black and white females ⁽⁴⁾. Unchangeable danger causes include a condensed cervix (< 25 mm before 28 weeks’ gestation) and a previous history of preterm labor ⁽⁵⁾. Behavioral danger causes include low body mass index of mother, smoking, drugs abuse, and a small pregnancy interval ⁽⁶⁾. Any history of cervical surgery may be lead to preterm delivery ⁽⁷⁾. In addition to that, urinary tract infections and periodontal illness also increase preterm labor ⁽⁸⁾. Management depend on gestational age of females, if > 34 weeks can admit to hospital for observation only and for encourage cervical dilation and effacement, fetal wellbeing and deal with any complications, but if < 34 weeks and associate with preterm delivery signs and symptoms must be admit, and give her tocolytic drugs for more than 48 hours to stop labor ⁽⁹⁾. Tocolytics are drugs used to suppress uterine contractions for women in preterm labor. The most widely used tocolytic are the betamimetics, however, these are associated with a high frequency of unpleasant and sometimes severe maternal side effects ⁽¹⁰⁾. Naturally, tocolytics are a given between 22 to 34 weeks of gestational and no contraindications ⁽¹¹⁾. The effectiveness of these drugs depend on an initial and correct diagnosis, fibronectin of fetus and length of cervix ⁽¹³⁾. Prevention of preterm labour has the priority in health care system programs since preventive measures are superior to treatment protocols. Prevention of preterm labor to be successful requires multiple approaches including public health efforts with educational health programs, modification of patient lifestyle, optimal obstetric protocols of healthcare, efficient approaches for prediction and diagnosis of threatened and established preterm labor and implementation of effective, tailored case management pathways according to case scenario ⁽¹⁷⁾. Sildenafil enhances smooth muscle relaxation. In addition, Sildenafil citrate may sensitize the myometrium to other tocolytic agents and this effect can prove the superiority of combination over tocolytics alone ⁽¹⁹⁾. It is a “phosphodiesterase 5 (PDE5) inhibitor” which increases nitric oxide (NO), which lead to reducing mother peripheral vascular resistance and making the low-resistance/high-caliber uteroplacental component for acceptable blood stream to the fetus ⁽²⁰⁾. The aim of this research study is to compare the effectiveness of vaginal Sildenafil citrate versus β_2 -adrenergic-receptor agonists

(Isoxsuprine) and calcium channel blocker (nifedipine) in prevention of premature labour in pregnant women.

Method:

The study performed on 60 pregnant women from those visiting to Obstetrics & Gynecology departments at Al- Kahdimyya Hospital/ Baghdad/ Iraq in the period from January 2019 to January 2021. The inclusive research criteria were; 18– 42 years old, BMI < 30 kg/m², gestation (24-34 weeks). These women included in the study considered as high risk for preterm labor due to presence of single or multiple pregnancies, polyhydramnios, short cervix, uterine fibroids, uterine abnormality as septate or bicornuate uterus and history of preterm labour in previous pregnancies. The exclusive research criteria included; presence of rupture membranes, trauma, placenta previa, RH iso immunity, major congenital fetal malformations, chronic maternal diseases: e.g. diabetes, hypertension, thyroid disease cardiac or renal disorders. A written informed consent obtained from all recruited subjects for the research study according to medical ethics committee of Al- Nahrain University. The recruited gestations were randomly allocated equally into two research groups: Group I included 30 cases received vaginal Sildenafil citrate (Viagra/ Pfizer/50 mg film coated tablets/ single dose daily at night) unless if there was side effect as vaginal irritation or itching the dose was stopped for five days and return back later on. On the other hand, the dose increased to two times daily if indicated as in triplet pregnancy, multiple fibroids, or severe uterine contraction. If uterine contraction was severe; an addition of β_2 -adrenergic-receptor agonists/ Isoxsuprine (duvadilan) 10 mg two times daily) and/ or calcium channel blocker (nifedipine 30 mg orally bolus dose then maintenance dose of 10 mg once daily if duvadilan alone was not effective in removing contraction. Group II included 30 cases who did not receive sildenafil and were treated with β_2 -adrenergic-receptor agonists/ Isoxsuprine (duvadilan) 10 mg two times daily) and/ or calcium channel blocker (nifedipine 30 mg orally bolus dose then maintenance dose of 10 mg once daily) if duvadilan alone was not effective. These drugs used only when these women have symptoms. Full clinical history taking including meticulous menstrual history for precise estimation of expected date of delivery taken. Full clinical physical examination and assessment, involving general, obstetric and local examinations done. Laboratory investigations e.g. CBC, RBS, kidney and liver function tests evaluated. Sonographic examination and assessment with Trans-abdominal sonography for fetal biometry (including BPD, HC, FL and AC), placental site and grading, amniotic fluid volume, fetal anomalies. Transvaginal sonography for cervical length (CL) measurement (at 24, 28 and 32 weeks of gestation). Follow up: All patients were followed up every 3-4 weeks until time of delivery and for one week later unless emergency conditions occur; earlier visit were indicated to increase the dose of the

drug to twice daily as in (trauma, fever, UTI, diarrhea, flu and or Covid 19 viral infection if present). Any episodes of premature labour contractions were clinically assessed carefully and recorded through abdominal examination and by CTG. vaginal examination for assessment of cervical dilatation performed. If manifestations of threatened preterm labour progressed and not controlled with the regimen in this study, the patients admitted to the hospital for further management until premature uterine contractions have resolved. Any complications developed recorded. The data analyzed using Statistical Package for Social Sciences (SPSS) version 22.0. Statistics including frequency mean and standard deviation calculated to describe the data. The groups compared by applying independent sample t-test (unpaired t-test between two groups) and chi square (for non-continuous data or percentage). The results considered statistically significant when p value was less than 0.05.

Results:

The present study was done on 60 pregnant females during their 2nd trimester who were suspected to be at risk of preterm labor. The females were divided into **control** group who received the routine treatment for prevention of preterm labor and **study** group who were treated with vaginal sildenafil in addition to routine therapy. The maternal parameters of the study groups were summarized in table 1 comparison was done for mean age of females between the control group and study group. It was 30.33 ± 6.68 years and 31.20 ± 6.61 years respectively. There was no significant difference ($p=0.615$) between them (table 1). The results illustrated that 15 (50%) of control group were primigravida, 8(26%) were para1, 3(10%) were para 2, 1(3.3%) were para3 and 3(10%) were para 4 or more. Regarding study group 11 (36.7%) were primigravida, 11 (36.7%) were para 1, 5 (16%) were para 2, 1 (3.3%) were para3 and 2(3.6%) were para 4 or more. For all groups there was no significant difference ($p=0.774$) between control and study groups regarding their parity. The past obstetrical history recorded that 12(40%) were having history of preterm labor in the control group and 14(46%) in study group but the difference was statistically not significant ($p=0.6$). In addition the abortion rate was calculated from the history of the females enrolled in the study. There was no history of previous abortions in 18 (60%) versus 22 (73.3%) in control and study groups, 1 abortion in 1 (3.3%) of control group and 1(3.3%) in study group. Two abortions were calculated in 8 (26.6%) of control group and 7 (23.3%) in study group. Three or more abortions were found in 3(10%) of control group but no cases were recorded in the study group. The uterine pathologies were studied in both groups and it was found that no uterine pathologies were documented in 9(30%) of control group and 13(43.3%) of study group. However, 12(40%) of control group were having congenital anomaly and 9(30%) were having acquired pathologies, while in the study

group 9(30%) were having congenital anomalies and 8(26.7%) were having acquired pathologies (table 1). The pregnancy occurred naturally in 23(78.7%) of control group and 18(60%) of the study group. Five (16.7%) of control group conceived through IVF and 2(6.7%) through IUI, while 5 (16.7%) of study group conceived through IVF and 7(23.35) were having their pregnancy following IUI (table 1). The frequency of post-partum hemorrhage (PPH) followed up clinically in both groups and classified into mild, moderate and severe hemorrhage. There was no PPH in 22(73%) and 15 (50%) in control and study groups respectively. Mild PPH was recorded in 7 (23%) in the control group and 13(43%) in the study group, while moderate PPH was not recorded in control group it was 2 (6.7%) in the study groups. Severe PPH was recorded in control group only in 1 (3.3%) of cases but was not found in any case of the study group. But in all grades of PPH the statistical analysis were not significant as shown in table 2, figure 1 and 2. The number of females with single, twin and triple pregnancies were similar in both groups which were 21(70%) being single fetus, 6(20%) were having twin and 3(10%) were having triple pregnancy as shown in table 3. Regarding the mean gestational age at time of labor in weeks, it was 34.12 ± 3.4 weeks in control group while the mean gestational age was 35.33 ± 2.67 weeks in the study group that is higher but not significant statistically. The mean neonatal body weight at time of labor was 2.46 ± 0.77 kg while the mean body weight of the neonates in the study group was higher but not significant in the study group 2.71 ± 0.75 kg. The live birth rate was higher in control group 81.67 % and 74.97 % in the study (figure 3) group. The fetal anomaly and fetal growth restriction (FGR) was higher in the control group than the study group but all these results were statistically not significant as shown in table 3 and figure 4.

Discussion:

Preterm birth is almost a major obstetric healthcare problem worldwide. It represents a major cause of neonatal, infant and child death and disability up to age of 5 years in the developed world and represents the leading cause of perinatal mortality and morbidity in the whole world ⁽²⁷⁾. The present study performed on pregnant females to evaluate the effectiveness of sildenafil on preventing preterm labor in suspected women. The results of the present study illustrated no significant difference between the study group who were treated with vaginal Sildenafil citrate (Viagra/ Pfizer/50 mg film coated tablets/ single dose daily at night) and the control group who did not receive sildenafil and were treated with β_2 -adrenergic-receptor agonists/Isoxsuprine (duvadilan) 10 mg two times daily) and/ or calcium channel blocker (nifedipine 30 mg orally bolus dose then maintenance dose of 10 mg once daily) if duvadilan alone was not effective regarding their age, parity, miscarriage rate and presence or absence

of any uterine pathology whether congenital or acquired. This random allocation and the lack of significant difference with respect to these characteristics of enrolled pregnant women is mandatory to avoid any bias in the primary outcome of pregnancy that can be attributed to such factors, thereby limiting any possible difference in the endometrial receptivity criteria and pregnancy outcome. The frequency of post-partum hemorrhage (PPH) followed up clinically in both groups and classified into mild, moderate and severe hemorrhage. Mild PPH cases were recorded more in the study group, while moderate PPH was not recorded in control group and it was 2 (6.7%) in the study groups. Severe PPH was recorded in control group only in 1 (3.3%) of cases but was not found in any case of the study group. But in all grades of PPH the statistical analysis were not significant as shown in table 2, figure 1 and 2. Nitric oxide is a key signaling molecule involved in the vasodilator response of smooth muscle cells. NO activates the cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway within smooth muscle cells to promote smooth muscle cell relaxation. Animal studies were among the first to identify NO as a vasodilator agent that increased uterine blood flow⁽²⁸⁾. Sildenafil citrate inhibits phosphodiesterase 5 (PDE5) maintaining activation of cGMP and PKG and maximizing the effect of existing NO thus facilitating smooth muscle cell relaxation⁽²⁹⁾. This mechanism may be the cause of post-partum hemorrhage in preterm labor when using sildenafil. The present study agree with previous studies which concluded that women with preterm labor diagnosis using tocolytic agents exhibit an increased risk of postoperative hemorrhage and that this risk varies with the use of different tocolytic agents⁽³⁰⁾. This study demonstrated that nitrates increased the risk of postoperative hemorrhage (more than three-fold increases) compared with β_2 adrenoreceptor agonist among women in preterm labor, Nitrates are also reported to cause significant adverse effects, including hypotension and tachycardia, among women in preterm labor⁽³¹⁾. In the present study the number of females with single, twin and triple pregnancies was similar in both groups as shown in table 3 so this risk factor was excluded to avoid any bias in the primary outcome of pregnancy. Regarding the mean gestational age at time of labor in weeks, it was 34.12 ± 3.4 weeks in control group while the mean gestational age was 35.33 ± 2.67 weeks in the study group, which is higher but not significant statistically. Tocolytic therapy used to delay preterm delivery is an important intervention in obstetrics. Although tocolytics have not shown to improve neonatal outcomes, they can delay preterm delivery long enough for antenatal corticosteroids to administer or for the mother to transport to a tertiary care facility. In premature neonates, antenatal corticosteroids reduce morbidity and mortality⁽³³⁾. The previous studies concluded that Prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes compared magnesium sulfate beta mimetic and the oxytocin receptor

blocker atosiban. The results of the present study showed that transvaginal sildenafil was superior to other routinely used tocolytics in delaying labor even not significant value that may be due to small sample size. In the present study the neonatal weight, and live birth rate was higher in the study group and this finding is in accordance with previous studies that sildenafil could be associated with increasing fetal weight at birth in placental insufficiency⁽³⁴⁾.

Conclusion:

Using of vaginal sildenafil citrate is an effective option for prevention of threatened preterm labor than therapeutic tocolytics that used routinely.

no conflict of interest

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References:

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. *Obstet Gynecol.* 2016 Oct;128(4):e155-64 .
2. Suman V, Luther EE. Preterm Labor. [Updated 2020 Nov 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK536939/>
3. Niesłuchowska-Hoxha A, Cnota W, Czuba B, Ruci A, Ciaciura-Jarno M, Jagielska A, Wójtowicz D, Kierach R, Dąbrowski K, Sidorowicz M, Skrzypulec-Plinta W, Włoch A, Borowski D, Węgrzyn P. A Retrospective Study on the Risk of Respiratory Distress Syndrome in Singleton Pregnancies with Preterm Premature Rupture of Membranes between 24+0 and 36+6 Weeks, Using Regression Analysis for Various Factors. *Biomed Res Int.* 2018 Oct 4;2018:7162478.
4. Hamilton BE, Martin JA, Osterman MJ. Births: preliminary data for 2015. *Natl Vital Stat Rep.* 2016;65(3):1-15
5. Hassan SS, Romero R, Vidyadhari D, et al.; PREGNANT Trial. Vaginal progesterone reduces the rate of preterm delivery in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.* 2011;38(1):18-31.

6. Zhong Y, Cahill AG, Macones GA, Zhu F, Odibo AO. The association between prepregnancy maternal body mass index and preterm delivery. *Am J Perinatol.* 2010;27(4):293-298.
7. Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia [published correction appears in *Obstet Gynecol.* 2008;112(4):945
8. Newnham JP, Newnham IA, Ball CM, et al. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstet Gynecol.* 2009;114(6):1239-1248.
9. Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. *Obstet Gynecol.* 2009 Mar;113(3):585-594.
10. Flenady V, Wojcieszek AM, Papatsonis DNM, Stock OM, Murray L, Jardine LA, Carbonne B. Calcium channel blockers for inhibiting preterm labour and birth. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD002255.
11. Suman V, Luther EE. Preterm Labor. [Updated 2020 Nov 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK536939/>
12. Hubinont C, Debieve F. Prevention of preterm labour: 2011 update on tocolysis. *J Pregnancy.* 2011;2011:941057.
13. Toivonen KI, Oinonen KA, Duchene KM. Preconception health behaviours: A scoping review. *Prev Med.* 2014; 96: 1– 15.
14. UL-Aini Q , Shoukat F, Akmal N, Khurshi K M, Rashid M. Comparison between Sildenafil Citrate & Nifedipine with Nifedipine Alone for the Treatment of Threatened Preterm Labour. *P J M H S* Vol. 14, NO. 2, APR – JUN 2020. 433-436.
15. Abdelhamid. Comparative study of sildenafil citrate versus dydrogesterone in prevention of preterm labour in pregnant women with short cervix. *AAMJ*, 2015, 13 (3); 397-403.
16. Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. *FertilSteril.* 2002 Nov; 78(5):1073-6.

17. Hale SA, Jones CW, Osol G, Schonberg A, Badger GJ, Bernstein IM. Sildenafil increases uterine blood flow in nonpregnant nulliparous women. *Reprod Sci.* 2010;17(4):358-365.
18. Lee HL, Lu KC, Foo J, et al. Different impacts of various tocolytic agents on increased risk of postoperative hemorrhage in preterm labor women undergoing Cesarean delivery: A population-based cohort study. *Medicine (Baltimore).* 2020;99(50):e23651.
19. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. *Cochrane Database Syst Rev* 2002;3:CD002860
20. Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. *Obstet Gynecol* 2009;113:585-94.
21. Ferreira RDDS, Negrini R, Bernardo WM, Simões R, Piato S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: A systematic review and meta-analysis. *PLoS One.* 2019;14(7):e0219732.

Parameters		Control group	Sildenafil group	p value
Age (years)		30.33 ± 6.68	31.20 ± 6.61	0.615
Parity	P0	15 (50%)	11 (36.7%)	0.774
	P1	8 (26.7%)	11 (36.7%)	
	P2	3 (10%)	5 (16.7%)	
	P3	1 (3.3%)	1 (3.3%)	
	P4 or more	3 (10%)	2 (3.6%)	
History of preterm labor %		12 (40%)	14 (46.6%)	0.602
Abortions	0	18	22	0.136
	1	1	1	
	2	8	7	

	3 and more	3	0	
Presence of uterine anomalies	Normal	9 (30 %)	13 (43.3)	0.545
	Congenital	12 (40 %)	9 (30 %)	
	Acquired	9 (30 %)	8 (26.7%)	
Type of pregnancy	Natural	23 (78.7%)	18 (60%)	0.184
	ART	5 (16.7%)	5 (16.7%)	
	IUI	2 (6.7%)	7 (23.3%)	

Table 1: Maternal parameters of the study groups

Severity of PPH	Control group	Sildenafil group	p value
No PPH	22 (73.3%)	15 (50%)	0.106
Mild PPH	7 (23.3%)	13 (43.3%)	
Moderate PPH	0	2 (6.7%)	

Table 2: Comparison of severity of PPH between the study groups

Severe PPH	1 (3.3 %)	0	
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Table 3: Neonatal parameters of the study groups

Parameters		Control group	Sildenafil group	p value
Single or multiple pregnancy	Single	21 (70 %)	21 (70%)	1.00
	Twin	6 (20 %)	6 (20%)	
	Triple	3 (10%)	3 (10%)	
Gestational age at time of labor (weeks)		34.12 ± 3.4	35.33 ± 2.67	0.145
Neonatal weight at time of labor (kg)		2.46 ± 0.77	2.71 ± 0.75	0.152
Live birth rate		81.67 %	74.97 %	0.492
Fetal anomaly (IUGR)		10 (25.6%)	6 (15.4%)	0.262

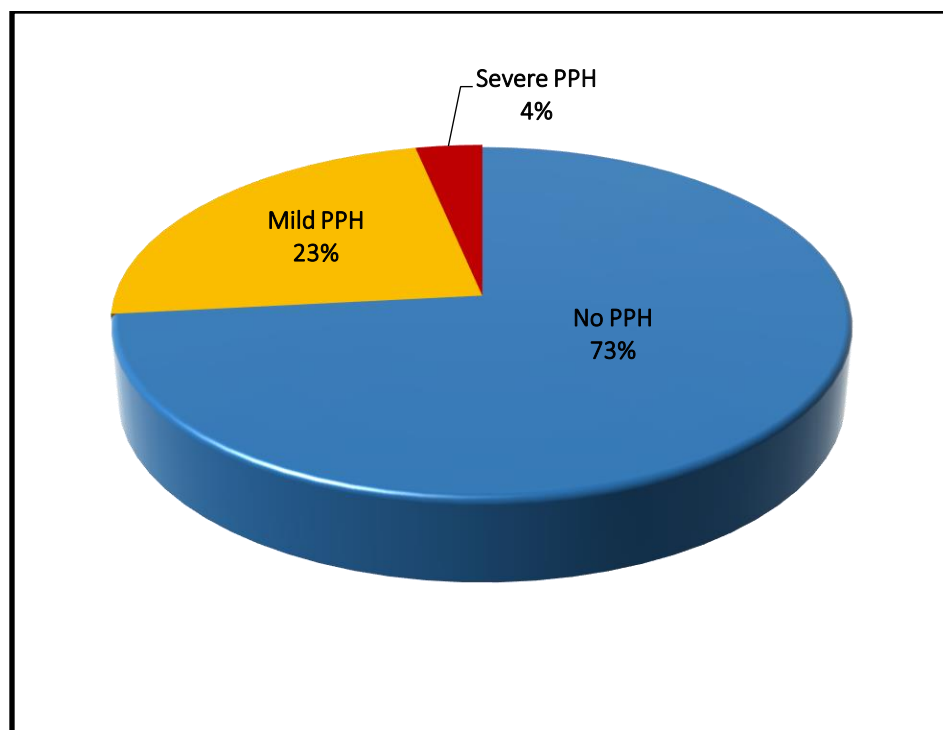


Figure 1: Frequencies of PPH severity in the control group

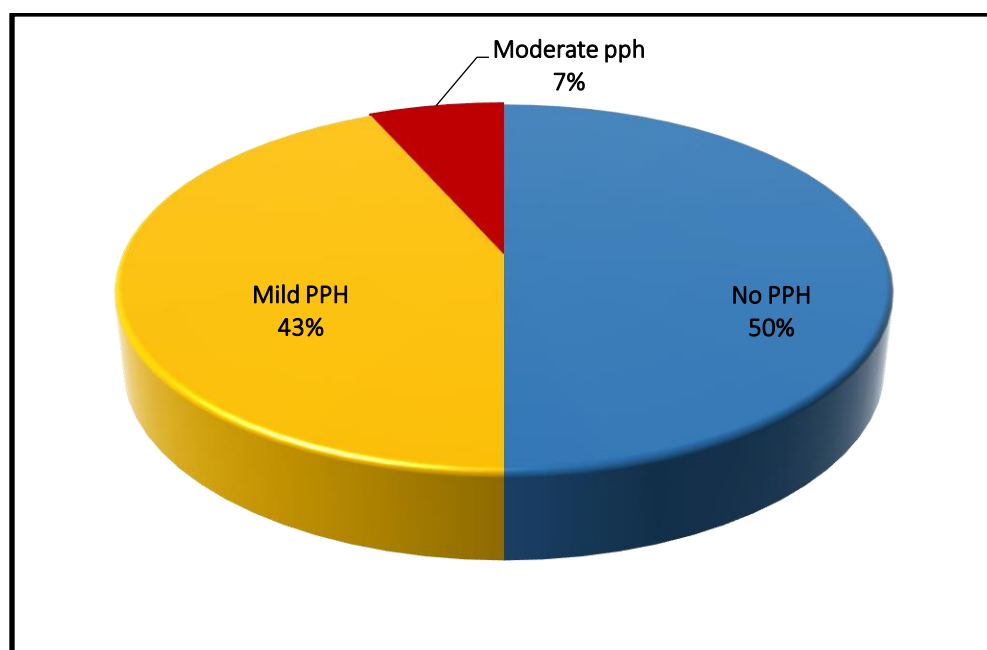
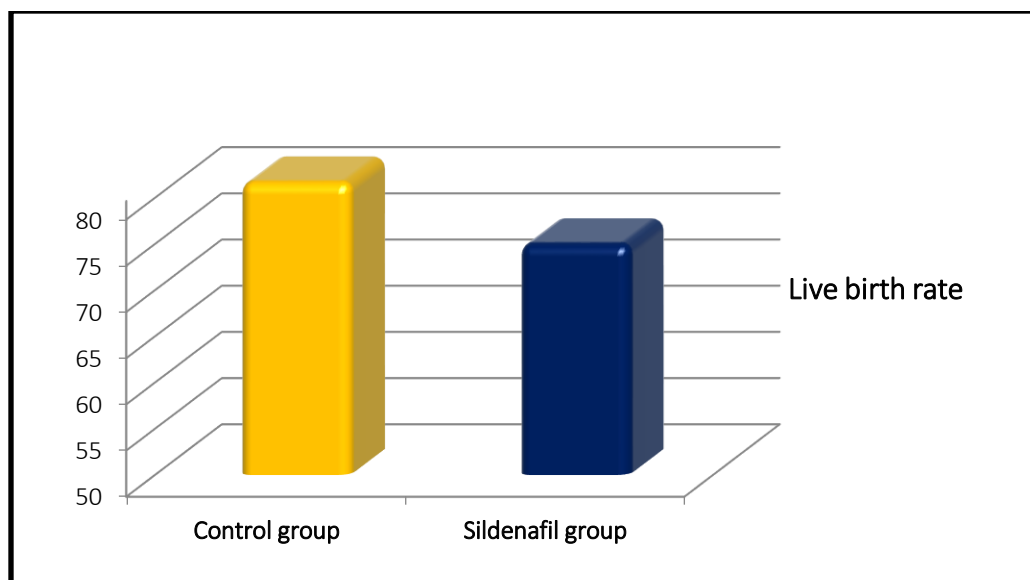
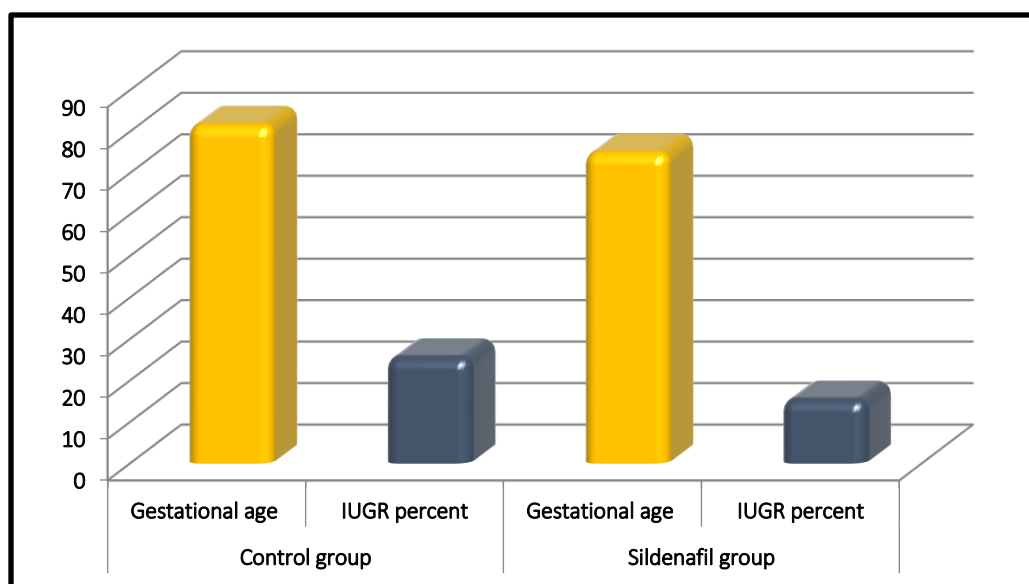


Figure 2: Frequencies of PPH severity in the sildenafil group



Figur 3: comparison of live birth rate between control & sildenafil group



Figur 4: comparison of gestational age at time of birth & IUGR percent between control & sildenafil group