



Sildenafil versus Nifedipine Treatment of PRETERM LABOR: RCT

Thesis

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By

Rahma Khalil El Kattan

M.B., B.CH, Cairo University

Under Supervision of

Prof. Mohamed Ahmed Al Kady

*Professor of Obstetrics and Gynecology
Faculty of Medicine-Ain Shams University*

Assist. Prof. Mohamed Hussain Mostafa

*Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine-Ain Shams University*

Faculty of Medicine
Ain Shams University
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List of Abbreviations

Abb.	Full term
<i>20a-HSD</i>	<i>20a-Hydroxysteroid Dehydrogenase</i>
<i>AR</i>	<i>Androgen Receptor</i>
<i>CAPs</i>	<i>Contraction-Associated Proteins</i>
<i>CCB</i>	<i>Calcium Channel Blocker</i>
<i>cGMP</i>	<i>Cyclic Guanosine Monophosphate</i>
<i>COX-2</i>	<i>Cyclooxygenase-2</i>
<i>CR1</i>	<i>Complement Receptor 1</i>
<i>CRH</i>	<i>Corticotropin-Releasing Hormone</i>
<i>DAMPs</i>	<i>Damage-Associated Molecular Patterns</i>
<i>FDA</i>	<i>Food and Drug Administration</i>
<i>HLA-C</i>	<i>Human Leukocyte Antigen-C</i>
<i>HPA</i>	<i>Hypothalamic-Pituitary-Adrenal</i>
<i>IGF1R</i>	<i>Insulin-Like Growth Factor 1 Receptor</i>
<i>IL-6</i>	<i>Interleukin-6</i>
<i>IUGR</i>	<i>Intrauterine Growth Restriction</i>
<i>KIR</i>	<i>Killer Cell Immunoglobulin-Like Receptor</i>
<i>LINE 1-HS</i>	<i>Long-Interspersed Nuclear Element 1 Homo Sapiens-Specific</i>
<i>LPS</i>	<i>Lipopolysaccharide</i>
<i>miRNAs</i>	<i>microRNAs (</i>
<i>MMPs</i>	<i>Matrix Metalloproteinases</i>
<i>NaOH</i>	<i>Sodium Hydroxide</i>
<i>NO</i>	<i>Nitric Oxide</i>
<i>PAI-1</i>	<i>Plasminogen Activator Inhibitor 1</i>
<i>PDE</i>	<i>Phosphodiesterase</i>
<i>PDE5</i>	<i>Phosphodiesterase Type 5</i>
<i>PG</i>	<i>Prostaglandin</i>
<i>PGE2</i>	<i>Prostaglandin E2</i>
<i>PPROM</i>	<i>Preterm Premature Rupture of Membranes</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>PR</i>	<i>Progesterone Receptor</i>
<i>PTGER2</i>	<i>Prostaglandin E Receptor 2 Gene</i>
<i>PTL</i>	<i>Preterm Labor</i>
<i>RAGE</i>	<i>Receptor for Advanced Glycation End Products</i>
<i>STAT5B</i>	<i>Silence Signal Transducer and Activator of Transcription 5b</i>
<i>TEA</i>	<i>Tetraethyl Ammonium</i>
<i>TNFα</i>	<i>Tumor Necrosis Factor-α</i>
<i>TP53</i>	<i>Tumor Protein 53</i>
<i>TPTL</i>	<i>Threatened Preterm Labor</i>
<i>VEGF</i>	<i>Vascular Endothelial Growth Factor</i>
<i>VEGF</i>	<i>Vascularendothelial Growth Factor</i>
<i>ZEB</i>	<i>Zinc Finger E-Box-Binding Homeobox</i>

ABSTRACT

Background: a normal pregnancy lasts 37 to 42 weeks, counting from the first day of the last menstrual period. A pregnancy that continues beyond 37 weeks is called a "term" pregnancy. Preterm labor is defined as labor that begins before 37 weeks of pregnancy. Approximately 12 percent of babies in the United States are born preterm; 80 percent of these are due to preterm labor that occurs on its own or after preterm premature rupture of the fetal membranes (or "broken bag of waters"). The remaining 20 percent are planned early deliveries that are done for maternal or fetal problems that prevent the woman from being able to safely continue with her pregnancy.

Aim of the Work: to assess the efficacy of sildenafil for stopping the labor for 48 hrs compared to nifedipine in women with preterm labor.

Patients and Methods: this prospective study was carried on pregnant women with preterm labor pain at Ain Shams University Hospital from March 2018 till September 2018. Study includes 88 patients which were distributed into two groups:

- **Group S:** received Sildenafil to stop preterm labor.
- **Group N:** received Nifedipine to stop preterm labor.

Results: in the present study we found that mean age in group receiving sildenafil (group S) was 26.55 years and in group receiving nifedipine (group N) was 26.75 years with insignificant differences between two groups as regard age p-value 0.798, also as regard BMI and parity there was insignificant differences between two groups as regard BMI p-value 0.727, 0.815 respectively, Mean Gestational age at admission was 27.1 weeks in group S and in group N was 28.16 with insignificant differences between two groups p-value 0.705.

Conclusion: administration of Sildenafil in women with preterm labor pain seems to be a promising future therapy of preterm labor with, limiting the teratogenic influence of the drugs on the fetus.

Keywords: Corticotropin-Releasing Hormone – Sildenafil - Nifedipine

INTRODUCTION

A normal pregnancy lasts 37 to 42 weeks, counting from the first day of the last menstrual period. A pregnancy that continues beyond 37 weeks is called a "term" pregnancy. Preterm labor is defined as labor that begins before 37 weeks of pregnancy. Approximately 12 percent of babies in the United States are born preterm; 80 percent of these are due to preterm labor that occurs on its own or after preterm premature rupture of the fetal membranes (or "broken bag of waters"). The remaining 20 percent are planned early deliveries that are done for maternal or fetal problems that prevent the woman from being able to safely continue with her pregnancy (*Funai et al., 2016*).

Not all women who have preterm labor will deliver their baby early; estimates are that between 30 and 50 percent of women who develop preterm labor will go on to deliver their infant at term. If preterm labor leads to an early delivery, the premature newborn is at risk for problems related to incomplete development of its organ systems. These problems include difficulty with breathing, staying warm, feeding, as well as injury to the eyes, intestines, and nervous system. Preterm birth is a major cause of newborn complications and death. Regular prenatal care can help to identify some, but not all, women at risk for preterm labor. Should preterm labor occur, measures can be taken to delay delivery and decrease the risk of newborn complications (*Funai et al., 2016*).

AIM OF THE WORK

This study aims to assess the efficacy of sildenafil for stopping the labor for 48 hrs compared to nifedipine in women with preterm labor.

Chapter 1

PRETERM LABOR

Definition

Preterm labor occurs when regular contractions result in the opening of cervix before 37 weeks of pregnancy. A full-term pregnancy should last about 40 weeks. If preterm contractions result in preterm labor, baby will be born early. The earlier premature birth happens, the greater the health risks for baby. Many premature babies (preemies) need special care in the neonatal intensive care unit. Preemies can also have long-term mental and physical disabilities. While the specific cause of preterm labor often isn't clear, certain risk factors may up the odds of early labor. But, preterm labor can also occur in pregnant women with no known risk factors. Still, it's a good idea to know if at risk of preterm labor and how you might help prevent it (*Lockwood, 2014*).

Symptoms

To stop premature labor, it's important to know the warning signs. Acting fast can make a big difference (*Johnson, 2017*):

- **Backache**, which usually will be in lower back. This may be constant or come and go, but it won't ease even if you change positions or do something else for comfort.

- **Contractions** every 10 minutes or more often
- **Cramping** in lower abdomen or menstrual-like cramps. These can feel like gas pains that may come with diarrhea.
- **Fluid leaking** from vagina.
- **Flu-like symptoms** such as nausea, vomiting, or diarrhea.
- **Increased pressure** in pelvis or vagina.
- **Increased vaginal discharge.**
- **Vaginal bleeding**, including light bleeding.

Some of these may hard to tell apart from normal symptoms of being pregnant, like backache (*Johnson, 2017*).

Causes of Preterm Labor

Researchers do not know what actually causes preterm labor in most women. However, we do know that certain conditions can increase the risk of preterm labor, including (*Simhan et al., 2017*):

- A previous preterm delivery.
- A history of cervical surgery, such as a LEEP or cone biopsy. Being pregnant with twins.
- Infection in the mother or in the membranes around the baby.

- Certain birth defects in the baby.
- High blood pressure in the mother.
- The bag of water breaks early.
- Too much amniotic fluid.
- First trimester bleeding.

The mother's health problems or lifestyle choices that can lead to preterm labor include **(Simhan et al., 2017):**

- Cigarette smoking.
- Illegal drug use, often cocaine and amphetamines.
- Physical or severe psychological stress.
- Poor weight gain during pregnancy.
- Obesity.

Problems with the placenta, uterus, or cervix that can lead to preterm labor include **(Sumhan et al., 2014):**

- When the cervix does not stay closed on its own (cervical incompetence).
- When the shape of the uterus is not normal.
- Poor function of the placenta, placental abruption, and placenta previa.

Risk factors

Preterm labor can affect any pregnancy and many women who have preterm labor have no known risk factors. Many factors have been associated with an increased risk of preterm labor, however, including (*Cunningham et al., 2014*):

- Previous preterm labor or premature birth, particularly in the most recent pregnancy or in more than one previous pregnancy.
- Pregnancy with twins, triplets or other multiples.
- Certain problems with the uterus, cervix or placenta.
- Smoking cigarettes or using illicit drugs.
- Certain infections, particularly of the genital tract.
- Some chronic conditions, such as high blood pressure and diabetes.
- Being underweight or overweight before pregnancy, or gaining too little or too much weight during pregnancy.
- Stressful life events, such as the death of a loved one.
- Red blood cell deficiency (anemia), particularly during early pregnancy.
- Too much amniotic fluid (polyhydramnios).
- Pregnancy complications, such as preeclampsia.

- Vaginal bleeding during pregnancy.
- Presence of a fetal birth defect.
- Little or no prenatal care.
- An interval of less than six months since the last pregnancy.

Also, having a short cervical length or the presence of fetal fibronectin a substance that acts like a glue between the fetal sac and the lining of the uterus in vaginal discharge has been linked to an increased risk of preterm labor. While some past research suggested that gum disease might be linked with premature birth, treatment of periodontal disease during pregnancy hasn't been proved to reduce the risk of premature birth (*Cunningham et al., 2014*).

Etiology and pathogenesis of spontaneous preterm delivery

Proximate causes of PTD include medically indicated PTDs (18.7 – 35.2% of cases) and spontaneous PTDs resulting from either preterm labor (PTL) with intact fetal membranes (23.2 – 64.1%) or preterm premature rupture of membranes (PPROM) (7.1 – 51.2%). There is compelling evidence to suggest that spontaneous PTD involves multiple underlying pathogenic pathways and etiologic factors. At least four distinct pathways have been defined: maternal/fetal stress, decidual - amnion – chorion inflammation, decidual hemorrhage, and