A Prospective Double-Blind, Randomized, Placebo-Controlled Trial on the Use of Letrozole Pretreatment with Misoprostol for Second-Trimester Medical Abortion

Thesis

Submitted for Partial Fulfillment of the MD Degree
in Obstetrics and Gynecology

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2016

بسم الله الرحمن الرحيم

﴿وَقُل رَّبِّ زِدْنِي عِلْماً﴾

سورة طـه الآيـــه رقم ١١٤

Acknowledgement

First of all, all gratitude is due to ***God*** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to ***Prof. Gasser Adly El-Bishry,*** *Professor of Obstetrics and Gynecology , faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

I would like also to express my sincere appreciation to ***Prof. Ihab Fouad Serag El-Din Allam,*** *Professor of Obstetrics and Gynecology, faculty of medicine , Ain Shams University, for his continuous directions and support throughout the whole work.*

Really I can hardly find the words to express my gratitude to ***Assistant Prof. Mostafa Fouad Gomaa,*** *Assistant professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University for his continuous directions and meticulous revision throughout the whole work. I really appreciate their patience and support.*

I owe much to. ***Assistant Prof.Mohamed Samir Sweed,*** *Assistant professor of Obstetrics and Gynecology for his continuous guidance, encouragement during the progress of this work and direct supervision.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Ahmed Mohammed Swidan

Contents

List of Abbreviations

EVA	:	Electric vacuum aspiration
MVA	:	Manual vacuum aspiration
OHSS	:	Ovarian hyperstimulation syndrome
AASS	:	Analysis and Sample Size software version 08.0.9
PR	:	Progesterone receptor
RR	:	Relative risk
NNT	:	Number needed to treat
IDX	:	Intact dilation and extraction
AIS	:	Aromatase inhibitors
ER	:	Estrogen receptor

List of tables

List of Figures

Use of Letrozole Pretreatment with Misoprostol for Second-Trimester Medical Abortion"

A Prospective Double-Blind, Randomized, Placebo-Controlled Trial"

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Abstract

Objective: To compare the success rate of letrozole and misoprostol versus misoprostol alone for medical termination of pregnancy in second trimester abortion.

Study design: two-arm placebo controlled trial.

Patients: Patients fulfilling inclusion criteria will be divided into two groups each one will be 200 patients(more than sample size number) to avoid the drop ín the size of the study
Group (A):
200 patients will receive misoprostol without letrozol
Group (B):
200 patients will receive misoprostol without placebo

Main outcome(s):letrozole role in induction of abortion.

Result(s): Only the need for oxytocin for augmentation of abortion was found to be a significant fact; between two groups

Conclusion: The conclusion of our study is there was a significant difference between letrozole group and placebo group in the need for oxytocin, completed medical abortion and surgical evacuation.

Key words: EVA: Electric vacuum aspiration; MVA :Manual vacuum aspiration; OHSS :Ovarian hyperstimulation syndrome; PR :Progest-erone receptor; RR: Relative risk; NNT: Number needed to treat

Introduction

Abortion is the termination of pregnancy by the removal or expulsion the fetus or embryo from the uterus before viability. An abortion can occur spontaneously, in which case it is often called a miscarriage, or it can be purposely induced. Modern medicine utilizes medications and surgical procedures for induced abortion (***Grimes et al., 2010).***

Progesterone is pivotal in the maintenance of pregnancy and the use of progesterone receptor (PR) antagonist, mifepristone, during pregnancy facilitates the abortion process ***(Gemzell et al., 2006).***

In the second trimester of pregnancy, the combined regimen of mifepristone followed by misoprostol produces a high abortion rate of 97-100% within 24h, with an induction-to-abortion interval of 5-10h ***(Kapp et al., 2007; Chai et al., 2009).***

However, mifepristone is expensive and not registered in many countries. The abortion rate of a misoprostol alone regimen is only 37-86% in 15-24 h depending on the regimen, route of administration and dosage used ***(Von Hertzen et al., 2009; Ngoc et al., 2011)***. The exploration of new regimens to achieve a safe second trimester abortion is important, especially in developing countries.

Letrozole is a third-generation aromatase inhibitor which is used to treat estrogen-dependent breast cancer. Aromatase, an enzyme of the cytochrome P450 superfamily and the product of CY195 gene, is expressed in the placenta and ovarian granulosa cells ***(Mitwally et al., 2005).***

It inhibits the aromatization of testosterone to estradiol and androstenedione to estrone. The use of third generation aromatase inhibitors will greatly suppress the estrogen level without affecting the progesterone and cortisol concentration ***(Shi et al., 2005).***

The use of letrozole pretreatment followed by vaginal misoprostol in the first trimester abortion is more effective than misoprostol alone, The use of letrozole in second trimester abortions seems to be promising with an abortion rate of 100% within 24h ***(Lee et al., 2011).***

Aim of the Work

To compare the success rate of letrozole and misoprostol versus misoprostol alone for medical termination of pregnancy in second trimester abortion.

Hypothesis:

Letrozole might be used before induction of abortion.

Research question:

Will letrozole help in prediction of outcome of induction of abortion?

Primary outcome:

Duration of induction of abortion.

Secondary outcome:

Dose of oxytocin after aborting the fetus.
The need of surgical evacuation of placenta.
Post abortive bleeding.
Other maternal morbidities.

Induction of Abortion

Abortion is the ending of pregnancy by removing a fetus or embryo from the womb before it can survive on its own, An abortion can also occur spontaneously and is then known as a miscarriage or may be caused purposely and is then called an induced abortions. The word abortion most often means an induced abortion ***(Grimes and Stuart 2010).***

Modern methods use medication or surgery for induced abortions. The drugs mifepristone and prostaglandin are as good as surgery during the first trimester ***(kulier et al.,2011),*** While medical methods may work in the second trimester, surgery has lower risk of side effects Birth control, such as the pill or intrauterine devices, can be started at once after an abortion ***(Kapp et al., 2013).***

When allowed by local law abortion in the developed world is and has long been one of the safest procedures in medicine ***(Wildschut et al.,2011; Grimes et al.,2006).***

Uncomplicated abortions do not cause any long term mental or physical problems ***(Lohr et al.,2014),*** The World Health Organization recommends safe and legal abortions be available to all women ***(WHO 2012),*** Every year unsafe abortions cause 47,000 deaths and 5 million hospital admissions ***(Raymond et al.,2014; Shah and Ahman 2009).***

About 44 million abortions occur each year in the world, with a little under half done unsafely, Abortion rates have changed little between 2003 and 2008 ***(Sedgh et al., 2012)***,before which they decreased for decades due to better education about family planning and birth control ***(Sedgh et al., 2008),***As of 2008, 40% of the world's women had access to legal abortions without limits as to reason, However there

are limits on how late in pregnancy abortion is allowed ***(Culwell we al.,2010***).

Since ancient times abortions have been done using herbal medicines, sharp tools, with force, or through other traditional methods ***(Joffe and Carole 2009),*** Abortion laws and cultural or religious views of abortions are different around the world. In some areas abortion is legal only in special cases such as rape, problems with the fetus, poverty, risk to a woman's health, or incest ***(Boland and Katzive 2008).***

In many places there is much debate over the moral, ethical, and legal issues of abortion. Those who are against abortion largely claim that an embryo or fetus is a human with a right to life and may compare it to murder ***(Pastor 2013; Dale 2014)*** Supporters point to a woman's right to decide over her own body and to human rights in general ***(Sifris and Ronli 2013).***

History of abortion

Induced abortion has long history, and can be traced back to civilizations as varied as China under Shennong (2700 BCE), Ancient Egypt with its Ebers Papyrus (1550 BCE), and the Roman Empire in the time of Juvenal (200 BCE) ***(Joffe and Carole 2009).***

There is evidence to suggest that pregnancies were terminated through a number of methods, including the administration of abortifacient herbs, the use of sharpened implements, the application of abdominal pressure, and other techniques. One of the earliest known artistic representations of abortion is in a bas relief at Angkor Wat .Found in a series of friezes that represent judgment after death in Hindu and

Buddhist culture, it depicts the technique of abdominal abortion ***(Potts et al., 2007).***

Some medical scholars and abortion opponents have suggested that the Hippocratic Oath forbade Ancient Greek physicians from performing abortions ***(Joffe and Carole 2009)***, other scholars disagree with this interpretation ***(Joffe and Carole 2009),*** and state the medical texts of Hippocratic Corpus contain descriptions of abortive techniques ***(Miles and Steven 2005)***

Aristotle, in his treatise on government Politics (350 BCE), condemns infanticide as a means of population control. He preferred abortion in such cases, with the restriction ***(Carrick and Paul 2001),*** that it must be practised on it before it has developed sensation and life; for the line between lawful and unlawful abortion will be marked by the fact of having sensation and being alive ***(Carrick and Paul 2001).***

In Christianity, Pope Sixtus V (1585-90) was the first Pope to declare that abortion is homicide regardless of the stage of pregnancy ***(BrindAmour and Katherine 2007),*** the Catholic Church had previously been divided on whether it believed that abortion was murder, and did not begin vigorously opposing abortion until the 19th century ***(Joffe and Carole 2009).***

Islamic tradition has traditionally permitted abortion until a point in time when Muslims believe the soul enters the fetusconsidered by various theologians to be at conception, 40 days after conception, 120 days after conception, or quickening. However, abortion is largely heavily restricted or forbidden in areas of high Islamic faith such as the Middle East and North Africa ***(Henderson et al., 2001).***

In Europe and North America, abortion techniques advanced starting in the 17th century. However, conservatism by most physicians with regards to sexual matters prevented the wide expansion of safe abortion techniques ***(Joffe and Carole 2009),*** Other medical practitioners in addition to some physicians advertised their services, and they were not widely regulated until the 19th century, when the practice was banned in both the United States and the United Kingdom ***(Joffe and Carole 2009).***

In the US, abortion was more dangerous than childbirth until about 1930 when incremental improvements in abortion procedures relative to childbirth made abortion safer. The Soviet Union (1919), Iceland (1935) and Sweden (1938) were among the first countries to legalize certain or all forms of abortion ***(Restivo et al., 2005).***

In 1935 Nazi Germany, a law was passed permitting abortions for those deemed "hereditarily ill", while women considered of German stock were specifically prohibited from having abortions, Beginning in the second half of the twentieth century, abortion was legalized in a greater number of countries, A bill passed by the state legislature of New York legalizing abortion was signed by Governor Nelson Rockefeller in April 1970 ***(Friedlander and Henry1995).***

Incidence

There are two commonly used methods of measuring the incidence of abortion:

Abortion rate: number of abortions per 1000 women between 15 and 44 years of age.

Abortion percentage: number of abortions out of 100 known pregnancies (pregnancies include live births, abortions and miscarriages) ***(Sedgh et al., 2012).***