

Fetal Fibronectin as a Predictor of Successful Induction of Mid-trimester Abortion

Thesis

*Submitted for Partial Fulfillment of Master Degree
in Obstetrics & Gynaecology*

By

Dina Ouni Amin Fares

M.B.B.Ch – Ain Shams University (2011)

Resident of Ob/Gyn, Ain Shams University Maternity Hospital

Under Supervision of

Prof. Abdel- Mégeed Ismail

Professor of Obstetrics and Gynecology

Faculty of Medicine

Ain Shams University

Dr. Amr Ahmed Mahmoud Riad

Lecturer of Obstetrics and Gynecology

Faculty of Medicine

Ain Shams University

Faculty of Medicine

Ain Shams University

2016



Acknowledgments

First and foremost, I feel always indebted to Allah the Most Beneficent and Merciful.

*I wish to express my deepest gratitude and thanks to **Prof. Abdel- Mégeed Ismail**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his generous supervision, unlimited help and giving me the privilege to work under his supervision.*

*My most sincere gratitude is also extended to **Dr. Amr Ahmed Mahmoud Riad**, Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his enthusiastic help, continuous supervision, guidance and support throughout this work.*

*Last but not least, I can't forget to thank all members of my Family, especially my **Parents** for pushing me forward in every step in the journey of my life.*

Candidate



Dina Ouni Amin Fares

List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables.....	ii
List of Figures	iii
Protocol.....	
Introduction	1
Aim of the Work.....	7
Review of Literature	
The Human Cervix	8
Induction of Abortion.....	26
Fetal Fibronectin	46
Patients and Methods.....	59
Results.....	68
Discussion	79
Summary	84
Conclusion.....	89
Recommendations	90
References	91
Arabic Summary	—

List of Abbreviations

<i>Abbr.</i>	<i>Full-term</i>
CDC	: Center of Disease Control
CRP	: C-reactive protein
D&E	: Dilatation and evacuation
D&X	: Dilatation and extraction
FDA	: Food and Drug Administration
fFN	: Fetal fibronectin
GA	: Gestational age
mAb	: Monoclonal antibodies
MRI	: Magnetic resonance imaging
pFN	: Plasma fibronectin
PGE1	: Prostaglandin E1
PTD	: Preterm delivery
sPTD	: Serum Preterm delivery
SPSS	: Statistical package for social sciences
TOP	: Termination of pregnancy
VIP	: Vasoactive intestinal peptide

List of Tables

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
Table (1):	CRF-1 Enrollment Data	66
Table (2):	CRF-2: Interventional data (patient characteristics).....	67
Table (3):	Demographic Data: Age, BMI, GA of Included Women (n=135)*	68
Table (4):	Abortion among the studied cases	69
Table (5):	Descriptive characteristics and intervals of the Induction-of-Abortion process among the studied cases.....	70
Table (6):	Difference between Women who were Positive for Cervicovaginal <i>fFN</i> (ng/mL) and Women who were Negative among the studied cases.....	71
Table (7):	Side effects among the studied cases	72
Table (8):	Correlation between <i>fFN</i> and other variables	74
Table (9):	Difference between Women who Expulsed the Fetus within 24 Hours and 24-48 Hours and Women who Did not regarding Cervicovaginal Fetal Fibronectin (ng/ml)	76
Table (10):	Diagnostic performance of <i>fFN</i> in prediction of abortion <24.0 hours	77
Table (11):	Diagnostic characteristics of positive <i>fFN</i> in prediction of abortion <24.0 hours	78

List of Figures

<i>Figure No.</i>	<i>Title</i>	<i>Page No.</i>
Figure (1):	Induction among the studied cases	69
Figure (2):	Induction among the studied cases	70
Figure (3):	<i>fFN</i> among the studied cases	71
Figure (4):	Side effects among the studied cases.....	73
Figure (5):	Correlation between FFN and GA.....	75
Figure (6):	Comparison between abortion times regarding FFN.....	76
Figure (7):	ROC curve for FFN in prediction of abortion <24.0 hours	77

Introduction

*A*bortion-related morbidity and mortality increase significantly as gestation advances. Abortions after 14 weeks of pregnancy constitute 10-15% of all abortions; however, they are responsible for two-thirds of all abortion-related complications and 50% of abortion related deaths (*Dilek et al., 2011*).

The development of safe and effective abortion techniques for second trimester pregnancy terminations and fetal demise is a major clinical challenge. The main aim of abortion induction is rapid, uneventful, and complete expulsion or delivery of a fetus. Termination of second trimester pregnancies can be achieved by various techniques, including prostaglandin analogues, hygroscopic dilators, and Foley balloon traction. Time period between beginning of induction to abortion or delivery of products of conception can be prolonged in the second trimester of pregnancy due to uterine unresponsiveness and unfavorable cervix (*Dilek et al., 2011*).

Prolonged administration of various methods and lower response rate to oxytocin infusion results in discomfort and increased anxiety for the woman. Therefore, cervical priming is the major step of second trimester pregnancy termination. The most employed method of termination of

pregnancy (TOP) is the application of the prostaglandin analogue misoprostol (*Ngai et al., 2003*).

Medical termination of mid-trimesteric pregnancy (medical induction of abortion) is the ending of pregnancy by a means other than surgery. It is often performed using agents that induce abortion (prostaglandins, RU486, Methotrexate) (*CDC, 2004*). Misoprostol (15-deoxy-16-hydroxy-16-methyl PG E₁) is a synthetic PG E₁ analogue. It was developed for the treatment and prevention of peptic ulcer by Searle in 1973 because of its gastric acid anti-secretory properties and its various mucosal protective properties (*Watkinson et al., 1998*).

Because of its cervical ripening and uterotonic property, misoprostol has become one of the most useful drugs in obstetrics and gynecology (*Ledger et al., 2007*).

Misoprostol has proven to be a very convenient and flexible drug because of its formulation as a tablet that is stable and that can be administered orally, rectally, vaginally and by the sublingual route (*Chong et al., 2004*).

Beginning with its abuse for illegal abortion in the late 1980s, misoprostol has quickly become established as one of the most effective drugs for terminating pregnancies in the

first and second trimesters, as well as for inducing labor in the third trimester (*Chong et al., 2004*).

Misoprostol in a dose of 400 mcg vaginally that can be repeated within 4 hours interval with an initial dose 800 mcg is the recommended dose of misoprostol in induction of abortion in the second trimester (*Danielsson, 2007*).

Misoprostol is currently the commonest prostaglandin analogue used for the purpose of medical abortion in the first trimester (*Ledger et al., 2007*). Cervical priming using misoprostol prior to uterine suction evacuation softens the cervix and lessens the force needed for dilation, thereby potentially reducing the probability of procedural complications (*Panchal et al., 2010*). A dose of 400 mcg misoprostol given three hours before the procedure was the optimal dose for vaginal application (*Meckstroth and Darney, 2003*).

Fetal fibronectin is a special form of glycoprotein found in plasma and extracellular matrix. Fetal Fibronectin (*fFN*) is an isoform of fibronectin, and has been identified in amniotic fluid, placental tissues and in choriodecidual cells (*Guller et al., 1993*).

By use of the monoclonal antibody FDC-6, it has become possible to identify minor structural differences,

permitting the differentiation between fetal and adult fibronectin (*Lockwood et al., 1991*).

In the late second and third trimester, a detectable level of *fFN* in cervical secretions is a powerful predictor of Preterm birth in women, who are still asymptomatic, and a useful predictor of the actual onset of labor (*Ahner et al., 1995*).

Before 20 weeks gestation, *fFN* is frequently found in the lower genital tract, supposedly due to absence of a complete fusion between the fetal membranes and the decidua. With advancing gestation, the progressive decline in detectable *fFN* levels parallels the fusion of the chorion, and the presence of *fFN*, thus, becomes abnormal after the 20th week (*Feinberg et al., 1991*).

Amniotic fluid contains a high concentration of fetal fibronectin, and it can also be found in the amnion and in the area between decidua parietalis and chorion. When the date of labor is imminent, fibronectin enters into cervical and vaginal secretions, a process thought to be set off by the noticeable increase in light contractions and the resulting movement of chorion against the decidual layer of the uterus so that the presence of fetal fibronectin in cervicovaginal secretions at the end of the pregnancy is an indicator of imminent birth (*Ahner et al., 1995*).

The major clinical use of *fFN* testing appears to be its ability to identify women who are unlikely to deliver within 7 to 14 days of *fFN* testing (**Anderson, 2000**). The presence of *fFN* levels greater than 50 ng/mL in cervicovaginal secretions at or under 35 weeks of pregnancy is associated with an increased likelihood of PTD (**Goldenberg et al., 1996**). The fetal *fibronectin* cutoff for a positive test is > 50 ng/mL (**Leitich and Kaider, 2003**) (**Lockwood et al., 1991**).

A positive assay result at 22 to 34 weeks had a positive predictive value for delivery within 1 week of 30% or within 2 weeks of 41%. The negative predictive value was 98% and 96%, respectively (**Lowe et al., 2004**). The less informative positive predictive value likely results from factors such as cervical manipulation and infection, which can stimulate fetal fibronectin release (**Goldenberg et al., 1996; Jackson et al., 1996**).

The presence of *fFN* in cervicovaginal secretions has been evaluated and has been found predictive of a shorter labor duration and lower caesarean section rate in patients, who underwent labor induction with prostaglandin pessaries in the third trimester (**Garite et al., 1996**).

The assumption that cervical ripening is intimately related to increased secretion of *fFN* is derived from

experimental observations, indicating fibronectins as important organizers of connective tissue (*Roulashti, 1998*).

Its cervical levels are correlated with spontaneous cervical ripening at term (*Ekamn et al., 1995*).

Successful prostaglandin E₂-induced cervical ripening seems to be related to a significant increase in cervical *fFN* levels (*Sennstrom et al., 1998*).

Aim of the Work

This study aims to assess the accuracy fetal fibronectin (*fFN*) in cervicovaginal secretions as a predictor of successful medical termination of mid-trimester missed miscarriage.

Research Question

In pregnant women with mid-trimester missed miscarriage and undergoing induction of abortion, Can the measurement of fetal fibronectin level be used to predict success of prostaglandins to induce miscarriage accurately?

Research hypothesis

In women with mid-trimester missed miscarriage and undergoing induction of abortion, fetal fibronectin concentration in cervicovaginal secretions may predict the success of induction accurately.

The Human Cervix

Gross Anatomy of the Cervix:

The cervix is divided into two portions the portio-vaginalis, which is the part protruding into the vagina and the portio-supravaginalis, which lies above the vagina and below the corpus. The portion of the cervix exposed to the vagina is the exocervix or portio-vaginalis (*Howard et al., 2008*).

The portio-vaginalis is covered by non-keratinizing squamous epithelium, its canal is lined by a columnar mucous secreting epithelium that is thrown into a series of V shaped folds that appear like the leaves of a palm and therefore called plicate palmatae. The endocervical canal is about 2 to 3 cm in length and opens proximally into the endometrial cavity at the internal os (*Johanthan et al., 2002*).

The upper border of the cervical canal is marked by the internal os, where the narrow cervical canal widens out into the endometrial cavity. The lower borer of the canal, the external os, contains the transition from squamous epithelium of the portio-vaginalis to the columnar epithelium of the endocervical canal (*Howard et al., 2008*).

Before childbirth, the external cervical os is small, regular and oval opening. After childbirth, the orifice is converted into a transverse slit that is divided such that there

are the so-called anterior and posterior lips of cervix. It torn deeply during delivery, it might heal in such a manner that it appears to be irregular, nodular or stellate. These changes are sufficiently characteristic to permit an examiner to ascertain with some certainty whether a given women has borne children by vaginal delivery (*Cunningham et al., 2010*).

Anteriorly, the upper boundary of the cervix is the internal os, which corresponds to the level at which the peritoneum is reflected upon the bladder. The supra-vaginal segment is covered by peritoneum on its posterior surface. This segment is attached to the cardinal ligaments anteriorly, and it is separated from the overlying bladder by loose connective tissue. The other segment is the lower vaginal portion of the cervix, also called the portio-vaginalis (*Cunningham et al., 2005*).

The normal human cervix in the nullipara is about 2.0cm to 2.5cm in its anteroposterior diameter and 2.5cm to 3.0cm in its lateral diameter. This difference is due to the shape of the cervical canal, which is straight in the sagital plane and spindle shaped in the frontal plane. The wall of the cervix is about 1.0cm thick throughout its length (*Danforth, 1983*).

The substance of the cervical wall is made up of dense fibrous connective tissue with only a small (about 10%) amount of smooth muscle. What smooth muscle that lies on