

IMMUNOLOGICAL CAUSES OF RECURRENT  
PREGNANCY WASTAGE

Essay

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

By

**Suzi Abd El-Aziz Abd El-Hamid**  
*(M.B.B.Ch.) Cairo University*

Supervisors

**Prof. Dr. Heba El Sawah**

Asst. Prof. of Obstetrics and Gynecology  
Faculty of Medicine, Cairo University

**Dr. Nawara Hashish**

Lecturer of Obstetrics and Gynecology  
Faculty of Medicine, Cairo University

Faculty of Medicine  
Cairo University  
2008

## **ABSTRACT**

This essay represents a discussion of the immunological causes of recurrent miscarriage & its management.

It discusses the immunology of normal pregnancy and the immunological factors relevant to recurrent spontaneous miscarriage. It reviews also some immunological diseases causing this problem & their management.

Key Words :

Anti cardiolipin antibodies - Antinuclear antib -  
Deoxyribonucleic acid ody .

## ACKNOWLEDGEMENT

First and for most thanks to ``**God**'' for his help to fulfill this work

I would like to express my deepest gratitude to **Prof. Dr. Heba El Sawah**, Asst. Prof. of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for her generous guidance, encouragement and support throughout this work.

I am extremely grateful to **Dr. Nawara Hashish**, Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for her supervision, precious advice and sincere help, during the whole work.

Last but not least, I feel indebted to my Friends, Colleagues and to any one who gave a hand while working on this Essay.

## LIST OF ABBREVIATIONS

ACAs	Anti cardiolipin antibodies
ACL	Anti-cardiolipin
ADCC	Antibody - dependent cell mediated cyto-toxicity
ANA	Antinuclear antibody
APAs	Anti phospholipid antibodies
aPTT	Activated partial thromboplastin time
ASA	Anti sperm antibodies
B <sub>2</sub> -GPI	B <sub>2</sub> Glycoprotein I
C <sub>3</sub>	Complement 3
C <sub>4</sub>	Complement 4
CSFs	Colony - stimulating factors
DES	Diethyl stilbestrol
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FVL	Factor V Leiden
GIFT	Gamete Intra Fallopian Transfer
GPL	Unit for immunoglobulin G directed to phospholipids (IgG)
HIV	Human Immunodeficiency virus
HLA	Human leukocyte antigen
IFN $\gamma$	Interferon $\gamma$
Ig	Immunoglobulin
IL	Interleukin
IKM	Idiopathic recurrent miscarriage
IVF	In vitro Fertilization
IVIG	Intravenous Immunoglobulin
KCT	Kaolin Clotting Time
LA	Lupus Anticoagulant
LDA	Low Dose Aspirin
LGLs	Large granular lymphocytes
LIF	Leukemia inhibitory factor

LMWII	Low molecular weight heparin
MHC	Major histocompatibility complex
MLC	Mixed lymphocyte culture
MPL	Unit for immunoglobulin M directed to phospholipids
mRNA	Messenger ribonucleic acid
MTNFR	Methylene tetrahydrofolate reductase
NK	Natural killer cells
NSAID	Non steroidal anti-inflammatory drug
PA	Phosphatidic acid
PCOS	Polycystic ovarian syndrome
PE	Phosphatidyl ethanolamine
PG	Phosphatidyl glycerol
PI	Phosphatidyl inositol
PS	Phosphatidy inserine
PIT	Partial thromboplastin time
RM	Recurrent miscarriage
RPLs	Recurrent pregnancy losses
RSA	Recurrent spontaneous abortion
TC	T. Cytotoxic
TCC	T. Cytotoxic Cell
Th	T-helper
TNF $\alpha$	Tumor necrosis factor a
VTE	Venous thrombo-embolism

## LIST OF FIGURES

<i>No. of Figure</i>	<i>Title</i>	<i>Page No.</i>
1.	Incidence of preclinical losses and clinical pregnancies	6
2.	The HLA complex on the Short arm of chromosome 6.	31

## LIST OF TABLES

<i>No. of Table</i>	<i>Title</i>	<i>Page No.</i>
1.	The risk of recurrent early pregnancy loss in young women	7
2.	Modified from Laura Fox-Lee and Danie J. Sckust: Recurrent Pregnancy loss	22,23
3.	Cellular and humoral components of innate and adaptive immunity	28
4.	Indicators to Identify Lupus Anticoagulant and Anti-phospholipid antibodies	57

## CONTENTS

	<i>Page</i>
<b>INTRODUCTION .....</b>	<b>1</b>
<b>REVIEW OF LITERATURE:</b>	
• <i>Chapter I: Aetiology and Incidence of Early Pregnancy Loss .....</i>	<b>4</b>
• <i>Chapter II: Overview of the immune system .....</i>	<b>24</b>
• <i>Chapter III: Investigations of Immunological Causes of Recurrent Miscarriage .....</i>	<b>55</b>
• <i>Chapter IV: Treatment of Immunological Recurrent Miscarriage .....</i>	<b>62</b>
<b>SUMMARY .....</b>	<b>77</b>
<b>REFERENCES .....</b>	<b>80</b>
<b>ARABIC SUMMARY .....</b>	



### INTRODUCTION

Early pregnancy loss is defined as the termination of pregnancy before 20 weeks gestation or with fetal weight of <500gm.

Recurrent abortion is defined as three or more consecutive pregnancies ending spontaneously before the 20<sup>th</sup> week of gestation.

Many causes are responsible for recurrent early pregnancy loss.

- Genetic factors
- Anatomic factors
- Immunologic factors
- Infective factors
- Endocrinal factors
- Idiopathic

Immunological factors account for more than 50% of these cases, the most important of which is APAS.

APAS is diagnosed on clinical & laboratory criteria. One of two clinical criteria that include vascular thrombosis or certain pregnancy morbidity must be present. In addition, at least two laboratory criteria that include LAC activity or medium to high

---

positive specific IgG or IgM AcAs must be confirmed on two occasions 6 weeks apart.

Different drugs are use for treatment of recurrent miscarriage due to APAS & other thrombophilic disorders as:

- Heparin
- Low dose aspirin
- Corticosteroids
- Intervenous immunoglobulins
- Progesterone

But the best treatment is the combination between low molecular weight heparin & aspirin.

Other immunological causes of recurrent miscarriage require further evaluation for better diagnosis & treatment.

### AIM OF THE WORK

The aim of this work is to study the immunological causes of early reproductive failure & the recent advances in its management.

CHAPTER ( I )

**Aetiology and Incidence of  
Early Pregnancy Loss**

**(A) Definitions:**

Spontaneous abortion or miscarriage is defined as the involuntary termination of pregnancy before 20 weeks of gestation (dated from the last menstrual period) or spontaneous expulsion of fetus below a fetal weight of 500 gm (*Speroff et al., 2005*).

Recurrent first trimesteric abortion is defined as the occurrence of three or more clinically recognized spontaneous losses before 12 weeks from last menstrual period (*Wilcox et al., 1988*).

Three different groups among recurrent pregnancy loss (RPL) patients can be identified and should be assessed separately because the risk of subsequent miscarriage among these groups varies (*Daya et al., 2002*).

1. The primary RPL group consists of women with three or more consecutive miscarriages with no pregnancy progressing beyond 20 weeks gestation.
2. The secondary RPL group consists of women who have had 3 or more miscarriages following a pregnancy that progressed beyond 20 weeks gestation, which might have ended in live birth, still birth, or neonatal death, and

3. The tertiary RPL group, consists of women who have had at least 3 miscarriages that are not consecutive but are interspersed with pregnancies that have progressed beyond 20 weeks gestation (and might have ended in live birth, still birth or neonatal death) (*Christiansen et al., 2005*).

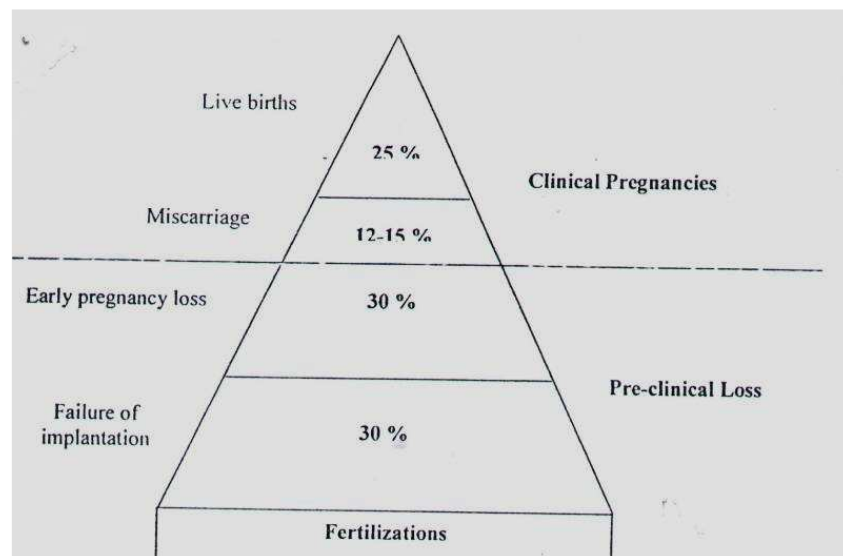
### **(B) Epidemiology:**

Of all recognized human pregnancies 15-20% end in spontaneous abortion. The actual incidence of spontaneous pregnancy loss is greater when early unconfirmed pregnancies are included, with the use of high sensitive hCG assays suggested - that up to 30% of pregnancies are lost between implantation and 6 weeks of gestational age (*Wilcox et al., 1988*). These estimates do not include instances where fertilized ovum fail to implant (*Warburton, 1987*).

In general, women in their first pregnancy, those whose only other pregnancy was electively terminated, and women whose only or last pregnancy was successful have a relatively low risk of spontaneous miscarriage (4-6%). Conversely, women whose only or last pregnancy ended in loss have a higher risk of miscarriage in their next pregnancy (19-24%) (*Regan et al., 1989*).

Miscarriage risk increases with the number of previous pregnancy losses but rarely exceeds 40-50%. Risk for pregnancy

loss also rises with increasing maternal age, moderately after age 35 and more rapidly after age 40 (*Speroff et al., 2005*).



**Fig. [1]:** Incidence of preclinical losses and clinical pregnancies (*Speroff et al., 2005*)

**Table [1]: The risk of recurrent early pregnancy loss in young women (*Clifford et al., 1997*)**

	<b>Number of prior miscarriages</b>	<b>% risk of miscarriage in next pregnancy</b>
Women who have had at least one live born infant	0	12%
	1	24%
	2	26%
	3	32%
	4	46%
	6	53%
Women who have not had at least one live born infant	2 or more	40-45%