بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY

The association between insulin resistance and unexplained recurrent miscarriage

A Thesis

Submitted for partial fulfillment of Master degree
in Obstetrics & Gynecology

By

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Ain Shams University
2021

Acknowledgments

First and foremost, I feel always indebted to **Allah**, *the* ***Most Beneficent*** *and* ***Merciful,*** *Who gave me the strength to accomplish this work.*

My deepest gratitude to my supervisor, **Prof. Dr. Hassan Awwad Bayoumy,** *Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his valuable guidance and expert supervision, in addition to his great deal of support and encouragement. I really have the honor to complete this work under his supervision.*

I would like to express my great and deep appreciation and thanks to **Prof. Dr. Wessam Magdy AbuelGhar,** *Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his meticulous supervision, and his patience in reviewing and correcting this work.*

I must express my deepest thanks to **Dr. Gihan ElSayed ElHawwary,** *ASSISSTANT PROFESSOR of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for guiding me throughout this work and for granting me much of her time. I greatly appreciate her efforts.*

Special thanks to my **Parents,** *my* **Husband** *and all my* **Family** *members for their continuous encouragement, enduring me and standing by me.*

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List of Abbreviations

Abbr.	Full-term
aCGH	**:** Array Comparative genome hybridization
ANA	**:** Antinuclear antibodies
APL	**:** Antiphospholipid
ART	**:** Assisted-reproductive technique
ASA	**:** Acetylsalicylic acid
ASRM	**:** American Society for Reproductive Medicine
BMI	**:** Body mass index
CCS	**:** Comprehensive chromosomal screening
CGH	**:** Comparative genome hybridization
ESHRE	**:** European Society of Human Reproduction and Embryology
FISH	**:** Fluorescence in situ hybridization
GDM	**:** Gestational diabetes mellitus
GH	**:** Growth hormone
GW	**:** Week of gestation
HGP	**:** Hepatic glucose production
HLA	**:** Human leukocyte antigen
HOMA	**:** Homeostasis model assessment
HSV	**:** Herpes simplex virus
HY	**:** Histocompatibility
IgA	**:** Immunoglobulin A
IGF-I	**:** Insulin-like growth factor–I

IgM : Immunoglobulin
IR : Insulin resistance
IRs : Insulin receptors
IST : Insulin sensitivity test
IUGR : Intrauterine growth retardation
IVF : In vitro fertilization
IVIG : Intravenous administration of immunoglobulins
LA : Lupus anticoagulant
LBR : Lamin B receptor
LH : Luteinising hormone
LIT : Lymphocyte transfer
LMWH : Low-molecular-weight heparin
LPD : Luteal phase defect
MRI : Magnetic resonance imaging
NK : Natural killer
OGTT : Oral glucose tolerance test
PCOS : Polycystic ovary syndrome
PGD : Preimplantation genetic diagnosis
PGS : Preimplantation genetic screening
PROMISE : Progesterone in Recurrent Miscarriage
RCOG : Royal College of Obstetricians and Gynecologists
RM : Recurrent miscarriage
SD : Standard deviation
SDF : Sperm DNA fragmentation

SPSS : Statistical package for social science

SSPG : Steady-state plasma glucose

SSPI : Steady-state plasma insulin

Th : T-helper cells

TNF : Tumor necrosis factor

TPO : Thyroid peroxidase antibodies

TSH : Thyroid stimulating hormone

UFH : Unfractionated heparin

URPL : Unexplained recurrent pregnancy loss

VTE : Thromboembolic events

2D : 2-dimnesional

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Introduction

Conventionally, the recurrent pregnancy loss was defined as three consecutive losses earlier than 20 weeks of gestation, but testing the women after 2 losses could spare them of another pregnancy failure; thus the definition was modified lowering the number of spontaneous losses to two ***(Mehmet et al., 2013).***

Recurrent pregnancy loss affects 2%–4% of reproductive-age couples ***(Kassie et al.,2015)***, representing a challenge for the physicians, affecting both naturally conceived pregnancies and those obtained after assisted reproductive technology treatment ***(Mehmet et al., 2013).***

In the etiology of RPL a broad spectrum of factors has been described: chromosome anomalies, uterine malformations or anomalies, immunological factors, hypothyroidism, cervical incompetence, antiphospholipid syndrome, bacterial infections, and polycystic ovary syndrome (PCOS) but half of the cases remain unexplained ***(Kassie et al., 2015).***

PCOS is the most common endocrine disorder in women, with prevalence between 6% and 15% (when the broader Rotterdam criteria are applied) ***(Johansson et al., 2014)***. The mechanisms through which pregnancy loss occurs in patients with PCOS include obesity, hyperinsulinemia, IR (insulin

resistance), hyperandrogenemia, poor endometrial receptivity, and elevated levels of LH ***(Xu et al., 2013).***

Glycemic control and insulin sensitivity are of the most important factors in reproductive pathophysiology. Impaired glucose tolerance, diabetes mellitus and Insulin Resistance (IR) have been long known to be linked to adverse reproductive outcomes, including infertility, miscarriages, and adverse pregnancy outcomes ***(Ispasoiu et al., 2013).***

Insulin resistance (IR) is a pathological condition in which cells fail to respond normally to the hormone insulin. To prevent hyperglycemia and noticeable organ damage over time, the body produces insulin when glucose starts to be released into the bloodstream from the digestion of carbohydrates (primarily) in the diet ***(Hong et al., 2013).***

Under normal conditions of insulin reactivity, this insulin response triggers glucose being taken into body cells, to be used for energy, and inhibits the body from using fat for energy, thereby causing the concentration of glucose in the blood to decrease as a result, staying within the normal range even when a large amount of carbohydrates is consumed. A habitually high intake of carbohydrates, simple sugars, and particularly fructose, e.g. with sweetened beverages, contributes to insulin resistance and has been linked to weight gain and obesity ***(Gallagher, 2017).***

If high and excess blood sugar from the digestion of primarily carbohydrates in the diet is not sufficiently absorbed by cells even in the presence of insulin, the increase in the level of blood sugar can result in the classic hyperglycemic triad of polyphagia (increased appetite), polydipsia (increased thirst), and polyuria (increased urination). Avoiding carbohydrates and sugars, a no-carbohydrate diet or fasting can reverse insulin resistance ***(Gallagher, 2017).***

Insulin resistance and hyperinsulinemia are claimed to be a potential cause of the high rate of pregnancy loss in patients with PCOS and have been linked to the metabolic and endocrine abnormalities associated with the physiopathology of recurrent pregnancy loss. Using the fasting blood glucose, fasting insulin, and HOMA (homeostasis model assessment) score, the insulin resistance was found three times higher in an unselected population of women with recurrent pregnancy loss when compared with normal population ***(Gutaj et al., 2015).***

Several studies demonstrated that the use of metformin in the treatment of PCOS reduces the risk of spontaneous abortion by decreasing the IR. It was therefore concluded that the IR is the key link between PCOS, obesity, and the recurrent pregnancy loss ***(Marchi et al., 2015).***