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List of Abbreviations

RPL	Recurrent Pregnancy Loss
hCG	Human chorionic gonadotropin
LMP	Last menstrual period
apL	Antiphospholipid
TORCH	Toxoplasmosis, rubella, cytomegalovirus and herpes
CMV	Cytomegalovirus
ETS	Environmental Tobacco Smoke
ISCN	International System for human cytogenetic Nomenclature
G-banding	Giemsa Banding
CNS	Central Nervous System
PCOS	Polycystic ovarian syndrome
ELIZA	Enzyme linked Immunosorbent Assay
DES	Diethyl stillbosterol

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INTRODUCTION

Recurrent spontaneous abortion is defined as two or more consecutive pregnancy losses prior to 22 weeks of gestation, usually occurring in approximately the same gestational week. (Rai and Regan 2006).

The World Health Organization (WHO, 1977) has defined spontaneous abortion as the expulsion or extraction from its mother of an embryo or fetus weighing 500g or less, which would normally be at 20-22 complete weeks of gestation

Early spontaneous abortions are defined as those that occur before the 12^{th} week of gestation, with late spontaneous abortions being those that occur from 12-20 weeks of pregnancy, and 500g or less (Kallen, 1988; Statistics Canada, 2004).

Spontaneous abortions may be subdivided into unrecognized and recognized spontaneous abortions (Nguyen and Wilcox, 2005) and into first and second trimester spontaneous abortions.

An unrecognized (subclinical) spontaneous abortion occurs after the conception but before the woman is aware she is pregnant, and is detected by measurement of human chorionic gonadotropin (hCG) level in blood or urine.

A recognized (clinical) spontaneous abortion occurs after the woman realizes she is pregnant. The risk of a clinically recognized spontaneous abortion has generally been estimated to 9-15% (Nybo Andersen et al., 2000; Gindler, 2001).

Environmental factors play an important role in the recurrent spontaneous abortion of pregnant mother (Gardella and Hill, 2000).

Several factors involved in human reproduction have been proposed as risk factors including genetic factors (chromosomal abnormalities or balanced translocations of either parent), uterine factors (malformations , trauma , tumors) , endocrine factors (uncontrolled diabetes mellitus, insulin resistance, untreated thyroid disease, hyper-prolactinaemia, luteal phase deficiency, hCG deficiency, hypersecretion of luteinizing hormone, polycystic ovary syndrome, premature ovarian failure), immune factors (antiphospholipid syndrome, alloimmune factors) thrombophilic defects (activated protein C- resistance, factor V Leiden mutation, defect protein C or S, defect anti-thrombin III, hyperhomocysteinemia, prothrombin, gene mutation) ,infectious agents (bacterial vaginosis, Chlamydia tracomatis, human papillomaviruses, toxoplasmosis, rubella, cytomegalovirus, herpes, listeria), environmental factors (heavy metals, organic solvents, smoking, caffeine, drugs, hyperthermia, pesticides) ,and psychological factors (trauma, stress).(Cramer and Wise 2000, Gardella and Hill 2000 , Li T.C. et al., 2002 , Dhont 2003, Christiansen et al., 2005, Arredondo and Noble 2006 , Kuttch and Triplett 2006 , Rai and Regan 2006).

Aim of the Present Work

The present study focuses on two main goals:

- Study the effects of genetic factors and environmental factors such as ionizing rays, X-rays, microwaves, ultrasound, and electromagnetic fields), chemical exposure (pesticides, herbicides, aerosol) prescription drugs, air pollution (vapour of cadmium, lead, cigarettes ….etc) drug abuse infectious agents (Cytomegalovirus, toxoplasma….etc) on recurrent spontaneous fetal loss.
- . Association study between the genetic and environmental causes participating in the recurrent spontaneous fetal losses.

Human Development

Human reproduction is a complicated process and the complex transition from a single fertilized ovum to a normally formed human being depends upon a series of precisely timed genetic and environmental interactions (Wilkie et al., 1994).

The development of the human embryo can be divided into three periods:

1- Preimplantation period:

Pregnancy occurs when a sperm penetrates an egg. This is called fertilization and usually takes place in the woman's fallopian tube. This fertilized egg immediately begins to divide into a growing cluster of cells. Between 5-7 days after ovulation the fertilized egg implants into the wall of uterus and starts forming the placenta. The placenta maintains and nourishes the baby by enabling the transfer of O2, CO2, amino acids, fats, vitamins and minerals from the mother's blood. It also allows transfer of waste substances from the growing baby. During this stage, the zygote undergoes cleavage by a series of mitotic divisions, which gives rise the embryo (Hay, 1998). Errors that occur during this early stage of embryogenesis cause the death of the embryo (Winter and Baraitser, 1998).

2- Embryonic period:

From the time of implantation into the wall of uterus until approximately eighth week of life the baby is known as embryo. Development is rapid during this stage as the specialized cells begin to form the vital organs, nervous system, bones, muscles and blood.During this period cells

differentiate to form different tissues and organs of the embryo. Most major malformations arise during this critical period of organogenesis (Hay, 1998).

3- Fetal period:

After the eighth week of pregnancy the developing baby is called a fetus. It is 2.4 cm. long with most of internal organs formed and external features such as eyes, nose, mouth and ears start to appear. (HON Foundation 2002).

As the fetus and placenta grow and place increasing demand on the mother, phenomenal alternations in metabolism occur. The most obvious physical changes are weight gain and altered body shape. Weight gain is due to increase in breast tissue, blood and water volume in the form of extra vascular and extra cellular fluid. Deposition of fat and protein and increased cellular water are added to maternal stores. The average weight gain during pregnancy is 12.5 kg. During second half of pregnancy plasma lipids increase but triglycerides, cholesterol and Lipoproteins decrease soon after delivery. The ratio of LDL to HDL increases during pregnancy (Moore 1994**)**.

The last stage of development lasts from the third month until birth, during this period few malformations may be arise (Smith and Donnai, 1997).

Recurrent Abortion

A) Definitions:

Recurrent pregnancy loss (RPL) is usually defined as two or more spontaneous pregnancy losses (not necessarily consecutive) in the absence of elective medication or surgical measures to terminate the pregnancy (Lee and Siliver 2000).

The term "miscarriage" is synonymous and often used with patient because the word "abortion" is associated with elective termination (Scroggins et al., 2000)

Spontaneous abortion or miscarriage is defined as the involuntary termination of pregnancy before 20 weeks of gestation (dated from the last menstrual period {LMP}) or spontaneous expulsion of fetus below a fetal weight of 500g (Speroff and Fritz 2005).

Miscarriages can be further divided into embryonic losses which occur before the ninth gestational week and into fetal losses which occur at or after the 9^{th} to 20^{th} weeks of gestation (Lee and Siliver 2000).

Three different groups among RPL patients can be identified and should be assessed separately because the risk of subsequent miscarriage among these groups varies (Daya 2002)

1- The primary RPL group consists of women with three or more consecutive miscarriage 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.

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).

Bricker and Farquharson, (2000). Classified pregnancy loss according to the gestational age into Pre-embryonic, embryonic and fetal.

Tab. (1): Pregnancy loss classification.

Types of pregnancy loss	Typical gestational (weeks)	Fetal heart activity	Principal diagnostic group	β-hCG level
Preembryonic	< 6	Never	Idiopathic	Low then fall
Embryonic	6 – 8	Never	Oligomenorrhea / idiopathic	Initial rise then fall
Fetal	> 8	Lost	Antiphospholipid syndrome	Rise then static or fall

-Another study confirmed that 70% of missed abortion, defined as an embryo without cardiac activity, had chromosomal abnormalities, most of which represented non–viable genetic defects (Philipp and Kalousek 2002).