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**Faculty of Basic Medical Science**



**“Fetal Cell Microchimerism and Female Autoimmune Diseases”**

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## ❖ **Abstract:**

Microchimerism is the presence of a small number of non-host stem cells originate from another individual. The most common source of microchimerism is pregnancy. During pregnancy, bi-directional trafficking of hematopoietic cells occurs through the placenta and these microchimeric cells persist for decades after childbirth. A possible role of microchimerism in the pathogenesis of some but not all autoimmune diseases has been suggested by recent studies. Contradictory reports exist regarding HLA allelic associations with persistent T lymphocyte microchimerism. Although much of the focus of past studies has been on microchimerism in the effector arm of the immune system, increasing evidence suggests that microchimeric cells may differentiate into many lineages in different tissues raising additional possible roles for these cells. The possibility of microchimerism in many organs should induce an exploration of how persistent mixtures of cells of different genetic backgrounds throughout the body may influence diverse physiologic processes during life.

## 1. **Introduction:**

### 1.1 **Microchimerism:**

1.1.1 **Definition:** is the presence of a small number of cells that originate from another individual and are therefore genetically distinct from the cells of the host individual. This phenomenon may be related to certain types of autoimmune diseases<sup>1</sup>.

### 1.2 **Feto-Maternal Microchimerism:**

1.2.1 **Definition:** also known as fetal cell microchimerism or fetal chimerism whereby cells from a fetus pass through the placenta and establish cell lineages within the mother. Fetal cells have been documented to persist and multiply in the mother for several decades<sup>2</sup>. A 2012 study at the Fred Hutchinson Cancer Research Center, Seattle, has detected cells with the Y chromosome in multiple areas of the brains of deceased women<sup>3</sup>.

1.3 **Relation between Microchimerism and Autoimmune Disease** Fetal microchimerism, which can be thought of as a form of trans-placental stem cell transplant, is becoming a plausible and unifying biological entity that helps to explain the etiology, the large diversity of tissue pathology, the predilection for females and the yearly increase in the incidence of autoimmune diseases in women. During their reproductive and post-reproductive years, women have a greater propensity than men to develop any one of a large variety of chronic autoimmune diseases.

## 2. **Discussion:**

### 2.1 **Fetal microchimerism:**

Fetal microchimerism is the transfer of intact living fetal cells from the fetal circulation into the maternal circulation and occurs in all pregnancies and increases with gestational age. Study by Dr Keelin O'Donoghue in 2004 and Adams Waldorf in 2009 indicate that microchimerism can be portrayed as a legacy of pregnancy that persists for decades via fetal cell engraftment in maternal bone marrow or other tissues<sup>4,5</sup>. The process of microchimerism is Two-way cell traffic between mother and fetus, the transfer of maternal cells into the fetal circulation is known as maternal Microchimerism<sup>6,7</sup>. The presence of fetal microchimeric cells can be detected for up to 30 days after induced or spontaneous abortion in maternal blood stream but more microchimeric cells are transferred after surgical abortions than after spontaneous abortions<sup>8</sup>. Fetal microchimeric cells of male embryos/fetuses can be selectively detected and magnified by assaying for the presence of the Y-chromosome-containing cells among a large number of maternal cells marked by XX chromosomes<sup>9</sup>.

Study by Dr J Lee Nelson and Ilona Hromadnikova in 1998 and 2008 detect Male fetal cells in both maternal synovial tissue and skin of patients with rheumatoid arthritis and in the skin and blood of women with systemic sclerosis<sup>10, 11</sup>. Also a research paper published in 2014 concluded that fetal cells play a role in maternal wound healing after pregnancy<sup>12</sup>.

## **2.2 Fetal Microchimerism and Autoimmune Disease:**

In the late 1990's the discovery of fetal microchimeric cells in maternal tissues led to the finding of a positive association between fetal microchimerism and autoimmune diseases in women. Research published by Péter Apari in 2009 concluded that the miscarriages may cause autoimmune diseases, and the males may be more capable to cause microchimerism-induced autoimmune-like diseases in the mother<sup>13</sup>. Study in 2004 concluded that microchimeric cells may differentiate into many lineages in different tissues raising additional possible roles for these cells. The possibility of microchimerism in many organs should induce an exploration of how persistent mixtures of cells of different genetic backgrounds throughout the body may influence diverse physiologic processes during life. This study suggests that there is many influencing factors and roles of microchimerism in autoimmune and non-autoimmune diseases, along with the environmental and genetic risk factors<sup>14</sup>. Other Study published in JAMA journal in 2004 and another by Lee Nelson in 2002 support for the concept that naturally acquired microchimerism can contribute to autoimmune diseases but at the same time suggest microchimerism may have beneficial effects to the host. It is likely that fetal and maternal microchimerism can have adverse, neutral, or beneficial effects on the host, depending on other factors such as specific HLA genes and the HLA relationship between cell populations<sup>15, 16</sup>. Research by Michele Leduc and others in 2009 suggesting that semi-allogenic fetal T cells trigger a graft-versus-host type of disease, and it has been supported by several studies showing an increased frequency of fetal-cell microchimerism (FMc) in women affected with systemic sclerosis. In addition, it is showing the transfer of various fetal progenitor cells to the mother during gestation. This research support for the concept that the fetal hematopoietic progenitors form T and B cells in maternal hematopoietic tissues, where they undergo an educational process probably resulting in tolerance to maternal antigens<sup>17</sup>. Within maternal tissues the fetal microchimeric progenitor immature T cells, also known as CD4 cells, are capable of self-renewal, proliferation, differentiation and activation. Activation of progenitor cells can result in the production of paracrine and autocrine inflammatory cytokines and chemokines that are involved in autoimmune diseases<sup>18, 19</sup>. The role of fetal microchimerism in transplant tolerance has remained an enigma. Unknown triggering agents that activate these fetal microchimeric immune cells to attack the maternal host cells resulting in an autoimmune disease, have not yet been definitely identified. Viral, bacterial agents, drugs or abnormal local tissue proteins that can serve as an antigen are among the suspected triggers. Study in 2008 indicate that microchimerism may also contribute to the risk of an autoimmune disease by providing HLA susceptibility alleles<sup>20</sup>. Some researchers in 2003 found that microchimerism in affected tissues is more likely to be demonstrable in women with autoimmune disease than in women with non-autoimmune diseases<sup>21</sup>. Another researchers in 2003 and 2006 demonstrate fetal microchimerism in Hashimoto's thyroiditis and Graves's Disease but found to be absent in normal thyroids<sup>22, 23</sup>.

## **2.3 Post-abortion and the incidence of fetal microchimerism:**

There is an increased fetal-to-maternal transfer of fetal undifferentiated progenitor cells during an abortion procedure as the placenta is being destroyed<sup>24, 25</sup>. Study by Fujimori K in 2008 concluded that the amount of fetal DNA found in maternal circulation after 30 days of abortion<sup>26</sup>. Also an article by Khosrotehrani et-al in 2004 concluded that since the embryonic circulatory system is established in

the first trimester of pregnancy, there is a larger number of hematopoietic progenitor T cells transferred during a first trimester termination of pregnancy<sup>27</sup>.

### 3. Conclusions:

Microchimerism is the presence of a small number of non-host stem cells originate from another individual. During pregnancy, bi-directional trafficking of hematopoietic cells through the placenta is occurs in all pregnancies and increases with gestational age, these microchimeric cells persist for decades after childbirth. Cells with the Y chromosome was detected in multiple areas of the brains of deceased women and also detected in both maternal synovial tissue and skin of patients with rheumatoid arthritis, and in the skin and blood of women with systemic sclerosis also some researchers demonstrate fetal microchimerism in hashimoto thyroiditis and graves disease, but found to be absent in normal thyroids. The discovery of fetal microchimeric cells in maternal tissues led to the finding of a positive association between fetal microchimerism and autoimmune diseases in women. Some researchers suggests that miscarriages may cause autoimmune diseases and there is many influencing factors and roles of microchimerism in autoimmune and non-autoimmune diseases, along with the environmental and genetic risk factors but at the same time may have beneficial effects to the host depending on other factors such as specific HLA genes and the HLA relationship between cell populations. Other studies indicate that miscarriages may cause autoimmune diseases because the placenta is being destroyed. The studying of Microchimerism and understand their origin and their role in pathogenesis of autoimmune diseases and the beneficial effects to the host is now very important.

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