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Short Communication

Interleukin-6 -174 G/C Polymorphism and Implantation Failure after Assisted Reproductive Technologies

Elena Chinni*

Atherosclerosis and Thrombosis Unit, Fondazione I.R.C.C.S. 'House for the Relief of Suffering', S. Giovanni Rotondo (Foggia), Italy

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***Corresponding author:** Elena Chinni, PhD, Atherosclerosis and Thrombosis Unit, Fondazione I.R.C.C.S. 'House for the Relief of Suffering', S. Giovanni Rotondo (Foggia), Italy, E-mail: e.chinni@operapadrepio.it

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Summary

This study evaluated the influence of the IL-6 G/C-174 polymorphism on Assisted Reproductive Technology (ART) outcomes. The analysis included 141 women with no pregnancy after at least two implantation failures following ART and 98 women who achieved pregnancy through ART. No association was found between this polymorphism and implantation failures in women undergoing ART.

Introduction

In recent decades, there has been a substantial increase in the worldwide use of assisted reproductive technologies (ART) procedures. Several studies suggest that placental dysfunction might influence perinatal outcomes after ART [1]. Interleukin-6 (IL-6), a proinflammatory cytokine, is involved in various physiological and pathophysiological processes [2]. Furthermore, it plays a role in human implantation [3]. IL-6–deficient mice have reduced fertility and a decrease in viable implantation sites [4]. The human IL-6 gene is located at chromosome 7p21–24 and has an upstream 303 bp promoter. It has been reported that the G/C polymorphism at position -174 could be associated with high/low IL-6 production status. Individuals who are homozygous G/G or heterozygous G/C could show normal IL-6 production, while individuals with the homozygous C/C variant could have reduced IL-6 production [5]. Previous studies described the association of IL-6 -174 G/C polymorphism with the development and progression of various inflammation-related human diseases, including coronary heart disease, neuroblastoma, systemic lupus erythematosus, HIV/AIDS and nephritis [6-10].

The association of IL-6 -174 G/C polymorphism with pregnancy complications, such as pre-eclampsia (PE), small for gestational age (SGA) infants, unexplained intrauterine fetal death (IUFD) and preterm delivery (PD), was also studied. Stonek et al., in a prospective cohort study from 1626 consecutive pregnant women, concluded that IL-6 -174 G/C is not a genetic marker for identifying women at increased risk of common pregnancy [11]. Later on, Sowmya S, et al. suggested that the IL-6 -174 G/C polymorphism, in non-Caucasian population, was significantly associated with preeclampsia compared to controls [12].

However, to our knowledge, there is no study on the impact of the IL-6 -174 G/C polymorphism on the risk for ART outcome. Thus, we wondered whether IL-6-G/C -174 polymorphism could be associated with the ART outcome in women without inherited or acquired thrombophilia.

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Materials and methods

We performed a case-control study involving women without any pregnancies after at least two implantation failures (IF) (cases) (n = 141) and women without inherited or acquired thrombophilia who obtained pregnancy after ART (controls) (n = 98). Informed consent was obtained from each woman.

Blood samples were collected and DNA extracted according to standard protocols [13]. IL-6 -174 G/C polymorphism was investigated by means of polymerase chain reaction (PCR) and subsequent Nla III restriction enzyme analysis. Briefly, PCR was carried out on 50-µL volume samples, in a GeneAmp PCR System 2700 thermal cycler. Each sample contained 0.5 µg of genomic DNA, 15 pmoles of each primer, 100 mM of dNTP, 10 mmol/L Tris-HCl pH 8.3, 50 mmol/L KCl, 1.5 mmol/L MgCl2, and 1 U thermostable Taq polymerase. The 30 cycles consisted of steps at 95 °C for 60 sec, at 58 °C for 50 sec and at 72 °C for 100 sec. Then, 20 µL volumes of the amplification products were digested for 2.5 hours at 37 °C with 2 U of the Nla III restriction enzyme. The fragments were fractionated by 4% agarose-gel electrophoresis, and visualized under UV light.

Hardy–Weinberg equilibrium was assessed for IL-6 -174 G/C polymorphism and deviation between the observed and expected frequencies was tested for significance using the χ^2 test.

Results

The genotypic distribution of -174 G/C IL-6 polymorphism is shown in Table 1. The frequencies of the genotypes CC, GC and GG and the calculated allele frequencies did not differ from those predicted from the Hardy-Weinberg equilibrium (χ^2=1.68; p = 0.4317). No significant difference in the distribution of genotypic and allelic frequencies between the cases and controls was observed. Fisher's exact test returns p values were consistently > 0.05.

Discussion

In the present study, we investigated the correlation of IL-6 gene -174 G/C polymorphism and ART outcome in women without inherited or acquired thrombophilia.

Table 1: Distribution of IL-6 genotypes and allelic frequencies in cases and controls.

	Case n (%)	Controls n (%)	χ2	OR (95% CI)	p-value
Codominant					
GG	83 (58.9%)	60 (61.2%)			
GC	52 (36.9%)	36 (36.7%)	0.25	2.08 (0.35-5.86)	0.47
CC	6 (4.2%)	2 (2.1%)	0.34	2.17 (0.38-16.15)	0.47
Dominant					
GC+GG	135	96			
CC	6	2	0.33	2.13 (0.38-15.64)	0,48
Allele frequency					
G	218	156			
C	64	40	0.23	1.14 (0.72-1.83)	0.57

Embryo implantation remains one of the last frontiers of reproductive medicine. It involves a complex interaction between the embryo and the uterus [14]. In first-trimester trophoblasts, IL-6 protein and mRNA are present in both cytotrophoblastic and syncytiotrophoblastic cells, playing a role in human implantation.

In this cohort of Caucasian women, the analysis of the IL-6 -174 G/C promoter polymorphism was not associated with implantation failures in women approaching ART. Future multi-ethnic studies involving diverse populations could allow us to expand and generalize the findings.

Genetic regulation of IL-6 production is known to influence human diseases, particularly those of an infectious or inflammatory nature [15]. It is possible that ART outcomes observed in our cohort of women do not depend on possible IL-6-induced inflammatory effects seen in other adverse conditions.

A key limitation of our study is the relatively small sample size. Larger studies are needed to confirm and extend these findings, potentially revealing more subtle biological patterns. Furthermore, future studies employing next-generation sequencing of multiple genes involved in embryo implantation, along with pathway-based analyses, may contribute to a better understanding of ART success.

This is the first study focused on IL-6 gene -174 G/C polymorphism and ART outcome.

In conclusion, the present data suggest that evaluation of the IL-6 G/C-174 polymorphism does not provide additional information for identifying subjects with a higher risk of IF.

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