A 10-years' experience in hereditary thrombophilia in IVF: Is there success after treatment?

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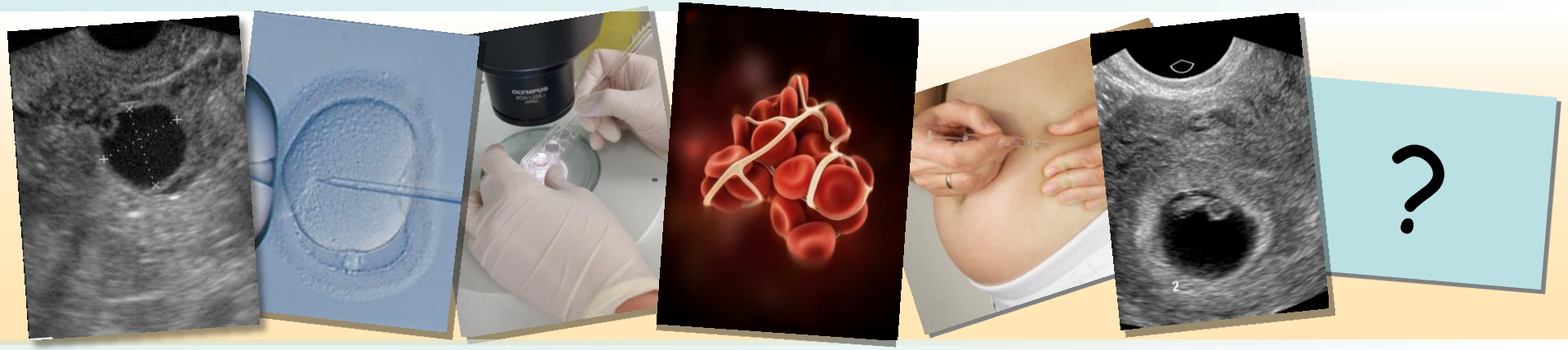
Introduction

Thrombophilia has been recently implicated in early pregnancy loss and IVF repeated implantation failure (RIF) mainly by impairing the initial vascularization processes occurring at implantation.



Objectives

The objective of this study was to determine the incidence of undiagnosed hereditary thrombophilic factors in cases with implantation failure in two or more previous IVF-embryo transfer cycles. Furthermore, to assess IVF success rates and pregnancy outcome following patient-specific anticoagulant treatment.

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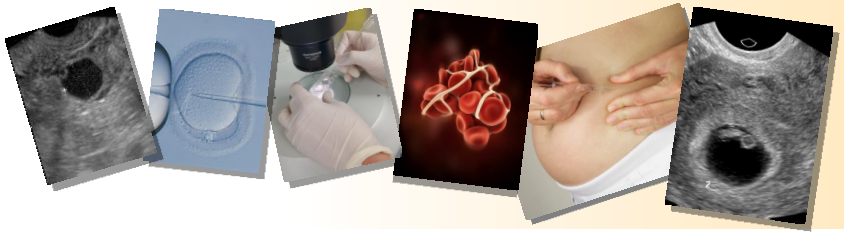

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Methods

The study included 518 patients, less than 42 years of age with normal karyotype, with at least one miscarriage (with normal embryo karyotype) and/or 2 embryo transfers with good grade embryo following IVF. All patients were tested for the presence of a set of mutated thrombophilic genes including factor V Leiden (FVL), Methylenetetrahydrofolate reductase (MTHFR) and Prothrombin (G20210A) using PCR amongst others (CVD kit).

Parameters like age, duration and cause of infertility, dose of gonadotropins, duration of stimulation, number of oocytes retrieved and embryos transferred and the outcome in terms of delivery (full term or premature), ectopic pregnancy or abortion are analyzed.

Thrombophilia Screening

Cardiovascular Disease Screening (Thrombophilia & Atherosclerosis 13 mutations) (CVD):

- Factor II Prothrombin (PT) G20210A mutation)
- Factor V Leiden mutation
- Factor V R2 H1299A mutation
- Factor XIII V34L mutation
- Fibrinogen-β 455 G>A mutation
- GPIa mutation
- GPIIIa (HPA-1 L33P) mutation
- PAI-1 (plasminogen activator inhibitor activator) mutation
- MTHFR C677T mutation
- MTHFR A1298C mutation
- ACE (angiotensin-converting enzyme) insertion/deletion (I/D) polymorphism
- APO B (apolipoprotein B) R3500Q mutation
- APO E (apolipoprotein E) E2/E3/E4 polymorphisms

Patients in need of a anticoagulant treatment were referred to an hematologist. Treatment was administered according to the BMI and the severity of thrombophilia either from the first day of IVF stimulation or the embryo transfer day. Minimum dosage administered was 4.500 Anti-Xa IU

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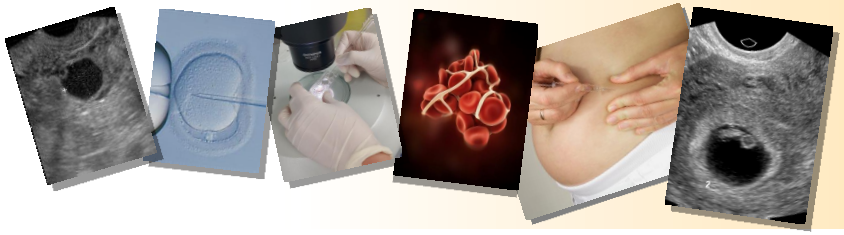

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Results

At least one inherited thrombophilic factor was detected in 78.1% of women with repeated IVF failure or pregnancy loss. Combined thrombophilia (two or more thrombophilic factors) was found in 43.8% of the cases analyzed. In depth analysis of the incidence of homozygotic and heterozygotic mutations, along the multiple mutations is performed.
After anticoagulant treatment, patients underwent a new controlled ovarian hyperstimulation protocol for IVF or had an embryo transfer using thawed embryos. The clinical pregnancy rate after treatment was 40.3% and the live birth rate 35.1%.

Cases	518
Mean Age	37,5
Primary Cause of infertility	Male
Total dose of Gn's	2000IU
Mean Days of stimulation	10
Mean number of oocytes	8
Mean embryos transferred	1,7
Outcome	
Cycles with Embryo transfer	479
Clinical Pregnancies	193
	40,3%
Live Birth Rate	35,1%

ΜΕΘΟΔΟΛΟΓΙΑ

Το παραληφθέν δείγμα, υπέστη διαδικασία απομόνωσης γενετικού υλικού DNA. Ποσότητα από το απομονωμένο γενετικό υλικό χρησιμοποιήθηκε προς εκλεκτική ενίσχυση (PCR) και υβριδοποίηση με πολλαπλούς ανιχνευτές για τις ακόλουθες 12 μεταλλαγές και πολυμορφισμούς: FV G1691 (Leiden), FV H1299R (R2), Prothrombin G20210A, Factor XIII V34L, b-Fibrinogen -455, PAI-1, GPIIIa L33P, MTHFR C677T, MTHFR A1298C, ACE I/D, Apo B R3500Q, Apo E. Οι μεταλλαγές καθώς και οι πολυμορφισμοί αυτοί, σχετίζονται σύμφωνα με διεθνή βιβλιογραφικά δεδομένα με προδιάθεση θρομβοφιλίας και καρδιαγγειακά νοσήματα. (CVD kit).

ΑΠΟΤΕΛΕΣΜΑΤΑ

Η μοριακή ανάλυση του παραληφθέντος δείγματος, ανέδειξε το ακόλουθο γενετικό profile αναφορικά με τις προαναφερόμενες μεταλλαγές.

ΜΕΤΑΛΛΑΓΕΣ-ΠΟΛΥΜΟΡΦΙΣΜΟΙ	ΓΟΝΟΤΥΠΟΣ
FV G1691 (Leiden)	Φυσιολογικός Γονότυπος
FV H1299R (R2)	Φυσιολογικός Γονότυπος
Prothrombin G20210A	Φυσιολογικός Γονότυπος
Factor XIII V34L	Ετερόζυγος Γονότυπος
b-Fibrinogen -455	Φυσιολογικός Γονότυπος
PAI-1	5G/4G
GPIIIa L33P	1b/1a
MTHFR C677T	Ετερόζυγος Γονότυπος
MTHFR A1298C	Φυσιολογικός Γονότυπος
ACE	Γονότυπος με deletion-insertion
Apo B R3500Q	Φυσιολογικός Γονότυπος
Apo E	E3/E3

Η αξιολόγηση των αποτελεσμάτων γίνεται από τον θεράποντα ιατρό με συνεκτίμηση των κλινικών ευρημάτων και του ιστορικού του/της ασθενούς.
Η ειδικότητα της εξέτασης προσεγγίζει το 99%.

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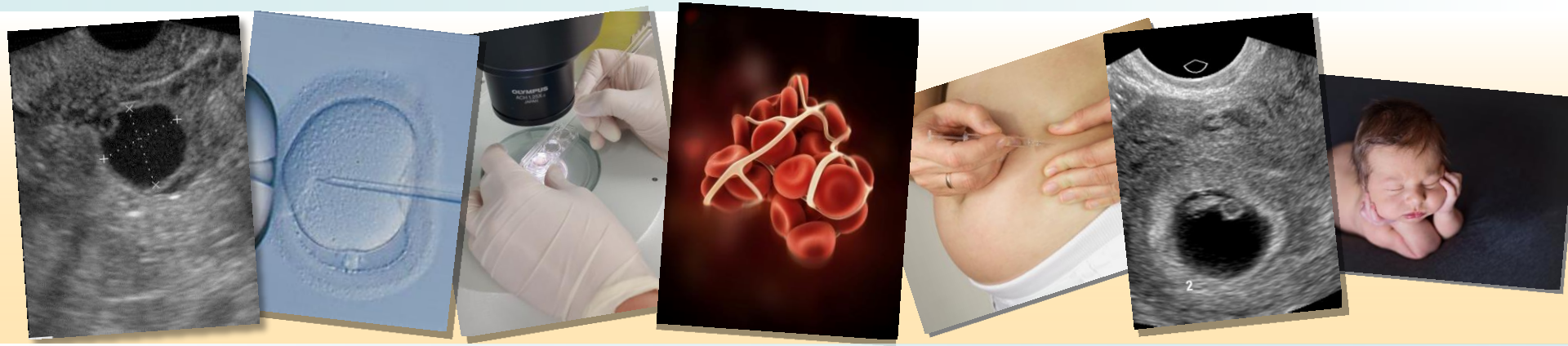
Discussion

Thrombophilia has a significant role in IVF-embryo transfer implantation failure. Our results show that screening and treating thrombophilia, increases the chances of a live birth in this group of patients with RIF.



Research made it possible… the picture story line is now full