Thrombophilia and repeated *in vitro* fertilisation and embryo transfer failure: An open issue

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Dear Sirs,

The association between thrombophilia and female infertility due to pregnancy loss is well known both for inherited thrombophilia and acquired thrombophilia (1), while the association between thrombophilia and unexplained female sterility is still matter of discussion in particular for women underwent to repeated *in vitro* fertilisation (IVF) and embryo transfer (ET) failures. Some authors, in fact, found an association between thrombophilia and\or hypofibrinolysis and repeated IVF failures (2) while other authors did not find a strong association between thrombophilia and repeated IVF-ET failures (3). There are not univocal points of view, in fact, concerning the role of thromboprophylaxis in order to increase the successful IVF in these subjects. Single IVF failure, in fact, is already considered *per se* for nearly 70% of cases independently from the presence or the absence of thrombophilia (3) or other underlying disease. The main issue is related to not univocal data on the frequency of IVF failures in carriers of thrombophilia compared to non-thrombophilic women because also the high relative frequency of IVF failures *per se*. Moreover all reported series show further differences in inclusion and exclusion criteria of studied patients. First of all the ethnic background seems to be different study by study as the different selection of control subjects.

However, although, the rate of thrombophilia in women with repeated IVF failures is always greater than 50% in all selected studies, several reports did not find a statistical significance when patients were compared to control subjects. Simur et al. selected 51 women with three or more IVF-ET failures with a frequency of 62% of thrombophilic defects without a statistical significance compared to control group (women with at least one uneventful pregnancy and without personal history of miscarriage) (4). Similarly, Martinelli et al. did not find a relationship between thrombophilia and repeated IVF-ET failures in 162 women with nearly 27% of inherited thrombophilic defects without statistical significance with control group (women with spontaneous and natural conception) (3). Vaquero et al. found nearly 24% of thrombophilic subjects with inherited thrombophilia in women with IVF failures compared to 20 non-pregnant healthy fertile females without statistical significance (5). Regarding acquired thrombophilia due to the presence of antiphospholipid antibodies Martinelli et al. did not find an association between patients with IVF-ET failures compared to controls (3), while Vaquero et al. found nearly 19% of women with IVF-ET failure with the presence of antiphospholipid antibodies versus none of control group, finding a statistical significance (5). Similarly, Qublan et al. found a significant increase of antiphospholipid antibodies in women with recurrent IVF-ET (three or more unsuccessful cycles) compared to healthy controls and also to women with successful IVF-ET (6).

Moreover, Qublan et al. found also a significant increase in the frequency of inherited thrombophilic defects in the same study group compared to both control groups (6); the same results were found also for combined thrombophilia (i.e. the presence of two or more thrombophilic defects) (6). Azem et al. also investigated on the role of inherited thrombophilia in women with recurrent IVF-ET (four or more failures) compared to healthy control and found a relevant and significant increase of inherited thrombophilic gene variant (7). Moreover, Coulam et al. reported in a small population of women with recurrent IVF-ET failure compared to healthy subjects not only an increased incidence of inherited thrombophilic defects but also a relevant increase of PAI 4G\5G gene variant thus suggesting also a possible involvement of hypofibrinolysis in this clinical setting (2). Regarding homocysteine metabolism, recently emerging data seem to be available on the homocysteine and folate metabolism and unexplained female sterility (8) and also MTHFR C677T gene variant and unexplained female sterility in women with IVF-ET failures (9).

This heterogeneity of reported data on this topic suggest that the role of thrombophilia in the pathophysiology of IVF-ET will be again matter of discussion and in particular that a more systematic way to program studies on this topic should be followed beginning from inclusion and exclusion criteria both of enrolled patients and control subjects. Reported studies from the literature, in fact, differ mainly because selected patients were enrolled after two or three or more IVF-ET failures. Furthermore, in this clinical setting there are not suggestions from any guideline to perform a thrombophilic screening in patients with repeated IVF-ET failures, while this kind of screening is usually suggested for recurrent miscarriages. Moreover, thrombophilia may be only one of further latent or clinical open disease that may alter the outcome of IVF-ET (e.g. thyroid abnormalities, chronic inflammatory disease, recurrent infection and so on) and this further clinical aspect should be considered also in the inclusion and exclusion criteria of patients in each study on this topic. Finally, also the ethnic background of enrolled patients and control subjects may play role in statistical, obstetric and clinical evaluation (e.g. women with normal spontaneous concep-

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tion with or without history of miscarriage, women with successful IVF-ET and so on).

Another aspect that may play a role in the differences that we may be found in previous studies may be related to the ethic and legal and local evaluation of women candidate to IVF procedures with following ET: such an institution (hospital, geographic area) does not permit more than two or threee IVF procedures with the approval of local ethic committee, while further procedures may be organised out of local hospital or geographic area (e.g. in other countries).

In conclusion, data available in the literature seems to open a new scenario in the clinical management of women with IVF-ET, in particular next studies should evaluate if an antithrombotic treatment, based on the administration of low-molecular-weight heparin, may have a positive effect on the outcome of women that experienced repeated IVF-ET failures

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