Prophylactic low molecular weight heparin in women with thrombophilia submitted to *in vitro* fertilization.

Running title: Treating thrombophilia in assisted reproduction.

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CAPSULE

Women with thrombophilia submitted to *in vitro* fertilization present increased early pregnancy loss and abortion rates, which is reversed by enoxaparin treatment following embryo transfer.

Abstract

Objective: to verify if low molecular weight heparin(LMWH) could increase pregnancy rates and/or decrease abortion rates in women with thrombophilia undergoing assisted reproduction cycles.

Design: Retrospective study.

Setting: Private infertility clinic.

Patients: Patients submitted to assisted reproduction (total n=104). Women without thrombophilia (controls, n=20), women with thrombophilia (untreated group, n=30), and women with thrombophilia, treated with daily enoxaparin from the day of embryo transfer until week 36 of gestation (treated group, n=54).

Interventions: Enoxaparin treatment for diagnosed thrombophilia. All women underwent controlled ovarian hyperstimulation, in vitro fertilization was performed by intracytoplasmic sperm injection, embryos were transferred on day three. Pregnancy was detected by β-hCG (biochemical) and fetal heart beat at weeks 5-6. Ongoing pregnancy was determined by ultrasound on week 12.

Main Outcome Measures: Implantation rate, ongoing pregnancy rate, live birth rate, early pregnancy loss rate, and abortion rate.

Results and conclusion: Patients in the Untreated Thrombophilia group presented significantly lower ongoing pregnancy rates and live birth rates, and significantly higher early pregnancy loss and abortion rates when compared to the Control or the Treated Thrombophilia groups. In women with diagnosed coagulation disorders, use of low molecular weight heparin is important in order to avoid miscarriages.

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48 Keywords: female infertility; thrombophilia; enoxaparin; abortion; *in vitro* fertilization.

Introduction

Recurrent pregnancy loss (RPL), defined as two or more consecutive miscarriages before the twentieth week of gestation, is observed in up to 5 % of women (1). While embryo aneuploidy may account for a large number of these, it has been shown that preimplantation genetic screened (PGS) embryo transfer cycles achieve a global pregnancy rate of under 40 %, with a per-pregnancy delivery rate of under 80 % (2). In a 2008 review article, Nelson and Greer had discussed that a potential cause for these losses was activation of the coagulation cascade during implantation and early formation of the placenta (3). This was based on previous reports that demonstrated increased pregnancy rates in women diagnosed with thrombophilia when treated with heparin for at least 14 days (4).

Pregnancy itself is a pro-thrombotic condition which increases the risk of thromboembolic events (5). Previous studies have shown that this state of hyper coagulation predisposes a number of complications, among which pregnancy loss (6) due to microthrombosis at the site of implantation (7) and altered trophoblast function (8). In women with thrombophilia, thus, there is a predisposition towards a state that leads to pregnancy loss. It is also noteworthy that women undergoing controlled ovarian hyperstimulation with gonadotropins have also been shown to present alterations in hemostasis (9). This has supported the rationale that anticoagulation therapy be employed as an adjuvant in assisted reproduction.

A 2018 meta-analysis on the use of low molecular weight heparin (LMWH) in assisted reproduction cycles in non-thrombophilic women concluded there was no evidence of increased gestation rates, although multicenter trials were still deemed

necessary (10). In women that do present thrombophilia, however, results are quite heterogeneous, as are the studies, which leads to difficulty in reaching a conclusion as to whether or not the use of LMWH would contribute to increasing pregnancy rates and/or decreasing abortion rates. In a recent review, Di Micco et al. discussed that some authors demonstrate a positive trend in the use of LMWH towards increasing gestation rates, while a cohort study that used LMWH with prednisolone did not (9).

It is clear, therefore, that there is still a need of a contributing body of evidence to demonstrate whether or not the use of LMWH during assisted reproduction treatments in women with thrombophilia produces effects on outcomes. In this manuscript, we set out to verify if LMWH could increase pregnancy rates and/or decrease abortion rates in women with thrombophilia undergoing assisted reproduction cycles.

Materials and Methods

Study design and patients

A retrospective study was carried out in order to verify outcomes in 104 patients who had been submitted to assisted reproduction. Women without thrombophilia were included as controls (n=20), while women with thrombophilia had either been treated with 40 mg daily enoxaparin (Treated Thrombophilia group), initiated at the day of embryo transfer, up to week 36 of gestation (n=54), or had remained untreated (Untreated Thrombophilia group, n=30). Institutional Review Board approval was received from the CAAE: 41006620.0.0000.0082 Faculdade de Medicina ABC (FMABC) This study is registered at clinicaltrials.gov (code NCT05225155).

Inclusion criteria were women submitted to IVF using an GnRH antagonist protocol, age 40 years old or less, primary or secondary infertility for at least 18 months. Exclusion criteria were women with BMI higher than 30Kg/m2, women that used a GnRH agonist analogue and women submitted to egg donation programs. Data was collected from patient's medical records from 2013 to 2018.

Patient data collected were age, height, weight, body mass index, length of infertility, type of infertility (primary or secondary), serum FSH, LH, estradiol, progesterone, and prolactin levels. The requested thrombophilia profile was: Factor V Leiden mutations, methylenetetrahydrofolate reductase mutations, serum homocysteine levels, protein S, protein C, anti-thrombin III, deficiency gene prothrombin., anti-cardiolipin, anti-phospholipid, lupus anti-coagulant, and anti-phosphatidylserine antibodies levels.

Thrombophilia is a coagulopathy that favours the blood`s hyperviscosity and hypercoagulability, working as a risk factor for thrombosis. It`s etiology can be associated both with genetic factors and acquired factors (such as infections, surgeries, chemotherapy or radiotherapy).

In our study, we included in the thrombophilia`s group patients with at least one altered laboratory test in addition to suggesting clinical data (such as recurrent miscarriages or implantation failures) or at least two altered laboratory tests even without suggesting clinical data.

After 14 days of embryo transfer, serum beta-hCG levels were measured (biochemical gestation). At five to six weeks, a transvaginal ultrasound was performed for detection of fetal heartbeat and to count gestational sacs. Ongoing pregnancy was detected by ultrasound at twelve weeks. Early pregnancy loss was considered after a positive result for biochemical gestation and a subsequent negative result at 5-6 weeks or at 12 weeks, and abortion was considered if an ongoing pregnancy did not lead to a birth. Implantation rates were calculated as the number of gestational sacs divided by the number of transferred embryos.

Treatments

All included patients had been submitted to *in vitro* fertilization (IVF) treatment using intracytoplasmic sperm injection (ICSI). Patients were initially subjected to controlled ovarian hyperstimulation under a short protocol. Gonadotropins were initiated on day 3 of the cycle, and GnRH antagonist (Cetrorrelix acetate) was administered when the leading follicle reached a diameter of 13 mm. When the leading follicle reached a

diameter of at least 18 mm, patients received either 250 mg of recombinant human chorionic gonadotropin or 3.75 mg of GnRH agonist (Triptorelin). Transvaginal ultrasound-guided oocyte retrieval was carried out 34-36 hours later. Luteal phase support was achieved with vaginal micronized progesterone at 800 mg/day and transdermic estradiol at 100 mcg every other day until 12 weeks of gestation (in negative outcome or in early pregnancy loss cases, luteal phase support was discontinued).

Statistical analysis

Data were analyzed using SPSS for Windows 18.0. Initially, descriptive statistics were carried out in order to calculate mean, standard deviation, 95 % confidence interval values of the means, medians, and interquartile ranges for numeric data, and frequencies for categorical data. Variables were initially tested for normality of distribution using a Kolmogorov-Smirnov test. For normally distributed variables, groups were compared by a One-Way Analysis of Variance (ANOVA) test, followed by a Least Significant Differences (LSD) post-hoc test. For variables that were not normally distributed, a non-parametric Kruskal-Wallis test was used, followed by a post-hoc Games-Howell test. A p-value of 5 % was considered significant. Main outcome measures were defined as pregnancy, early pregnancy loss, and abortion rates. Secondary outcomes were implantation and live birth rates.

In order to verify the effect of Enoxaparin treatment over non-treatment, a logistic regression model was constructed, using live birth and abortion as dependent binary variables, and use of Enoxaparin as an independent variable. Odds ratios for occurrence

of a live birth and for non-occurrence of abortion were calculated, and the model was considered significant at the 5 % level.

Results

Clinical and treatment characteristics

Clinical characteristics from the included patients are presented in table 1. No differences were observed for patient age, weight, height, body mass index, and serum FSH, LH, Progesterone, and Prolactin levels. Women in the Untreated Thrombophilia group had a lower duration of infertility when compared to controls, while women from the Treated Thrombophilia group had higher serum estradiol levels when compared to women from the Control group. Frequencies of coagulation defects in both Thrombophilia groups are presented in table 2. Both groups were similar in most defects of coagulation measured in this study, with the exception of anti-phosphatidylserine antibodies, which were significantly higher in the Treated Thrombophilia group.

Treatment data are presented in table 3. No differences were observed in daily FSH dose and numbers of follicles, MII oocytes, fertilized oocytes, day three embryos, and transferred embryos. Implantation rate was significantly higher in the Treated Thrombophilia group, when compared to the Untreated Thrombophilia group.

Effect of enoxaparin treatment on pregnancy and live birth rates

Effects of daily enoxaparin on pregnancy and birth rates are presented in Figure 1. No differences were observed in biochemical pregnancy or in gestation at five to six weeks (positive fetal heartbeat). Patients in the Untreated Thrombophilia group presented significantly lower ongoing pregnancy rates (at 12 weeks) and live birth rates when compared both to Controls and to patients in the Treated Thrombophilia group. The

calculated odds-ratio for achieving a live birth when treating women with thrombophilia using Enoxaparin was 5.586 (95 % confidence interval of 2.0 – 15.3).

Effect of enoxaparin on early pregnancy loss and abortion rates

Effects of daily enoxaparin on early pregnancy loss and abortion rates are presented in Figure 2. Patients in the Untreated Thrombophilia group presented significantly higher early pregnancy loss and abortion rates when compared to the Control or the Treated Thrombophilia groups. The calculated odds-ratio for occurrence of abortion when treating women with thrombophilia using Enoxaparin was 0.129 (95 % confidence interval of 0.03 – 0.5).

Discussion and Conclusion

Pregnancy loss, which is the outcome of all pregnancies that do not lead to at least one live birth (11), is associated with important psychological trauma to the women and their partners (12). Approximately one-third of pregnancies lead to pregnancy loss, usually in the first or early second trimester (13). In assisted reproduction, global pregnancy rates are at the 40 % threshold even when euploid embryos are selectively transferred, with a per-pregnancy delivery rate capped at 80 % (2).

Thrombotic alterations have long been associated to pregnancy loss, mainly due to microthrombosis at the site of implantation and altered trophoblast function (6–8). In women undergoing assisted reproduction, controlled ovarian hyperstimulation potentiates altered hemostasis (9). This has led to the proposition that treating women with diagnosed thrombophilia during *in vitro* fertilization could potentially decrease pregnancy loss due to these complications. While this has been studied in the past, there is no consensus as to whether or not there is benefit in prophylactic treatment of these women (9,10). In our study, we collected retrospective data from eighty-four women with thrombophilia, of which thirty had remained untreated, while fifty-four had received prophylactic enoxaparin in order to avoid potential pregnancy loss. We included twenty women without thrombophilia as a control group.

In our data, the group of women with untreated thrombophilia had a significantly lower duration of infertility. It should be noted, however, that all groups presented at least three years of infertility on average, so that this lower duration of infertility does not stem from a coexisting condition that would lead to immediate referral for infertility treatment.

Minimum duration of infertility in the Untreated Thrombosis group was eighteen months, which further corroborates this finding. Another clinical finding in this study was that women from the Treated Thrombophilia group presented higher serum estradiol levels. While there is still much debate over means of determining the risk of ovarian hyperstimulation syndrome (OHSS) in assisted reproduction cycles, increased estradiol levels are considered important markers that should cause for caution (14). Moreover, it has been demonstrated that thrombophilia is higher in prevalence in women who suffer severe OHSS (14), which is an important cause for concern. However, it should be noted that, in our study, mean serum estradiol levels measured on day three were well within the normal range for all groups (15).

When both thrombophilia groups were compared for coagulation defects, the main altered function was methylenetetrahydrofolate reductase, altered in over 85 % of the patients in this study. Because it was shown that the MTHFR 677T allele mutation was associated not only to recurrent pregnancy loss but also to increased embryo aneuploidy, this is an important point when considering patient counselling and the potential use of preimplantation screening in assisted reproduction cycles (16). Although it is controversial its role as a thrombophilia biomarker, a metanalisis that included 99 studies showed mutation of C677T homozygosis can contribute in elevating homocystein and higher risk of developing venous thrombosis and pulmonary embolism in caucasian women (Zeng et al, 2019). The second most altered coagulation marker in our study was the presence of anti-phosphatidylserine antibodies (αPS), significantly more altered in the Treated Thrombophilia than in the Untreated Thrombophilia group. While still considered a “non-criteria” factor in antiphospholipid syndrome, Žigon et al. demonstrated that alterations to

αPS and Prothrombin antibodies are the main alteration associated to recurrent miscarriages, closely followed by anticardiolipin antibodies (17). While in our study both groups fulfilled requirements for enoxaparin treatment, one cannot rule out a possible bias in having treated mostly patients with increased alterations in αPS. Importantly, however, this treated group presented abortion rates comparable to women without any alteration in coagulation.

Regarding cycle characteristics in our study, women in the Treated Thrombophilia group presented significantly higher implantation rates when compared to the Untreated Thrombophilia group. In 2008, Qublan et al. had observed a similar effect in a randomized controlled trial that included 42 patients in the treatment arm, 41 in the placebo control group (18). Other treatment traits did not differ between groups in our study.

Our results further demonstrated an important decrease in ongoing pregnancy (by ultrasound, detected at twelve weeks) and live birth rates, with a respective increase in early pregnancy loss and abortion rates, in patients with thrombophilia that were not treated. Moreover, patients treated with Enoxaparin presented more than five times the chance of achieving a live birth, and an almost eight-fold decrease in the odds of an abortion in that cycle. A 2014 Cochrane review was not able to find any studies that met bias standards and that demonstrated any effect regarding the use of LMWH on outcomes (19). Authors of that review concluded they did not support the use of anticoagulants in women with unexplained recurrent miscarriage, but that for women with inherited thrombophilia, further studies were still warranted (19). Similarly, a 2013 systematic review and meta-analysis was only able to include one randomized controlled study that had included women with at least one coagulation defect (20). While their focus

was on studying the effect of LMWH on recurrent implantation failure itself (independent on diagnosed thrombophilia in the women included in the study), removal of the study that did contain a coagulation defect also removed any positive effect of LMWH on pregnancy rates (20).

In general, current literature regarding prophylactic anticoagulant therapies in assisted reproduction are heterogeneous in nature. Most available literature employs aspirin or LMWH with aspirin, with quite diverse results and study designs. A previous study that randomized the use of LMWH in patients with thrombophilia undergoing *in vitro* fertilization observed that treatment was associated to increased pregnancy rates, increased live birth rates, and increased implantation rates, and to a decrease in the occurrence of miscarriages (18).

It is especially noteworthy that women with recurrent pregnancy loss present impaired expression of heparanase (HPSE) and heparin-binding epidermal growth factor-like growth factor (HB-EGF) (21,22), and that LMWH has been shown to increased HB-EGF expression and secretion (23). Moreover, treatment with LMWH by itself is able to improve extravillous trophoblast invasiveness (23). It has also been demonstrated that LMWH improves trophoblast proliferation, and that adding HB-EGF improves trophoblast differentiation (24). This observed improvement in trophoblast differentiation and survival, caused by LMWH treatment, has further been demonstrated to be dependent on HB-EGF (25), which demonstrates that LMWH is not merely an anticoagulant, but also presents a causative effect on trophoblast proliferation and survival. While beyond the scope of this current manuscript, it is quite interesting to observe that, during assisted reproduction,

276 treatment with LMWH could lead to a mechanistic improvement in implantation which
277 agrees with our findings.

278 Given the lack of specific studies that focus on the use of LMWH in patients with
279 thrombophilia undergoing assisted reproduction, we collected data on patients from our
280 clinical setting. Our results allow us to conclude that, in women with thrombophilia
281 submitted to *in vitro* fertilization, the use of LMWH was associated to increased
282 implantation rates, increased ongoing pregnancy rates, and increased live birth rates, and
283 to decreased early pregnancy loss and abortion rates. Moreover, treatment with daily
284 enoxaparin was able to return these rates to values comparable with women without
285 thrombophilia.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

Consubstanced Opinion of ERC - Faculdade de Medicina do ABC

Title of research: “Prophylactic low molecular weight heparin in women with thrombophilia submitted to in vitro fertilization”

Researcher: JOSÉ ROBERTO LAMBERT

Thematic Area: Human Reproduction

Institutional Review Board of Faculdade de Medicina ABC approved the study protocol under the number: CAAE:41006620.0.0000.0082

Proposing institution: Fundação do ABC – FMABC

Opinion data: 4.564.243

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Table Legends

Table 1. Clinical characteristics of women without thrombophilia (Control group), women with untreated thrombophilia (Untreated Thrombophilia group), and women with thrombophilia treated with Enoxaparin (Treated Thrombophilia group). Groups were compared with One-Way Analysis of Variance, with a post-hoc Least Significant Differences test, or by a Kruskal-Wallis test, followed by a Games-Howell post-hoc test. Differences were considered significant at the 5 % threshold.

Table 2. Coagulation defects in women with untreated thrombophilia (Untreated Thrombophilia group), and women with thrombophilia treated with Enoxaparin (Treated Thrombophilia group). Groups were compared with a Chi-square test. Differences were considered significant at the 5 % threshold.

Table 3. Treatment characteristics of women without thrombophilia (Control group), women with untreated thrombophilia (Untreated Thrombophilia group), and women with thrombophilia treated with Enoxaparin (Treated Thrombophilia group). Groups were compared with One-Way Analysis of Variance, with a post-hoc Least Significant Differences test, or by a Kruskal-Wallis test, followed by a Games-Howell post-hoc test. Differences were considered significant at the 5 % threshold.

Figure Legends

Figure 1. Pregnancy and live birth rates in women without thrombophilia (Control group), women with untreated thrombophilia (Untreated Thrombophilia group), and women with thrombophilia treated with Enoxaparin (Treated Thrombophilia group). Groups were compared using a Chi-Square test. Differences were considered significant at the 5 % threshold.

Figure 2. Early pregnancy loss and abortion rates in women without thrombophilia (Control group), women with untreated thrombophilia (Untreated Thrombophilia group), and women with thrombophilia treated with Enoxaparin (Treated Thrombophilia group). Groups were compared using a Chi-Square test. Differences were considered significant at the 5 % threshold.