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Case Report

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Recurrent Early Pregnancy Losses Methylenetetrahydrofolate Reductase Poymorphisms Treatment

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Summary

Four women report not having been able to get pregnant for years, the youngest since 20 and the oldest since 37. Antecedents, from fertility centers where they were treated, report that treated with folic acid they had recurrent early pregnancy losses. without achieving an etiological diagnosis. One received two implants with egg donation, one with heparin, and both failed. In another, assisted fertilization with heparin and hydroxychloroquine was unsuccessful and in 3 of its 7 losses, trisomy 21 was proven. When we had the opportunity to attend to these patients, we asked for the determination of biotypes of Methylenetetrahydrofolate Reductase, in three C677T in one T677T and in three A1298C and one A1298A. In all of them, instead of folic acid, L-5-Methyltetrahydrofolate was indicated along with vitamins C, D, E, B and salts of Ca, Fe, Mg, K and heparin. Six pregnancies were achieved as 2 patients had 2.

Result: Six healthy newborns, the oldest is currently 14 years old, the youngest 15 months.

Keywords: Loss, Pregnancies, Treatment, Prevention

Introduction

In Recurrent Early Pregnancy Loss (REPL) affecting 1% of women of childbearing age, after treatment according to etiology in a fertilization center, including heparin in thrombophilias and Folic Acid (FA) supplementation in 50%, the etiology is not firmly known to establish effective treatment as a result [1]. Mutational polymorphisms have been identified in enzymes, such as Methylenetetrahydrofolate Reductase (MTHFR) with natural biotypes C677C and A1298A, and variants mainly CT and AC respectively, with a decrease between 30 and 60% of activity, which occur in about 40% of the population. This enzyme is essential for transmethylation processes in folate metabolism, of vital importance in embryonic development, placental growth and DNA stability. Consequently, since the first decade of the current century, associations of the referred variants with various pathologies that we refer to in a previous work [2] have been postulated, including gestational pathologies, such as those presented in this case.

Clinical Cases

Four patients with a history, a total of 19 failure of pregnancy, who we then attended achieved 6 pregnancies on the first attempt that developed normally until the birth of six healthy children. Particularities that provide useful data for situations that are still a source of uncertainty, both for diagnosis and for prevention and treatment, cause the presentation of this casuistry [Table 1].

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Table 1: Recurrent Early Pregnancy Losses. Methylenetetrahydrofolate Reductase.

Background			Genotypes				Treatment				Result
Age	REPL	Week	Ovod	Transfer	MTHFR	Age	L-5-MTHF	HBPM	Ovod	Transfer	
37	3	8,8,12			C677T A1298C	42	Yes	Yes			HN
						45	Yes	No			HN
20	3	6,8,8	Yes		T677T A1298A	49	Yes	Yes	Yes		HN
32	7	9,6,8,8,12,7,5		Yes	C677T A1298AC	42	Yes	Yes		Yes	HN
						48	Yes	Yes	Yes		HN
34	3	9,10,7			C677T A1298C	38	Yes	Yes			HN

Note*: REPL: Recurrent early pregnancy loss. Ovod: Egg donation. Transfer: Transference. MTHFR: Methylenetetrahy drofolate reductase. L-5-MTHF: L-5-Methyltetrahydrofolate. LMWH: Low molecular weight heparin. HN: Healthy Newborn.

1) While abroad, after 3 REPL, seeking a pregnancy, she was medicated with very high dose of Folic Acid (FA), then another professional stopped FA and started medication with L-5-MTHF and LMWH with which pregnancy was achieved, which we followed up in Argentina until a successful term. In her second pregnancy, which we attended from the beginning with L-5-MTHF and LMWH, by her own decision the patient did not administer LMWH, which did not hinder its normal development until a successful term.

2) After the 3 REPL, he was given 2 Ovod with FA, the second with the addition of LMWH and both failed. When we had the opportunity to attend to the patient, we indicated Ovod with L-5-MTHF and LMWH, achieving normal pregnancy development.

3) After 7 REPL hypophribrinolysis was detected due to Plasminogen Activator Inhibitor (PAI) polymorphism with homozygous variant biotype 4G/4G and received 1Transfer with LMWH and hydroxychloroquine that did not prevent pregnancy loss. When we had the opportunity to care for the patient, in a new Transfer we indicated LMWH with L-5-MTHF instead of FA, achieving normal pregnancy development. A second successful pregnancy was also achieved, this time, due to age, with Ovod.

4) With a history of 4 REPL, we treated her with L-5-MTHF and LMWH. She had normal development of pregnancy giving birth to the currently 15 months-old children.

Discussion

In Background: 16 REPL, plus 2 Ovod and 1 Transfer are 19 failures, all with FA.

Treatments of REPL with FA and LMWH are generally successful when thrombophilias, either congenital or acquired, are present. Congenital, hereditary thrombophilias can be due to coagulation disorders such as resistance to activated protein C, mutation of factor V Leiden, G20210A mutation of prothrombin, or protein S deficiency; or by the polymorphism of the Plasminogen Activator Inhibitor (PAI) gene with variant, heterozygous 4G/5G or homozygous 4G/4G genotypes, determinants of deficient fibrinolytic activity, instead of the natural 5G/5G genotype, Acquired thrombophilias can be due to immunological alterations that determine antiphospholipid antibodies, some even anticardiolipins. Variants in the MTHFR polymorphism, the most common C677T and A1298T, with less activity, very rarely produce pathogenic effects, as they only act as concurrent factors with other factors such as tobacco [3], alcohol [4] or other polymorphisms that have been less studied so far. Associations with various pathological conditions have been postulated, including REPL. When there is no favorable response with FA treatment and in cases of thrombophilia with LMWH, it is necessary instead of increasing the doses of FA, to change it to L-5-MTHF, a compound that is not marketed in Argentina (such as Metafolin, Levomefolic Acid, or Quatrefolic tablets of 1 and 5 mg).

Natural folate, present in fruits and vegetables, is mostly with reduced molecules while FA, a product of synthesis, is completely oxidized. The FA for its reduction in the liver by the enzyme Dihydrofolate Reductase (DHFR) of limited functionality, passes first to dihydrofolate, then to tetrahydrofolate and only then, by the action of MTHFR, which acts directly on natural folate, are metabolically active compounds generated. This initiates the transmethylation processes of vital importance in embryonic development and DNA stability. Given the limited activity of DHFR, doses of 1 mg/day or at most 5 mg/day of FA should not be exceeded to avoid high levels of this unmetabolized product, which can cause adverse effects [5,6]. It should be noted that, following what was implemented in 1998 in the United States, in Argentina as in more than 80 countries, FA is added to wheat flour to provide an estimated intake per person of between 100 and 200 µg per day, as indicated on the product label, excluding those destined for export. Likewise, preventive measures should be taken during medication with methotrexate, which is known to have an anti-folic action

due to its inhibitory action on DHFR, ensuring the contribution of natural folate, or better yet, providing L-5-MTHF.

Variants of MTHFR, especially C677T rather than A1298C, are referred to as a risk factor for REPL [7,8]. They are also recognized as concurrent factors in associations with a higher risk for chromosomal alterations, such as Down syndrome, as observed in 3 of the 7 REPL of patient 3. In 29 countries, the frequency with which these genotypes occur have been studied6. In Argentina, they are determined by PCR techniques [9], but they were not tested in the population to determine their frequency, nor in pathologies where they may have a participation. There are also associations of T677T with risk for trisomies such as 13, 18 and not only with the most common, trisomy 21 or Dow [10-12] syndrome. Four patients who had suffered a total of 19 pregnancy failures and the subsequent achievement of 6 healthy newborns, medicated with L-5-MTHF to replace AF, is a notable difference that supports the study in REPL, of MTHFR polymorphisms to ensure a normal development of pregnancy. It is illustrative in Antecedents, patient number 2, that after 1 Ovod. who failed received LMWH in his second Ovod. which also failed. It is also illustrative that patient 1 in her second pregnancy, by her own decision did not carry out the administration of LMWH, which did not hinder its normal development until a successful term. This would make one think in the first instance that heparin could be dispensed with, however, this is not the case.

Patient number 3 after her sixth REPL, with the diagnosis in the fertilization center where she was treated, of hereditary thrombophilia due to hypofibrinolysis with homozygous variant genotype 4G/4G of the PAI, received Transfer with LMWH and hydroxychloroquine that failed, and when treated with L-5-MTHF and LMWH in a new Transfer. the development of the pregnancy to normal term was achieved. This is also how she normally went through her second pregnancy, due to her age, after Ovod. with L-5-MTHF and LMWH. If she had not received heparin, she would probably have also lost these pregnancies due to the presence of the 4G/4G variant genotype of the PAI. MTHFR polymorphisms, so far known, do not have, or perhaps only very weak thrombophilic action, their eventual association with REPL is due to the decreased activity of their variants, for transmethylation processes of vital importance in the development of gestation and DNA stability, but they can coexist with PAI polymorphisms, causing hereditary thrombophilia; different from patient 4, in whom they had also requested in Background, genotypic determination of the PAI, which showed homozygous natural genotype 5G/G5 and normal fibrinolytic activity, which possibly made the indication of heparin unnecessary. It should be noted that of the various fertilization centers that treated the patients, only 2 of them requested genotypic determination of the PAI, which should be included in all fertilization centers against REpl for diagnoses of hereditary hemophilia.

Conclusion

In patients with a history of REPL, treated according to etiology, including heparin for cases of thrombophilias or when this is not completely ruled out, and continue with REPL, or failure of Ovod or Transfer, if MTHFR polymorphisms are found with variants such as C677T and A1298C, or others than natural ones: C677C and A1298A make it necessary to replace the FA with L-5-MTHF [5,6,13], in the preventive treatment of new pregnancies. Eventually, patients who do not respond to this medication would make it necessary to investigate biotypes of MTHFR in the male partner. If this does not show the presence of natural biotypes, they should also be treated with L-5-MTHF 3 months before attempting a pregnancy. Testicular deficiency for methylation is not corrected by FA, but rather aggravates it [14].

Conflict of Interest

None to declare.

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None.

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