Inherited thrombophilic states and coexisting chromosomal polymorphisms as a cause of recurrent pregnancy loss. Case series report.

Gisela Valer Chavez, MD[1]. Ither Sandoval, MD[2] ;
1. Naprotecnologia y Fertilidad Natural Perú
2. President of the Peruvian Society of Obstetrics and Gynecology.

Background

Although still controversial, some genetic polymorphisms of prothrombin (FII G 20210A), Factor V (Factor V Leiden, FVL) and methylene tetrahydrofolate reductase (MTHFR, C677T gene variant) genes were strongly associated with recurrent miscarriages, although 50% of RPL remains idiopathic.

Genetic polymorphism may impair the MTHFR activity and the related metabolization of food folates and folic acid in 5-MTHF. A carrier of one of the two main MTHFR isoforms (C677T or A1298C) should be supplemented with 5-MTHF rather than folic acid to bypass the bottleneck created by the deficiency of MTHFR. Recent studies also indicate that chromosomal polymorphisms may cause certain clinical effects, such as infertility and spontaneous miscarriage.

We present two patients with RPL, successfully treated through restorative reproductive medicine obtaining a healthy live birth and an ongoing 19week pregnancy, both diagnosed inherited thrombophilic disorders and coexisting chromosomal polymorphisms as a cause of recurrent pregnancy loss in Peru.

REFERENCES

1)The ESHRE Guideline Group on RPL and others, ESHRE guideline: recurrent pregnancy loss, *Human Reproduction Open*, Volume 2018, Issue 2, 2018, hoy004

(2) Mierla, D. and Stoian, V.. "Chromosomal Polymorphisms Involved in Reproductive Failure in the Romanian Population" Balkan Journal of Medical Genetics, vol.15, no.2, 2013, pp.23-28.

(3) Torabi R, Zarei S, Zeraati H, Zarnani AH, Akhondi MM, Hadavi R, Shiraz ES, Jeddi-Tehrani M. Combination of thrombophilic gene polymorphisms as a cause of increased the risk of recurrent pregnancy loss. J Reprod Infertil. 2012 Apr;13(2):89-94. PMID: 23926530; PMCID: PMC3719334.

(4) Ocak Z, Özlü T, Ozyurt O. Association of recurrent pregnancy loss with chromosomal abnormalities and hereditary thrombophilias. Afr Health Sci. 2013 Jun;13(2):447-52. doi: 10.4314/ahs.v13i2.35. PMID: 24235948; PMCID: PMC3824507.

(5) Karata S, Aydin Y, Ocer F, Buyru A, Balci H. Hereditary thrombophilia, anti-beta2 glycoprotein 1 IgM, and anti-annexin V antibodies in recurrent pregnancy loss. Am J Reprod Immunol. 2012 Mar;67(3):251-5. doi: 10.1111/j.1600-0897.2011.01092.x. Epub 2011 Nov 22. PMID: 22103678.

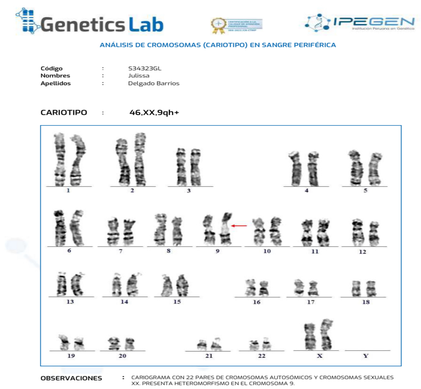
CASES PRESENTATION

Case 1: 38 y/o female. RPL at 26 and 34 y/o.
Case 2: 41 y/o female. RPL at 38 and 39 y/o.

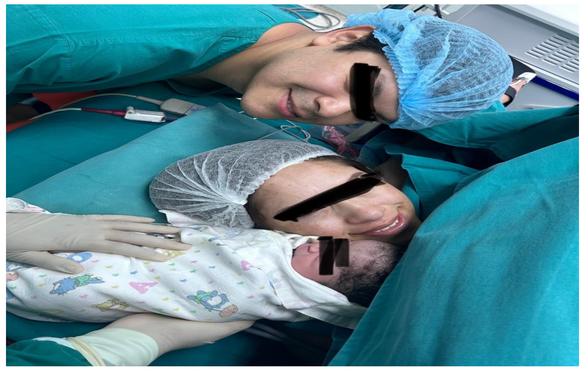
Medical history case 1: Unremarkable
Medical history case 2: Sister: Autoimmune glomerulonephritis
PE case 1: Unremarkable. BMI 22.
PE case 2: Unremarkable. BMI 20.

Laboratory case 1:
1/28/23: FSH: 14.32 Insulin: 6.28 E2: 51 P4: 22.7 Glucose: 100mg/dl
2/9/23: **Anti-thrombin III: 68% (80-130**) AMH:0,05
PTT: 25.5 (26-60)
Karyotype (10/10/22): 46 XX, 16qh+
C677T heterozygous mutation on MTHFR gen.
Currently 19 w healthy pregnancy.

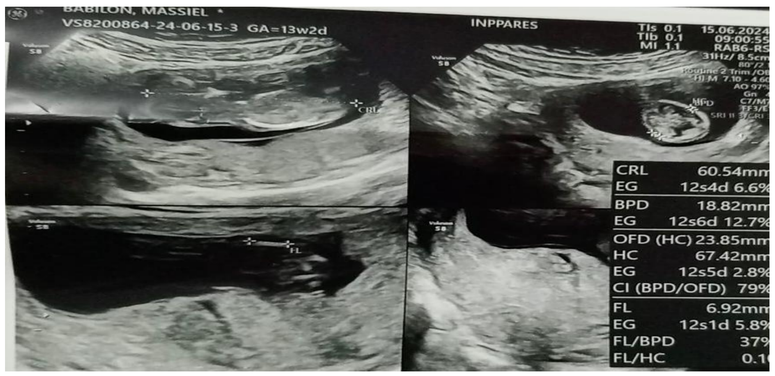
Laboratory case 2:
5/29/23: Glucose: 96mg/dl, AMH 0.39, P4: 19.6ng/mL, Vitamin D: 24,8.
Karyotype: 46, XX, 9qh+ (Figure 1). 46 XY, 21pstk+.
C677T homozygous mutation on MTHFR gen.
Homocysteine: 8.42 (0-15)
6/2/23: BHCG (+) 6512 mg/dl .
Male 38.5w newborn was born on 01/19/2024. 3200g
Treatment:
Case 1: Methylfolate 5 mg / ASA 81 mg/day/ Progesterone 400mg/d until HCG positive. Then switched to enoxaparin 40 mg SC/24h.
Case 2: Methylfolate 5 mg / Vit B12 250 mcg/ ASA 81 mg/day until 60 days after delivery.
Progesterone 400mg/d until 14 weeks.



Case 2:Karyotype and healthy newborn 38.5w, 3200g.



Case 1: US 13W2d



DISCUSSION

The restorative reproductive medicine approach is “patient centered”, tailoring the investigations that should be carried out in each woman or couple with RPL, based on her age, fertility/sub-fertility, pregnancy. history, family history, previous investigations and/or treatments.
Pro-thrombophilic factors have also been suggested as one of the major causes of RM. In fact, some genetic polymorphisms of prothrombin (FII G 20210A), Factor V (Factor V Leiden, FVL) and methylene tetrahydrofolate reductase (MTHFR, C677T gene variant) genes were strongly associated with recurrent miscarriages.
These factors of inherited thrombophilia disturb normal placental vascularization and formation leading to fetal growth restrictions, pregnancy failure, placental abruption and therefore miscarriages or stillbirth. In these patients, we have found two common polymorphisms of MTHFR, the MTHFR 677C/T and MTHFR 1298A/C, result in the most common forms of hyperhomocystinemia and increased thrombotic tendency. Most of studies show the association of these two polymorphisms with RPL.
These two patients were supplemented with 5-MTHF rather than folic acid to bypass the bottleneck created by the deficiency of MTHFR. Then, we prescribed a low molecular weight heparin to our case 1 patient who has an associated antithrombin III deficiency.
Recent guidelines for recurrent pregnancy loss (RPL) indicate that parental karyotyping is not routinely recommended in couples with RPL. However, it could be performed after individual assessment of risk as in these cases.

CONCLUSIONS

Parental karyotyping and screening for hereditary thrombophilia should be conducted in RPL patients, in order to define a more precise prognosis and treatment from a “patient centered” perspective to RPL women/couples being treated in a restorative reproductive approach. More research needs to be conducted in women/couples with RPL presenting chromosomal polymorphisms and hereditary thrombophilia.