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Title:

THE PRESENCE OF MTHFR GENE POLYMORPHISMS IT'S NOT ASSOCIATED WITH IMPAIRED CLINICAL IVF OUTCOMES AFTER A EUPLOID EMBRYO TRANSFER.

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Objective:

The Enzyme methylenetetrahydrofolate reductase (MTHFR) plays an important role in the metabolism of folic acid and is crucial for reproductive function. Despite the fact that many studies have explored the relationship between carriers of a single copy of the MTHFR gene polymorphism and aspects of human reproduction, the biochemical influence and clinical relevance of these polymorphisms are still debated. Some publications have suggested an influence of some MTHFR variants on implantation potential and (IVF) cycle remains clinically uncertain (Ivanov et al. 2011, Laanpere et al. 2011; Soldo et al. 2012). This study aims to evaluate the effect on embryo transfer outcome in patients with a MTHFR polymorphism.

Design:

Retrospective cohort analysis from an academic, private IVF center.

Materials and Methods:

Patients who underwent IVF with preimplantation genetic testing (PGT) and subsequent euploid embryo transfer (ET) of a vitrified-warmed blastocyst from Jan 2010 to January 2018. Trophectoderm biopsies (Day 5-6) were analyzed by Next-Generation Sequencing or quantitative Polymerase Chain Reaction (qPCR). Natural language processing was performed on the center's electronic medical records. to identify a cohort of women with who had undergone MTHFR testing. Cases involving the transfer of fresh and/or multiple embryos were excluded. Patients diagnosed with uterine factor infertility, ovum donation, and severe male factor infertility were excluded. All patients testing positive for any MTHFR variant were instructed to take folic acid, vitamin B6, and vitamin B12 supplements. Data were evaluated using a GEE model that accounted for patients who underwent multiple cycles and controlled for oocyte age, body mass index, anti-Müllerian hormone, basal antral follicle count, and endometrial thickness at embryo transfer (ET). A sample size of 67 patients per group was needed to detect a 20% difference in implantation rates with 80% power (A=0.05).

Results:

Of the 496 euploid, single, vitrified-thawed blastocyst transfers, patients found to be MTHFR polymorphism positive (n=393) and negative (n=103) created the study cohorts. Demographic characteristics of the populations were comparable. Significant differences were found in BMI, FSH, number of previous ET, and prior euploid ET cycles. Patients had a similar implantation rate (67.9% vs. 63.6% (p=0.39)), clinical pregnancy rate (80% vs 69.6% (p=0.06)) and pregnancy loss rate (33.9% vs 39.6% (p=0.44)) respectively. The diagnoses of recurrent

pregnancy loss were comparable in both cohorts (38.0% vs 34.0%, P=0.36) (Table 1). A positive gene variant was not found to significantly modify the odds of implantation (adjusted OR= 0.96 [CI 95% -0.5–1.7]), clinical pregnancy (OR=1.39 (CI95% 0.7-2.4)), clinical pregnancy loss (OR= 1.08 (CI95% 0.53 - 2.17), ongoing pregnancy (OR= 1.17 (CI95%0.62 - 2.2), and multiple pregnancy (OR= 1.99 (CI95% 0.10-39.05) (Table 2). Additionally, no differences in IVF outcomes were demonstrated after comparing common polymorphisms C677, A1298C and compound mutations (Table 3).

Conclusions

Patients who test positive for a MTHFR polymorphism have comparable ET outcomes to the general infertile population pursuing a euploid FET. Patients can be reassured that a MTHFR gene variant does not adversely associate with embryo quality or implantation potential. As we uncover the clinical influence of more gene variants with more advanced technologies, prevalence and randomized prospective studies will help us understand and achieve greater insight about the relation of this and other different genetic variants, and will help us to create effective and sophisticated personalized and genomic medicine approaches.

Support

None.

Table 1:

Demographic characteristics of populations and clinical outcomes based on the presence of a MTHFR polymorphism.

Demographic characteristics of populations. MTHFR polymoprhism present vs absent.						
Variable	***MTHFR NEG***		***MTHFR POS***		Difference	
	n=103		n=393		P value	Sign
	Mean	SD	Mean	SD		
Oocyte Age	**35.92**	4.03	**35.69**	3.80	0.59	NS
BMI	**22.34**	3.72	**23.53**	4.79	0.007	*
Day 3 FSH	**5.36**	3.00	**6.50**	6.61	0.02	*
AMH	**3.35**	2.61	**4.11**	5.12	0.08	NS
BAFC	**10.20**	6.44	**10.73**	7.21	0.52	NS
Endometrial Type at Transfer	**3.00**	3.00	**3.00**	3.00	0.25	NS
Endo Thickness At Transfer	**9.20**	2.38	**9.05**	1.89	0.54	NS
Gravida	**1.84**	1.74	**1.74**	1.60	0.6	NS
Para	**0.52**	0.61	**0.38**	0.64	0.06	NS
Previous Transfers	**1.02**	1.06	**1.37**	1.49	0.007	*
Previous Euploid Transfers	**0.75**	0.86	**1.02**	1.17	0.009	*
Previous Ovulation induction Cycles	**2.75**	3.40	**3.03**	3.02	0.41	NS
Prior Losses	**0.42**	0.75	**0.46**	0.67	0.56	NS

Clinical outcomes comparison. MTHFR present vs absent.							
Variable	***MTHFR NEG***		***MTHFR POS***		Difference	Sign	
Rates	n=103		n=393		P value	OR + CI95%	Sign

Implantation rate	67.9%	70/103	63.6%	250/393	0.39	0.81 (0.51-1.29)	NS
Clinical pregnancy rate	80.0%	56/70	69.6%	174/250	0.06	0.66 (0.42-1.02)	NS
Clinical loss rate	33.9%	19/56	39.6%	69/170	0.44	1.27 (0.68 - 2.4)	NS
Ongoing pregnancy rate	52.8%	37/70	42.0%	105/250	0.1	0.64 (0.37-1.09)	NS
Multiple pregnancy rate	0.0%	0/70	0.1%	3/250	0.35	1.99 (0.10-39.05)	NS
RPL diagnosis	38.0%	40/103	34.0%	134/393	0.36	0.81 (0.51-1.27)	NS

Table 2:

GEE Model. Clinical outcomes comparison. MTHFR present vs absent. Controlling for age, amh, bmi, endometrial type and thickness.

GEE Model. Clinical outcomes comparison. MTHFR present vs absent. Controlling for age, amh, bmi, endo type and thickness.							
Variable	***MTHFR NEGATIVE***		***MTHFR POSITIVE***		Difference		
Rates	n=103		n=393		P value	L'Beta + CI95%	
Implantation rate	67.9%	70/103	63.6%	250/393	0.9	0.96 (0.52-1.77)	NS
Clinical pregnancy	80.0%	56/70	69.6%	174/250	0.24	1.39 (0.7-2.4)	NS
Clinical loss	33.9%	19/56	39.6%	69/170	0.82	1.08 (0.53 - 2.17)	NS
Ongoing pregnancy	52.8%	37/70	42.0%	105/250	0.62	1.17 (0.62 - 2.2)	NS
Multiple pregnancy	0.0%	0/70	0.1%	3/250	0.35	OR 1.99 (0.10-39.05)	NS

Table 3:

Clinical outcomes per Type of MTHFR polymorphism. Heterozygous, Homozygous, Compound. Multivariate analysis controlling for age, bmi, amh, endometrial thickness and type at transfer.

Clinical outcomes per Type of MTHFR polymorphism. Heterozygous, Homozygous, Compound. Multivariate analysis controlling for age, bmi, amh, endometrial thickness and type at transfer.												
Rates	**Negative Mut**		**C677T Heterozygous**		**C677T Homozygous**		**A1298C Heterozygous**		**A1298C Homozygous**		**Compound Mut**	
	n=103		n=113 (28.7%)		n=78 (19.8%)		n=95 (24.1%)		n=30 (7.6%)		n=77 (19.5%)	
Implantation rate	67.9 %	70/103	64.6 %	73/113	61.5 %	48/78	66.3%	63/95	70.0 %	21/30	58.40 %	45/77
OR 95% CI	Reference		0.9 (0.4 - 1.8)		1.3 (0.6 - 2.9)		0.9 (0.4 - 1.9)		0.15 (0.01 - 1.2)		1.4 (0.6 -3.1)	
Clinical pregnancy	80.0 %	56/70	72.6 %	53/73	64.5 %	31/48	80.9%	51/63	76.1 %	16/21	66.60 %	30/45
OR + 95% CI	Reference		1.2 (0.6 - 2.4)		1.73 (0.79 - 3.7)		1.4 (0.7 - 2.9)		0.3 (0.09 - 1.4)		2.08 (0.97 - 4.4)	
Clinical loss	33.9 %	19/56	35.8 %	19/53	35.4 %	11/31	39.2%	20/51	43.7 %	7/16	40%	12/30
OR + 95% CI	Reference		1.4 (0.5 - 2.8)		1.5 (0.4 - 5.1)		0.5 (0.1 - 1.6)		1.1 (0.2 - 5.1)		0.9 (0.2 - 3.0)	
Ongoing pregnancy	52.8 %	37/70	46.5 %	34/73	41.6 %	20/48	49.2%	31/63	30.0 %	09/30	40.00 %	18/45
OR + 95% CI	Reference		0.9 (0.3 - 2.1)		0.9 (0.3 - 2.7)		2.0 (0.7 - 5.2)		0.8 (0.2 - 3.2)		1.4 (0.5 - 4.1)	
Multiple pregnancy	0.0%	0/70	0.0%	0/73	0.0%	0/48	0.1%	1/63	0.4%	1/21	0.12%	1/77

OR + 95% CI	Reference	N/A	N/A	N/A	N/A	N/A