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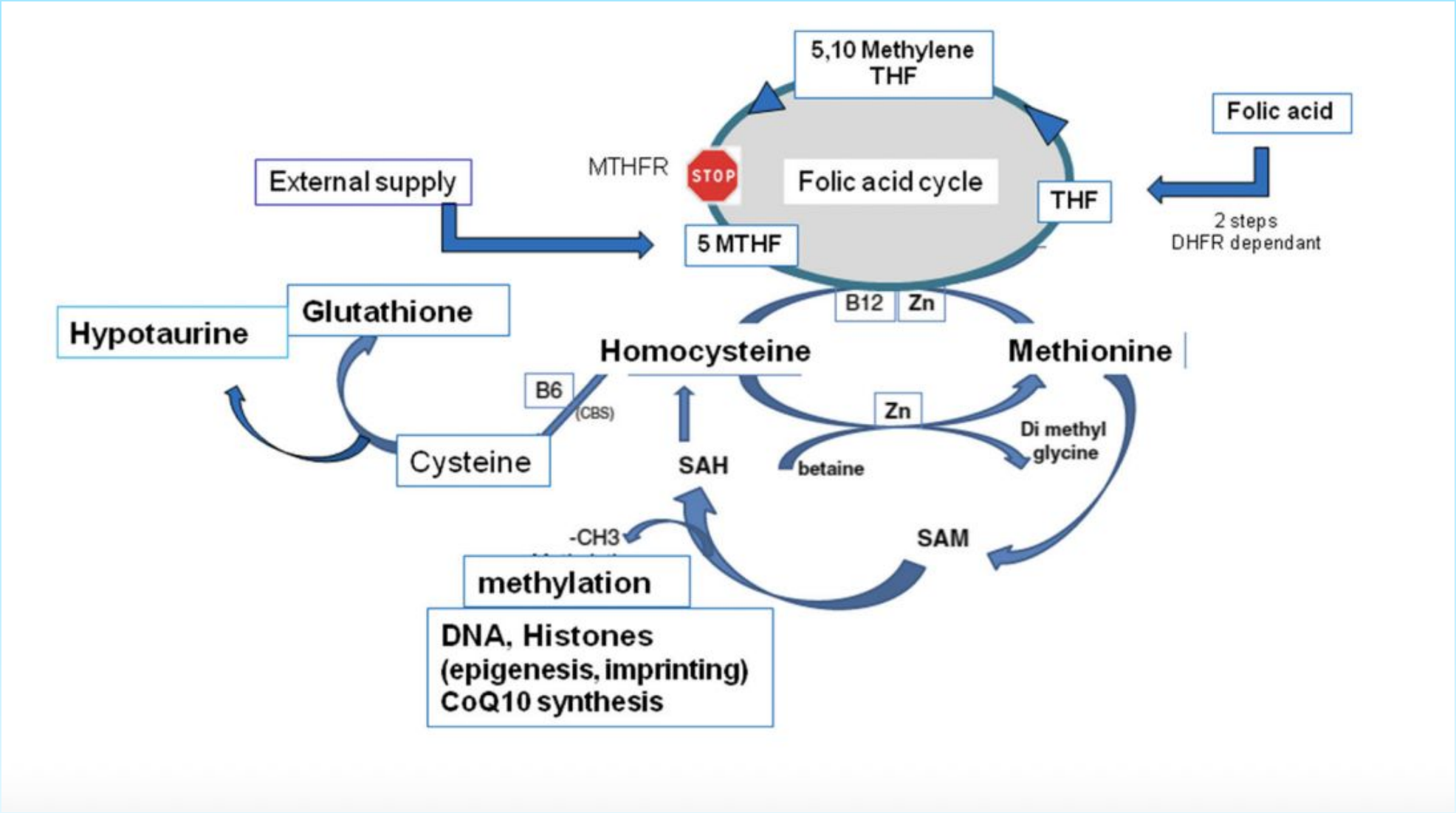
The effectiveness of L-methyltetrahydrofolate (5-MTHF) versus folic acid supplementation in reducing the risk of miscarriage and total adverse pregnancy outcomes in women of reproductive age (18-45) carrying methylenetetrahydrofolate reductase (MTHFR) polymorphisms experiencing ongoing fertility issues.

A Systematic Review with Meta-analysis

BACKGROUND

- Recurrent pregnancy loss (RPL) is the occurrence of three or more consecutive pregnancy losses before the 20th week of gestation in the UK or two or more in the USA and Europe[1,2,3].
- Hyperhomocysteinemia is a known risk factor for RPL[4].
- Polymorphisms affecting the MTHFR gene are common in those with hyperhomocysteinemia, due its role within the folate cycle[5].


5,10 Methylene THF
Folic acid
MTHFR
STOP
Folic acid cycle
External supply
THF
5 MTHF
2 steps
DHFR dependant
B12
Zn
Hypotaurine
Glutathione
Homocysteine
Methionine
B6
(CBS)
Zn
Di methyl glycine
Cysteine
SAH
betaine
-CH3
SAM
methylation
DNA, Histones
(epigenesis, imprinting)
CoQ10 synthesis

BACKGROUND

- MTHFR is responsible for the remethylation of homocysteine to methionine by converting 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate[6].
- The build-up of homocysteine as a result of inactive MTHFR has been found to impair DNA methylation causing DNA damage and increase platelet aggregation through endothelial damage [7].
- The associated thrombophilia increases the risk of RPL and miscarriage at varying gestational stages[8].

BACKGROUND

- Folic acid is commonly recommended during pregnancy, however effectiveness in those with MTHFR remains controversial.

- To effectively remethylate homocysteine into methionine, folic acid must be converted into its bioactive form 5-methylfolate (5-MTHF).

- Defected MTHFR genes have been found to produce 17% (MTHFR C1298C) to 75% (MTHFR T677T) less 5-MTHF than healthy genes[9].

- *This raises an important question – should we recommend 5-MTHF to those with MTHFR polymorphisms and would vitamin B12 enhance the effects?*

BACKGROUND

- Despite the research showing a strong association, the evidence behind treatment remains inconclusive.
- Some studies have drawn conclusions that 5-MTHF should be recommended for couples pre and during pregnancy [10, 11]. However, others oppose this stance suggesting 5-MTHF to have little effect on pregnancy outcomes, stating it as an unnecessary expense [12].
- MTHFR polymorphisms are often overlooked in clinical decision making, however increasing miscarriage rates, coupled with this generic ‘one size fits all’ approach presents opportunity for improvement towards more individualised public health recommendations.

AIM OF THE STUDY

This study aims to investigate the effectiveness of 5-MTHF interventions in reducing the risk of adverse pregnancy outcomes in those carrying MTHFR polymorphisms.

RESEARCH METHODS

- Following PRIMSA, a systematic review with meta-analysis was carried out searching MEDLINE, PubMed, PsycINFO and CINAHL.

  Two meta-analyses were carried out on
  - primary outcomes: miscarriage risk
  - secondary outcomes: total adverse pregnancy risk - a composite of non-pregnancy, pre-eclampsia, pre-term labour and miscarriages.

- The dichotomous data was analysed using a random-effects model assessing risk ratio (RR) at 95% confidence intervals (CI).

RESULTS

- Four studies were included in the meta-analyses. The first analysis revealed a non-significant relationship between 5-MTHF and miscarriage risk (Z= 1.69, P= 0.009, (95% CI) RR = 0.45, I^2= 86%).
- Subgroup analyses revealed a significant effect in RPL populations only (Z=1.96, P=0.05) and comparing 5-MTHF to high-dose FA (Z = 2.22, P = 0.03).
- A second meta-analysis revealed 5-MTHF to significantly reduce (Z = 2.49, P= 0.01, RR = 0.57, I^2 = 85%) the risk of total adverse pregnancy outcomes (RR = 0.57).
- GRADE analysis revealed both analyses to be very low quality.

QUALITY ASSESSMENT RISK OF BIAS (ROB2)

Study	D1	D2	D3	D4	D5	D6	D7	D8	Overall
Essmat (2021)	−	+	+	+	×	+	+		−
Servy et al (2018)	×	+	+	−	+	×	+		−
Cirillo et al (2021)	×	−	−	×	+	×	+		×
Hekmadoost et al (2015)	+	+	+	+	−	+	+	+	+

CONCLUSION

- 5-MTHF demonstrates a potential to reduce adverse pregnancy risk in those with MTHFR, especially for miscarriages in those experiencing RPL.
- However, the results are tempered by high heterogeneity, warranting caution over the uncertainty of findings.
- The study highlights the need for further research to address gaps, scrutinise heterogeneity and produce more robust findings for tailored guidelines in individuals with MTHFR polymorphisms.

THANK YOU FOR LISTEN

Please email me any questions, which I can pass on to the student who carried out the study

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