Higher early pregnancy maternal BMI is associated with vitamin B12 insufficiency: systematic review and meta-analysis

N Sukumar¹, N Mudalige², Y Weldeselassie¹, O Oyinbole¹, P Saravanan¹

¹Warwick Medical School, University of Warwick, Coventry, UK; ²Ministry of Health, Nutrition and Indigenous Medicine, Sri Lanka

Background

- Vitamin B12 insufficiency occurs in 20 – 30% of pregnant women¹
- Associated with adverse lipid profile, disordered cholesterol biosynthesis and gestational diabetes mellitus (GDM)^{2,3}
- It is not yet proven if these observations are mediated by maternal BMI

Aim

To study the association between early pregnancy maternal BMI and vitamin B12 levels during pregnancy

Methods

- A search of 4 electronic databases was performed from inception until January 2019
- Title and abstract screening, full text review and data extraction was done independently by 2 authors
- The systematic review was divided into 3 sub-reviews based on different outcomes reported:-
 - Mean BMI in women with and without B12 insufficiency
 - Mean (or median) BMI in obese vs. normal BMI women
 - Linear relationship between B12 and BMI as continuous variables
- RevMan was used to do meta-analysis for **sub-review A**

Results

- 1404 abstracts screened, 98 articles selected for full-text review
- Total of 16 studies were included in the quantitative analysis.
- Additional 2 studies only considered in qualitative analysis as no quantitative measure of association between B12 and folate were provided

- Outcome A: Mean BMI in B12 deficient and non-deficient women**
- Pregnant women author-defined B12 insufficiency had higher BMI in early pregnancy BMI than vitamin B12-replete women (pooled mean 1.71kg/m², 95%CI 0.56, 2.87) (Figure)
 - Considerable heterogeneity between studies (I²=71%)

Outcome B: Mean B12 in obese/overweight vs normal weight women

- 8 results from 6 studies were available, 2 studies reported B12 results from more than 1 trimester (Table 1)
- 4 results showed significantly lower B12 values in overweight/obese women compared to normal BMI

First author, Publication year	Country	Adverse BMI outcome threshold (kg/m²)	Trimester of B12 measurement	B12 measure / units	Adverse BMI outcome		Normal BMI outcome		p
					n	Vitamin B-12	n	Vitamin B-12	
Berglund, 2016	Spain	Normal 18.5-25; overweight 25-30	2	Mean ± SD / pg/ml	54	321±124	129	309±136	0.156
Berglund, 2016	Spain	Normal 18.5-25; overweight 25-30	3	Mean ± SD / pg/ml	53	307±101	128	257±91	0.012
Bjørke-Monsen, 2016	Norway	Normal 18.5–24.9; obese > 35.0	2	Median (IQR) / pmol/l	90	268 (204–317)	1827	314 (254–386)	N/R
Krikke, 2015	Netherlands	Normal <18.5; obese>30	1	Median / pg/ml	NR	252.99	NR	303.29	<0.001
Lai, 2018	Singapore	Normal 18.5 - 22.9; obese >27.5	3	Median (IQR) / pmol/l	131	187 (139, 226)	457	220 (175, 273)	N/R
Mohd-Shukri, 2015	UK	Normal <25; obese >40	2	Mean ± SD / ng/l	25	240±88	25	389±138	<0.0001
Mohd-Shukri, 2015	UK	Normal <25; obese >40	3	Mean ± SD / ng/l	25	202± 56	25	262±96	0.02
O'Malley, 2018	Ireland	Normal <25; obese ≥ 30	1	Median (IQR) / pmol/l	97	203.0 (102.5)	263	208.0 (125.3)	0.03

Table 1 Mean (or median) B12 in overweight/obese women (n=475) vs. normal BMI (n= 2854)

Outcome C: Linear relationship between B12 and BMI

- All 6 studies showed negative association between pre-pregnancy or antenatal BMI and B12 levels; 5 statistically significant (Table 2)
- 2 additional studies (Koebnick 2002 and Dayaldasani 2014) reported that BMI had *no independent effect* on B12 but no direction or strength of association stated

First author, year	Country	n	Trimester of BMI measurement	Unit of BMI	Trimester of B12 measurement	Unit of B12	Effect size on B12 per unit change in BMI (95% CI)	p	Adjustment
Bergen, 2012	Netherlands	5805	1	1 SDS (4.41 kg/m²)	1	SDS	-0.13 (-0.15, -0.10)	<0.001	Gestational age
Bjørke-Monsen, 2016	Norway	2797	Pre-pregnancy	5 categories	2	pmol/l	-16.7 (-22.0, -11.4)	<0.001	Age, parity, supplements, neopterin
Knight, 2015	UK	995	3	Log (kg/m²)	3	Log (pmol/l)	-0.25	<0.001	None
							-0.59 (-0.74, -0.44)	<0.001	Age, Townsend score, smoking, vegetarianism, supplement, parity, Hct
Krikke, 2015	Netherlands	3879	Pre-pregnancy	kg/m²	1	pg/ml	-2.22 (-3.27, -1.17)	N/R	Gestational age
O'Malley, 2018	Ireland	496	1	kg/m²	1	pmol/l	-0.10	0.03	None
Sukumar 2016	UK	344	1	Log (kg/m²)	3	pmol/l	-0.21	0.001	Age, parity, ethnicity, smoking, gestational age, serum folate, supplements

Table 2 Linear association between maternal BMI and B12 levels in unadjusted and adjusted models (n=14 316)

Conclusions

- A systematic review of 16 studies including more than 18000 women show that higher BMI in early pregnancy is associated with lower B12 levels in all 3 trimesters
- Sub-group analysis shows that this relationship may be linear across the spectrum of B12 levels.
- However, causality and direction of effect not proven
- The independent effect of obesity on B12 status during pregnancy needs to be investigated in a prospective study
- If confirmed, correcting B12 deficiency may improve adiposity and risk of GDM during pregnancy.

References:-

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