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(54) Title: RIBOFLAVIN FOR USE IN CONTROLLING BLOOD PRESSURE DURING PREGNANCY

(57) Abstract: Riboflavin can be used during pregnancy to control blood pressure in women having the MTHFR677TT genotype, particularly during the first trimester.



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IBOFLAVIN FOR USE IN CONTROLLING BLOOD PRESSURE DURING PREGNANCY**BRIEF DESCRIPTION OF THE INVENTION**

This invention is directed to the use of riboflavin as an active ingredient for controlling blood pressure during pregnancy.

BACKGROUND OF THE INVENTION

Hypertension affects up to 15% of all pregnancies and can lead to serious hypertensive disorders which are the major causes of fetal and maternal morbidity and mortality worldwide. Disturbances in one-carbon metabolism have been linked with adverse pregnancy complications, such as gestational hypertension and pre-eclampsia.

The risk of gestational hypertension and pre-eclampsia was shown to be reduced by folic acid supplementation during pregnancy, albeit the evidence is somewhat conflicting. Such inconsistencies might be explained by intra- and inter-population genetic variation.

The C677T polymorphism in the gene encoding the folate-metabolising enzyme methylenetetrahydrofolate reductase (MTHFR) has been implicated in hypertension and hypertension in pregnancy.

It would be desirable to be able to control blood pressure in pregnant women safely, especially in those women who do not traditionally respond well to commonly used anti-hypertensive agents.

DETAILED DESCRIPTION OF THE INVENTION

We have found that blood pressure (BP) is higher in non-pregnant women of reproductive age with the MTHFR 677TT genotype. Pregnant women were recruited from antenatal clinics and screened for *MTHFR* genotype. Biomarker status of riboflavin was determined using the functional assay erythrocyte glutathione reductase activation coefficient (EGRac). Of 1709 participants recruited and screened, 11.5% were identified with the variant *MTHFR* genotype. Within the first trimester, an atypical pattern of BP was observed in these women, in that both systolic and diastolic BP increased from the 8th to 16th gestational week (GW), compared with the expected decrease in BP over this time, as previously reported and found here in women without this polymorphism (CC/CT

genotypes combined). At the 12th GW, after adjusting for maternal and gestational age, women with the TT genotype compared to CC or CT genotypes had significantly higher systolic BP (P 0.026), diastolic BP (P 0.050) and hypertension rate (10.4 vs 4.0 or 5.4%; P 0.048).

- 5 When these results were stratified by riboflavin, the BP phenotype owing to this polymorphism was exacerbated among women with suboptimal status (i.e. $EGRac > 1.26$), with median (95% CI) systolic BP of 118.5 (114.6, 121.5) mmHg compared to 114.5 (111.7, 119.2) mmHg in those with optimal status ($EGRac \leq 1.26$) within the TT genotype group. We have found that the TT genotype is associated with higher BP during the first trimester of pregnancy and riboflavin may have an
- 10 important modulating effect on BP in these women.

Thus one aspect of this invention is the use of riboflavin for controlling hypertension in pregnant women by administering riboflavin either as a sole medicament or in combination with a known anti-hypertensive agent. Preferred daily dosages contain at least 1-10 mg per day. As riboflavin is

15 generally known to be well tolerated at even high levels, dosages up to and even exceeding 100 mg per day could safely be used.

EXAMPLES

20 EXAMPLE 1

EXAMPLE 2

A human clinical trial is run based on the following protocol:

- A randomised controlled trial to investigate the effect of intervention with riboflavin, alone or in
- 25 combination with 5 MTHF, on blood pressure in pregnant women stratified by *MTHFR* genotype
- **Aims:**
- a. To compare Blood Pressure (BP) in pregnancy across the three *MTHFR* 677 genotypes: (observational study)
 - Hypothesis: Women with the variant TT genotype will have higher BP in pregnancy and
 - 30 a greater increase in BP from the 16th to the 36th gestational week.
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- b. To examine the effect of riboflavin supplementation on BP in pregnant women with the TT genotype (RCT)
 - Hypothesis: Riboflavin supplementation will maintain healthier BP in pregnant women with the TT genotype.
- 5 •
 - To examine the effect of supplementation with riboflavin in combination with 5-methyltetrahydrofolate (5-MTHF) on BP in pregnant women with the TT genotype (RCT).
 - Hypothesis: Combined supplementation, compared to riboflavin alone, will generate a better BP response in TT women.
- 10 • c. To compare BP of newborns across the three different *MTHFR* 677 genotypes.
- Hypothesis: Newborns with the TT genotype will have higher BP than those with the CC genotype

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CLAIMS

1. A method of controlling hypertension in a pregnant woman comprising administering a daily dose of riboflavin.

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2. A method according to claim 1, further comprising administering an antihypertensive medicament.

3. Use of riboflavin to control hypertension in a pregnant woman.

10 4. Use of riboflavin in the manufacture of a medicament to control blood pressure in a pregnant woman.

Figure 1

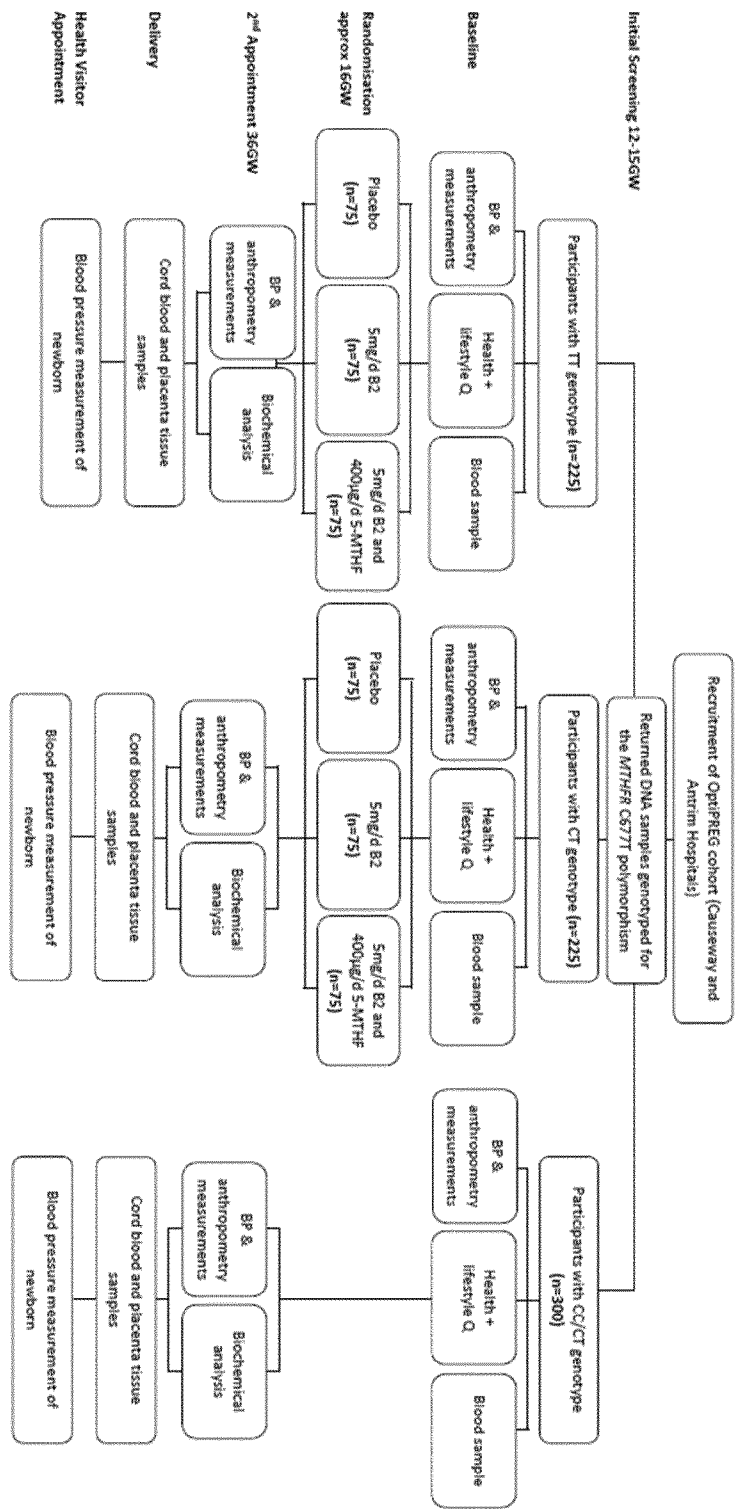


Figure 2

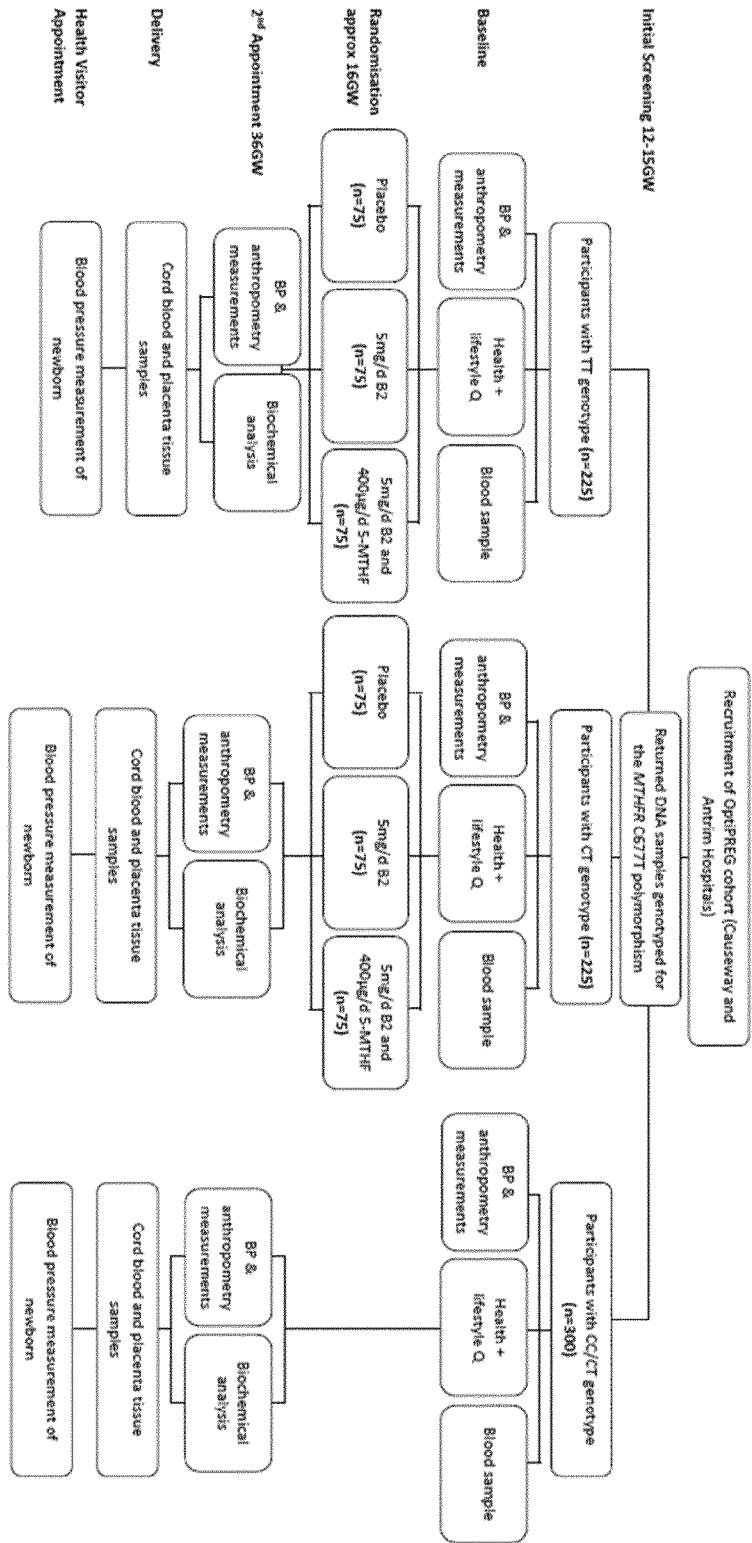


Figure 3

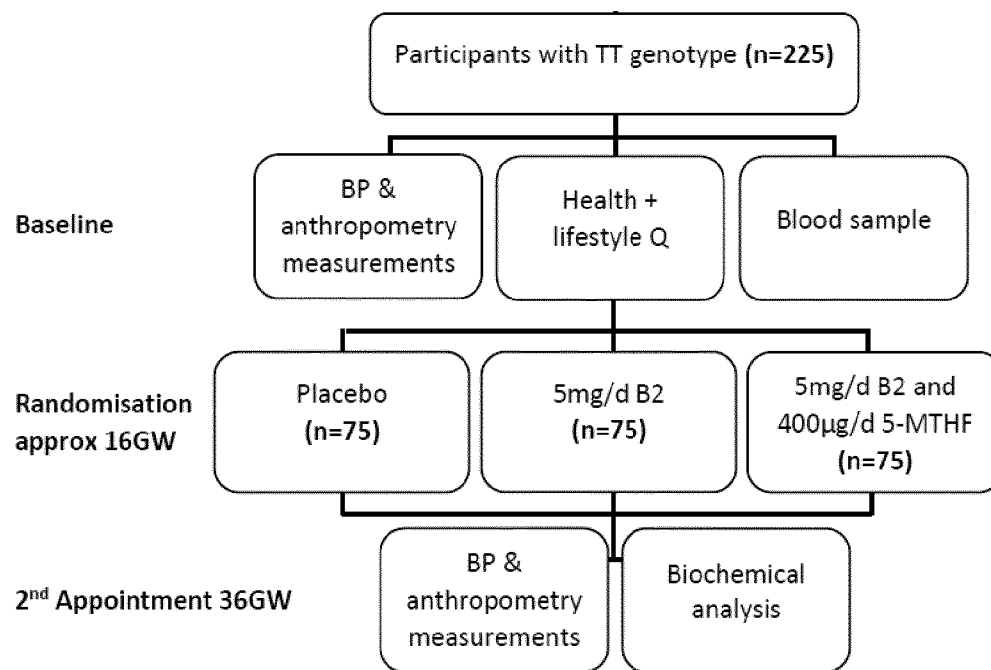
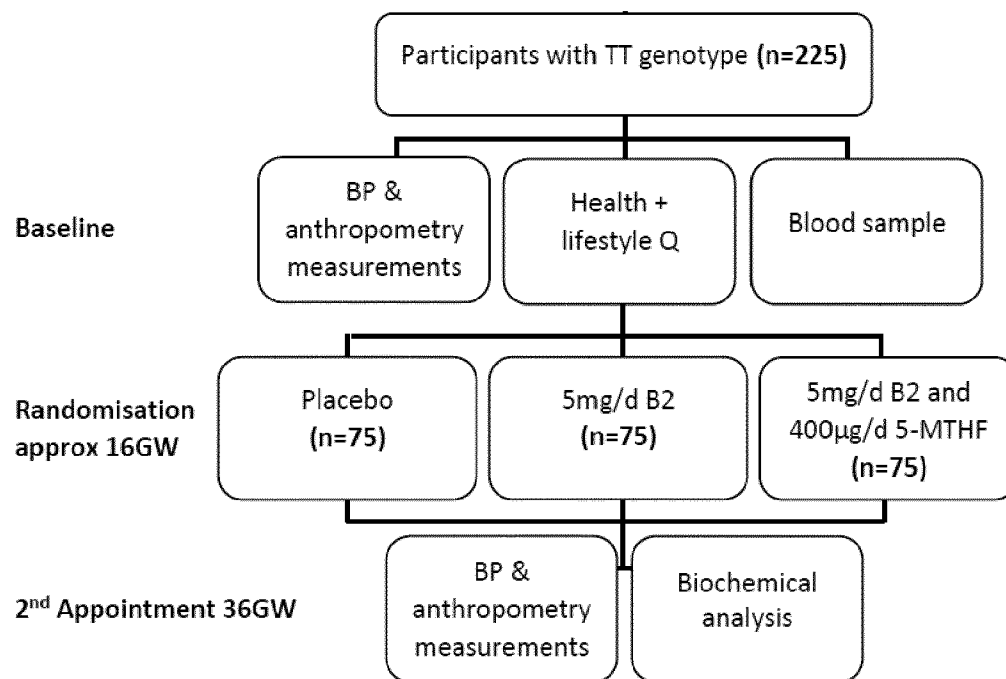


Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/078266

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/525 A23K20/174 A23L33/155
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A23L C11C A23K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCNULTY HELENE ET AL: "Riboflavin,MTHFRgenotype and blood pressure: A personalized approach to prevention and treatment of hypertension", MOLECULAR ASPECTS OF MEDICINE, PERGAMON PRESS, OXFORD, GB, vol. 53, 6 October 2016 (2016-10-06), pages 2-9, XP029886060, ISSN: 0098-2997, DOI: 10.1016/J.MAM.2016.10.002 the whole document ----- -/--	1-4



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 2017, O'SULLIVAN E ET AL: "Riboflavin, MTHFR 677C->T and blood pressure in pregnant and non-pregnant women", XP002801630, Database accession no. EMB-619736570 abstract & PROCEEDINGS OF THE NUTRITION SOCIETY 2017 CAMBRIDGE UNIVERSITY PRESS NLD, vol. 76, no. OCE3, 2017, pages E51 CONF 20170621 to 20170623 Belfast-Nutrition, ISSN: 1475-2719 -----	1-4
X	"Abstracts from the 2019 Annual Scientific Meeting of the British and Irish Hypertension Society (BIHS)", JOURNAL OF HUMAN HYPERTENSION, NATURE PUBLISHING GROUP, GB, vol. 33, no. 1, 16 September 2019 (2019-09-16), pages 1-29, XP036886532, ISSN: 0950-9240, DOI: 10.1038/S41371-019-0217-8 [retrieved on 2019-09-16] abstract -----	1-4
A	CICERO ARRIGO F G ET AL: "Nutraceuticals and Blood Pressure Control: Results from Clinical Trials and Meta-Analyses", HIGH BLOOD PRESSURE & CARDIOVASCULAR PREVENTION : THE OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF HYPERTENSION, ADIS INTERNATIONAL LTD, NZ, vol. 22, no. 3, 1 September 2015 (2015-09-01), pages 203-213, XP009512614, ISSN: 1179-1985, DOI: 10.1007/S40292-015-0081-8 abstract -----	1-4