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HOW TO BEET HYPERTENSION IN PREGNANCY: IS THERE MORE TO BEETROOT JUICE THAN NITRATE?

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Pregnancy is associated with a number of structural and functional cardiovascular adaptations that ensure the fetus is adequately supplied with nutrients throughout all phases of growth and development. Failure to meet the increased metabolic demands can lead to significant maternal and fetal morbidity. Maternal hypertension, either pre-existing or developing during pregnancy, is complicated by the limitations of our current anti-hypertensive medication. The mainstays of anti-hypertensive treatment, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists/blockers (ARBs/Sartans) and thiazide diuretics are associated with an increased risk of congenital abnormalities to the developing fetus (NICE, 2019). As such, there remains a need to increase the available options for treatment of hypertension in pregnancy.

Nitric oxide (NO), derived from the oxidative metabolism of L-arginine by the enzyme nitric oxide synthase (NOS), plays an important role in lowering peripheral vascular resistance critical to the maternal adaption to pregnancy (Hata *et al.*, 1998). A decrease in NO bioavailability is also associated with poor maternal adaptation and fetal growth restriction (Kusinski *et al.*, 2012). Dietary nitrate can be reduced in the body to nitrite (and possibly further to NO) in a NOS-independent manner, and an increased dietary nitrate consumption has been shown to decrease blood pressure (Kapil *et al.*, 2010; Kerley *et al.*, 2018). Beetroot juice is known to be a rich source of nitrate. In their paper, Tropea *et al.*, (2020) have investigated whether this juice can improve endothelial function in pregnant eNOS^{-/-} knock-out mice, and importantly whether this is actually due to nitrate.

The eNOS^{-/-} knock-out mouse model has been shown to have elevated blood pressure, endothelial dysfunction and fetal growth restriction (Kusinski *et al.*, 2012), and similar responses were seen by Tropea *et al.*, (2020). For six days, in the second-half of pregnancy (day 12.5 – 18.5, term 22 days) these mice received either water, normal beetroot juice or beetroot juice with a significantly reduced nitrate content. Plasma nitrate concentrations were raised only in the beetroot juice supplemented animals, while plasma nitrite was only in the eNOS^{-/-} mice on beetroot juice. The low-nitrate beetroot juice did not affect the plasma concentrations of either nitrate or nitrite. Despite this, the nitrate depleted beetroot juice and the normal (nitrate-rich) beetroot juice both decreased blood pressure

and restored uterine artery endothelial function. However, despite this increase in uterine artery reactivity there neither peak systolic velocity nor fetal growth improved.

An important feature of this work is the use of the appropriate controls. With the development of nitrate-depleted beetroot juice (Gilchrist *et al.*, 2014) this would seem to be the ideal 'placebo control' and surely more relevant than just providing mice with regular drinking water. However, this also implies nitrate is the only bioactive constituent of beetroot juice, and yet the effect size of a beetroot juice intervention has been shown to be lower when compared to a nitrate-depleted beetroot juice than to another control (Bahadoran *et al.*, 2017). Indeed, in their paper, Tropea *et al.*, (2020) show positive effects on blood pressure and vascular reactivity in both beetroot juice groups, irrespective of whether nitrate was present or not. Had the nitrate-depleted juice been the only control, it would have appeared that there was no effect of supplementation at all.

The importance of maternal endothelial dysfunction and a loss of NO bioavailability in fetal growth restriction is evident by the use of experimental models such as the eNOS^{-/-} knock out mice (Kusinski *et al.*, 2012). In some models, the pharmacological amelioration of endothelial dysfunction has been shown to prevent growth restriction (Sekimoto *et al.*, 2020). Supplementation with beetroot juice (either with or without nitrate) was shown to improve vascular reactivity of isolated uterine arteries in this mouse model and has also been shown to improve microvascular function in humans with Raynaud's disease (Shepherd *et al.*, 2019).

Taken together, the study by Tropea *et al.*, 2020 suggests that beetroot juice may produce a favourable cardiovascular outcome in a manner that is independent of its nitrate content. While the reduction in blood pressure did not translate into an increase in late gestational fetal size, it had no negative impact on fetal growth either. In a condition where treatment options are limited because of potential risk to mother and fetus, a dietary supplement that is both safe and effective could be hard to beat.

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