Immune memory and recurrent hypertension: Translational studies in women who had hypertension in pregnancy

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Background

Hypertension is a complex and multifactorial condition that remains a major risk factor for cardiovascular diseases including myocardial infarction, heart failure and stroke. Underlying mechanisms for raised blood pressure include activation of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, renal failure, volume overload and oxidative stress [1]. In recent years it has been demonstrated that hypertension is also associated with inflammation in the cardiovascular system and beyond [2]. Inflammation is both an independent pathogenetic factor for hypertension but also a common pathway into which other mechanisms merge.

In most patients, hypertension is a progressive condition and rarely reverts to normotension. Exceptions include those with hypertension predominantly caused by adverse lifestyle factors such as obesity, increased salt intake or lack of exercise which, once successfully addressed, can lead to improved blood pressure control.

One particular group of people with hypertension are women who experience hypertensive disorders of pregnancy. In the majority of these women hypertension is limited to the second half of pregnancy and blood pressure normalises after delivery. Nevertheless, these women are at increased risk of developing hypertension and overt cardiovascular disease later in life [3]. The increased risk particularly relates to women who had preeclampsia but also extends to those with milder forms of hypertension in pregnancy.

This raises the possibility that a “hypertensive memory” exists and first hypertensive episode triggers pathogenetic mechanisms that mediate hypertension and vascular damage. In rodent models there is evidence that experimentally induced transient episodes of hypertension lead to an immune memory effect that on repeat exposure to a hypertensive trigger aggravates the blood pressure response [4]. Very recent data from our collaborators indicate a role of the sympathetic nervous system to mediate the immune memory [5].

As such it is now very important to translate these preclinical data to humans and the clinical course of increased hypertension risk after hypertensive episodes during pregnancy creates such unique opportunity.

Aims and hypothesis

We aim to study the mechanisms that translate a transient episode of hypertension during pregnancy to hypertension later in life. We will conduct two studies:

- We will obtain data on hypertensive pregnancies from various clinical sources (data from our own studies in this field; data from our collaborators; medical record linkage; UK Biobank) and study the relationship between hypertension later in life with antihypertensive treatment in pregnancy.

  We hypothesise that treatment with beta blockers during pregnancy will be associated with blunting of the immune memory and thereby translate in lower incidence of hypertension in later life compared to other agents such as calcium channel blockers.

- We will study if women who had hypertension in pregnancy are characterised by a alterations in their immune phenotype. We will study if these women are more responsive to hypertensive triggers compared to women who had normotensive pregnancies and if this response is linked to altered immune responses.

  We hypothesise that hypertension in pregnancy triggers an immune memory effect that mediates response to hypertensive triggers and leads to hypertension later in life.

Study outline

Both aspects of the study will run in parallel. For the first part we will explore a number of large-scale datasets from our collaborators and our own research and clinical data. The clinical fellow will be trained in methods of epidemiology that are relevant to answer this question.

For the second part of the study we aim to recruit a total of 50 women who had hypertension in pregnancy 3-5 year ago but are now normotensive and 50 controls who had normotensive pregnancies. We will also include a control group of normotensive men. We will conduct detailed blood pressure, non-invasive vascular and immune phenotyping at baseline and then expose participants to one week of high salt diet after which phenotyping will be repeated. In secondary analysis we will study if responses differ depending on the type of antihypertensive treatment that was prescribed during pregnancy.

Opportunities for the fellow

This is a translational clinical research project that offers training in epidemiology, clinical cardiovascular research and immunology of cardiovascular diseases. It combines population science, clinical science and experimental research. The fellow will lead the clinical research study and all phenotyping exercises with particular focus on laboratory work. By covering other aspects of cardiovascular immunology, hypertension research in pregnancy and the wider field of sex and gender differences in cardiovascular diseases in our groups the fellow will have the opportunity to branch out into other areas and add further value to the project.

References

1. Cameron AC, Dominiczak AF, Touyz RM. Hypertension. In: Touyz RM, Delles C (eds.): Textbook of Vascular Medicine. Springer, Cham, 2019.
2. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension* 2017;70:660-7.
3. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. *J Hypertens* 2010;28:1349-55.
4. Itani HA, Xiao L, Saleh MA, Wu J, Pilkinton MA, Dale BL, Barbaro NR, Foss JD, Kirabo A, Montaniel KR, Norlander AE, Chen W, Sato R, Navar LG, Mallal SA, Madhur MS, Bernstein KE, Harrison DG. CD70 exacerbates blood pressure elevation and renal damage in response to repeated hypertensive stimuli. *Circ Res* 2016;118:1233-43.
5. Xiao L, Do Carmo L, Foss JD, Chen W, Harrison DG. Sympathetic enhancement of memory T cell homing and hypertension sensitization. *Circ Res* 2020; in press