BMJ Open  Endovascular ultrasound renal denervation to lower blood pressure in young hypertensive women planning pregnancy: study protocol for a multicentre randomised, blinded and sham controlled proof of concept study

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ABSTRACT

Introduction A major issue confronting clinicians treating hypertension in pregnancy is the limited number of pharmacological options. Endovascular catheter-based renal denervation (RDN) is a new method to lower blood pressure (BP) in patients with hypertension by reducing the activity of the renal sympathetic nervous system. Drugs that affect this system are safe in pregnant women. So there is reasonable evidence that RDN performed before pregnancy should not have deleterious effects for the fetus. Because the efficacy of RDN may be greater in younger patients and in women, we may expect a larger proportion of BP normalisation in young hypertensive women, but this remains to be proven. Our primary objective is to quantify the proportion of BP normalisation with RDN in this population.

Methods and analysis WHY-RDN is a multicentre randomised sham-controlled trial conducted in six French hypertension centres that will include 80 women with essential hypertension treated or untreated, who are planning a pregnancy in the next 2 years and will be randomly assigned to RDN or classic renal arteriography and sham RDN in a ratio of 1:1. The primary outcome is the normalisation of 24-hour BP (<130/80 mm Hg) at 2-month post procedure off treatment. Sample size is calculated with the following assumptions: 5% one-sided significance level (α), 80% power (1- β), expected responder rates of 24% and 3% in the treatment and control group, respectively. Secondary outcomes include the absence of adverse outcomes for a future pregnancy, the variations of BP in ambulatory and home BP measurements and the evaluation of treatment prescribed.

Ethics and dissemination WHY-RDN has been approved by the French Ethics Committee (Tours, Region Centre, Ouest 1- number 2021T1-28 HPS). This project is being carried out in accordance with national and international guidelines. The findings of this study will be disseminated by publication.

Trial registration number ClinicalTrials.gov, NCT05563337.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised, double blind, controlled versus sham trial.
⇒ Blood pressure measured by 24 hours ambulatory monitoring and home blood pressure.
⇒ Proof of concept trial with a sample size too low to evaluate the effects on possible events during pregnancy.
⇒ A comparative trial between renal denervation and pharmacological treatment in this population will be required to evaluate the effects on pregnancy.

INTRODUCTION

Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal morbidity and mortality worldwide. Chronic hypertension increases the risk of pre-eclampsia which occurs in 2–8% of pregnancies,1 placental abruption and fetal growth restriction. Given the rising prevalence of obesity and metabolic syndrome among women of childbearing age and advancing maternal age, it is anticipated that this situation will only worsen.2 Hypertensive disorders of pregnancy are classified as either chronic hypertension diagnosed before pregnancy or before 20 weeks’ gestation, gestational hypertension diagnosed after 20 weeks’ gestation or pre-eclampsia, defined as gestational hypertension with proteinuria or other evidence of end organ damage. Severe hypertension during pregnancy is usually defined as office blood pressure (BP)>160/110 mm Hg. While there is agreement that chronic hypertension increases the risk of hypertensive disorders during pregnancy, the interest of lowering BP...
in pregnant women with mild-to-moderate hypertension and the target BP to achieve have long been a matter of debate, with special concerns for the risk of small for gestational age infants. Recent data show that antihypertensive treatment is effective to reduce hypertensive disorders in this population, and the link between hypertensive treatment and low birth weight is probably due to hypertension severity and not to the use of medications. A major issue confronting clinicians treating hypertension in pregnancy is the limited number of pharmacological options that can be safely used during pregnancy including methyldopa, nifedipine, beta-blockers (predominantly labetalol) and hydralazine (no more available in some countries). These drugs are used less and less in other settings because of the high prevalence of side effects and insufficient data on long-term efficacy in reducing morbidity and mortality. Few trials have compared the relative efficacy of these medications used during pregnancy, and they were underpowered to show differences in maternal and perinatal outcomes.

Normal pregnancy is associated with an increase of sympathetic nervous system (SNS) activity at rest and on stimulation of cardiovascular reflexes; this heightened sympathetic activity returns to baseline after delivery. In pregnancy, however, peripheral arterial resistance is reduced, likely due to the vasodilatory effect of the increased concentrations of oestrogen and progesterone. These changes maintain optimal uteroplacental blood flow and increase renal plasma flow by the end of the first trimester. Overactivity of the SNS plays an important role in gestational hypertension and pre-eclampsia is characterised by an inability of vasodilatory factors to effectively counteract the sympathetic vasoconstrictor effect. This is the rationale to use alpha-methyldopa, and/or beta-blockers to reduce the SNS overactivity in gestational hypertension. Even though efficient in reducing hypertension complications during pregnancy, one of the major issues is non-adherence to these treatments knowing the hesitancy of women to take medicines during pregnancy, as shown for aspirin in women with high risk pregnancies. Outside pregnancy, non-adherence to antihypertensive treatment is high in young patients exceeding 50%, especially in women.

An alternative method to reduce SNS activity is ablation of both afferent and efferent sympathetic renal nerves with endovascular catheter-based renal denervation (RDN) which could be of interest prior pregnancy to reduce any occurrence of SNS overactivity and the risk of pre-eclampsia in young hypertensive women. This new technique has emerged as an adjunctive BP-lowering treatment. Indeed, sham-controlled trials with optimised designs to reduce or eliminate variability and variation of adjunctive medications, improved procedural performance and further standardised endpoints ascertainment, have confirmed the BP lowering efficacy of both ultrasound RDN and radiofrequency-based RDN in the absence of antihypertensive medications in mild-to-moderate hypertension and in the presence of antihypertensive medications in uncontrolled and resistant hypertension without an excess incidence of adverse events.

Interestingly, in the RADIANCE-HTN SOLO off-medication trial using ultrasound RDN, 34.8% of patients in the RDN group were still off-medications at 6 months as compared with 15.5% in the sham group. This suggest a potential interest of RDN prior pregnancy to lower BP while reducing exposure to medications, especially since younger age and female sex may be associated with a stronger BP lowering response to RDN. However, the average age in the trials is 58 years, and the proportion of women, especially young women, is small, as illustrated in table 1. Even though there are no data on the potential effects of RDN on uteroplacental blood flow, pharmacological blockade of the SNS does not compromise the circulatory responses to hypovolaemia or shock in pregnant sheep. Moreover, SNS blockade is safe in pregnant women and fetal haemodynamics are not modified by labetalol, a combined beta and alpha blocker. It is thus expected that RDN performed for chronic hypertension before pregnancy should not have deleterious effects for the fetus. To date, the safety and effectiveness of RDN prior pregnancy have never been systematically evaluated in a dedicated trial.

We thus designed a sham-controlled proof-of-concept and pilot study in a small sample of young women with primary hypertension to assess (1) the BP lowering efficacy of RDN performed before pregnancy, and (2) its safety during pregnancy and delivery for the mother and the child.

**METHODS AND ANALYSIS**

**Study design**

The design of this study is a prospective, multicentre, randomised, blinded with parallel group RDN versus sham which will enrol women with essential hypertension and planning a pregnancy in the next 2 years. Study will...
be performed in six University Hospitals in France. Local approval was required and obtained and the study was registered at ClinicalTrials.gov.

**Study population and eligibility criteria**

All women between 18 and 40 years old, with mild-to-moderate essential hypertension will be considered eligible if they complied with all of the following criteria at randomisation (figure 1):

**Inclusion criteria**

- ≥18 years and ≤40 years.
- Free, informed, written consent signed by the participant and the investigating physician (no later than the day of inclusion and before any examination required by the research).
- Not pregnant but planning to be pregnant in the near future (<2 years).
- Patient using effective contraception (hormonal or intrauterine device), preferably micro-progestational, during the screening phase and the 2-month post-procedure follow-up.
- Essential hypertension confirmed and documented by a previous complete search for secondary hypertension (creatinine, proteinuria, renine, aldosterone, TSH (Thyroid Stimulating Hormone), cortisol, metanephrines, angioscanner of renal arteries and adrenal glands).
- Clinical BP measured in sitting position, in consultation ≥140/90 mm Hg <180/110 mm Hg during the selection visit (D0) - despite taking 0–2 antihypertensive treatments(s) stably for at least 4 weeks.
- Person able to understand and agree to follow all study procedures.
- Person who is affiliated or beneficiary of a social security plan.

**Non-inclusion criteria:**

- Men of any age.
- Women whose age is <18 years or >40.
- Orthostatic hypotension.
- Hypertension from secondary causes (other than sleep apnoea).
- Documented contraindication or proven severe allergy to iodinated contrast.
- Contraindication to use anticoagulants.
- Renal insufficiency with eGFR (estimated Glomerular Filtration Rate) estimated at <60 mL/min/1.73 m².
- Antihypertensive treatment with more than two active ingredients.
- Type 1 diabetes or uncontrolled type 2 diabetes (plasma HbA1c (Hemoglobin A1c) level ≥9%).
- History of chronic inflammatory bowel disease such as Crohn’s disease or ulcerative colitis.
- Brachial circumference >40 cm.
- Any history of cerebrovascular event (stroke, transient ischaemic attack).
- Any history of serious cardiovascular event (myocardial infarction, acute heart failure requiring hospitalisation, coronary artery bypass surgery).
- Proven and confirmed episodes of stable or unstable angina in the 12 months preceding consent.
- Proven history of persistent or permanent atrial fibrillation.
- Presence of an active implantable medical device (eg, neuromodulator/spinal modulator, baroreflex stimulator,…).
- Oxygen therapy or permanent ventilation other than CPAP (Continuous Positive Airway Pressure) for sleep apnoea.
- Primary pulmonary hypertension.
- Limited life expectancy (<1 year).
- Unresolved history of drug or alcohol abuse.
- Not have sufficient ability to understand or follow instructions.
- In the investigator’s opinion she is unlikely to be willing or able to comply why the requirements of the
Evidence of active infection within 7 days of procedure.

- Participation in another trial of an investigational drug or device (participation in a non-interventional study is tolerated).
- Pregnant or nursing mother.
- Person unable to give consent.
- Person deprived of liberty by judicial or administrative decision.
- Adults under legal protection.

Exclusion criteria
- Documented daytime systolic ambulatory BP ≤135 mm Hg and ≥160 mm Hg after 4 weeks washout/run-in period.
- Suitable renal anatomy not compatible with the RDN procedure by CTA (Computed Tomography Angiography) of good quality performed within 1 year prior to consent.
- Patient does not have at least one artery on each side that can be treated with two or more ablations.
- Renal artery anatomy, on either side, ineligible for treatment including:
  - Main renal artery diameter <3.0 mm and >8 mm.
  - Main renal artery length <20 mm.
  - A single functioning kidney (low differentiation or small kidney).
  - Presence of abnormal kidney tumours.
  - Renal artery aneurysm.
  - Pre-existing renal stent or history of renal artery angioplasty.
  - Prior renal denervation procedure.
  - Fibromuscular disease of the renal arteries.
  - Presence of renal artery stenosis of any origin ≥30%.
- Iliac/femoral artery stenosis or calcification precluding insertion of the Paradise catheter.
- Evidence of active infection within 7 days of procedure.

Justification of the sample size

This study is a pilot ‘proof of concept’ study to evaluate RDN in hypertensive women planning a pregnancy. In the RADIANCE-HTN SOLO trial, the percentage of patients who had normalisation of their 24 hours BP (<130/80 mm Hg) in the absence of antihypertensive treatment was 24% in the RDN group and 3% in the control group at 2 months post procedure. Assuming responder rates of 24% and 3%, respectively, in the treatment and control groups, a sample size of 80 subjects would provide approximately 80% power to compare responder rates on the basis of an exact binomial test with one-sided α=0.05. A larger difference between groups would provide more power.

Medical evaluation and enrolment procedure

Following the medical evaluation and after checking the eligibility criteria, the investigating physician gives detailed information and obtains the free and written informed consent (online supplemental file) of the participant. During this first visit (online supplemental table 1), demographic variables of participants will be collected: age, body mass index, office BP, lifestyle (smoking and drinking), medical history, physical examination and current treatments. After this first visit, all antihypertensive treatment will be stopped and each woman will be provided with a validated home (H) BP device (Omron Confort M3) and trained in HBP measurements.

Baseline evaluation

After a 4 weeks washout period, a 24 hours ABPM (ambulatory blood pressure measurement) will be performed. Women will be withdrawn from the study and considered ‘screenfailure’ if the mean daytime systolic BP (SBP) is ≤135 mm Hg or >160 mm Hg. If the woman remains eligible (daytime SBP >135 mm Hg and <160 mm Hg) a CT angiogram of the renal arteries will be performed to confirm anatomical compatibility if an examination less than 1 year old is unavailable.

Intervention and randomisation

Eighty women with essential hypertension who meet the selection criteria will undergo a renal arteriography during which they will be immediately randomised either to the treatment group with RDN or to the sham group in a ratio of 1:1 by computer-based software stratified by centre.

The allocation sequence will be generated by the society Clinfile who produce the e-CRF (electronic Case Report Form).

The result of randomisation will not be known neither to the patient nor by the medical team ensuring the clinical follow-up. The unblinded research assistant and the interventional investigator are responsible for maintaining the confidentiality and security of the assigned group.

The period of blinding will end at the last visit under the protocol: 1 month after the end of pregnancy. In case of emergency and absolute necessity for the health of the participant, the investigator may ask to unblind the study group.

Renal nerve ablation will be performed with the Paradise endovascular ultrasound renal denervation system (ReCor Medical, Palo Alto, California, USA). A minimum of two sonication of 7 s each will be delivered in the main branch of the right and left renal artery, separated longitudinally by 5 mm, according to individual treatment plans developed on the basis of the prerandomisation CT angiography.

The woman will stay off antihypertensive treatment for 2 months after the procedure. Home BP measurement will be sent monthly to the blinded clinical investigator.

Follow-up visits

Two months after the procedure a new 24 hours ABPM off treatment will be performed (primary efficacy endpoint).
The woman will be able to stop her contraception and start a pregnancy. An antihypertensive treatment can also be started after this ABPM with a targeted daytime SBP<135 mm Hg (first-line labetalol, (100–200 mg)). BP will then be monitored through home BP measurements (mean target SBP<135 mm Hg) sent to the medical team every 3–6 months until the start of pregnancy with the possibility of increasing treatment as described in table 2.

### Pregnancy and follow-up

In order to coordinate the medical and obstetrical follow-up as well as possible, women should inform the investigating centre as soon as they know they are pregnant. During the pregnancy, they will be monitored as part of their routine care by their obstetrician. They will perform HBPM (Home Blood Pressure) monthly with the device provided and send the results to the investigating team.

During the 6th-month of pregnancy, an on-site visit with APBM will be performed. The investigator will adjust the antihypertensive treatments according to the results of the HBPM and APBM.

At all times the safety and well-being of the woman are of primary concern.

### Last follow-up

Women should come back for a final study consultation with the investigator, 30 days after the end of the pregnancy and a last 24 hours ABPM will be performed. All data related to the delivery will be collected, especially adverse events.

### Outcomes

The primary outcome is the normalisation of 24 hours BP (<130/80 mm Hg) at 2-month follow-up off treatment. ABPM will be recorded with Diasys 3 plus monitors (Novacor, France) fulfilling European Society of Hypertension and ISO 81060–2: 2013 requirements.

The most important secondary endpoints are consequences of the RDN procedure performed outside pregnancy on a future pregnancy; comparison between the two groups of 24-hour ABPM variations from D30 at 2-month follow-up, 6-month pregnancy and 1 month after end of pregnancy; comparison of home BP variations from D30 between groups at 2 months follow-up, 6 months pregnancy and 1 month after end of pregnancy; number of antihypertensive treatments used after the 2 months follow-up in the two groups.

The secondary outcomes will include the number of potential complications of pregnancy in the two groups such as HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome, severe hypertension (>160/110 mm Hg), early termination of pregnancy, pre-eclampsia, placental abruption, prematurity (<37 weeks) and serious maternal complications.

### Data management, statistical analyses and quality assurance

#### Data management

To collect the data, the investigators and study coordinators will use an electronic case report form. Each researcher and study monitor will have unique access to the eCRF to include new patient and add data from each follow-up. Each correction performed on entered data will be tracked by an audit trail. Checks are programmed to verify the consistency and completeness of the data entered in the e-CRF. The list of checks to be implemented is defined jointly by the coordinating investigator, the data manager and the e-tools project leader in the study’s data validation plan.

#### Data analysis

The primary analysis will be done on an intention-to-treat basis. A ‘per protocol’ sensitivity analysis will also be carried out. The numbers of eligible, randomised patients followed-up, dropped out of study or lost to follow-up will be documented as well as major deviations from the protocol and reasons for leaving the study will be described.

For the primary endpoint, the absolute difference in the 24-hour mean SBP measured by ABPM just before randomisation and at the end time, that is, after 2 months post-randomisation, will be compared by analysis of covariance adjusted to the value of the basis of diurnal SBP in ABPM. The percentage of normalisation of BP over 24 hours (PAS<130 mm Hg) will be compared between the two groups.

The most important secondary endpoints will be analysed after pregnancy: comparison between the two groups of 24-hour ABPM and home BP variations from D30, 2-month follow-up, 6-month pregnancy and 1 month after birth; number of antihypertensive treatments used after the 2 months follow-up in the two groups. The secondary outcomes will also include the number of potential complications of pregnancy in the two groups such as HELLP syndrome, severe hypertension (>160/110 mm Hg), early termination of pregnancy, pre-eclampsia, placental abruption, prematurity (<37 weeks) and serious maternal complications.

### Serious adverse event

On signing the consent form, the investigator is responsible for collecting all adverse events. The investigator reports all serious and non-serious adverse events (biological and clinical adverse vents) that occur between the

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Permitted escalation of antihypertensive medication</th>
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<td>3</td>
<td>Alphaméthyl-dopa (Aldomet) 250–500 mg/j</td>
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<td>4</td>
<td>Nicardipine 50–100 mg/j</td>
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</table>
The Paradise system (device used for RDN) has been evaluated in multiple clinical studies with few reported adverse event especially related to the device. The risks of the procedure are therefore limited to short-term pain and standard catheter-related risks.

Quality assurance
A clinical researcher appointed by the sponsor will regularly visit each centre investigator, during the implementation of the research, one or more times during research according to the frequency of the inclusions and at the end of the research. During these visits, and in accordance with the risk-based monitoring plan, informed consent, compliance with the research protocol and quality of the data collected will be reviewed.

An audit may be conducted at any time by persons appointed by the sponsor and independent of the persons conducting the research. Its purpose is to verify the participants’ safety and respect for their rights, compliance with applicable regulations and the reliability of data.

Duration and schedule
The study started with the opening of the Bordeaux centre in January 2023 and the opening of centres will be completed in June 2023. The duration of the study for each participant will depend on her pregnancy and will be a maximum of 3 years and 10 months. The overall study is expected to take 5 years to complete (2028).

ETHICS AND DISSEMINATION
The study has been approved by Ethics Committee of Tours, Region Centre, Ouest 1 (Approval N°2021T1-28 HPS) and it has received the authorisation from the French National Agency of safety of drugs and health products. The research is conducted in accordance with this protocol. Each amendment to the protocol will be submitted to the ethics committee before being communicated to the investigators. Except in emergency situations that require the implementation of specific therapeutic acts, the investigator(s) undertake(s) to respect the protocol in all points especially with regard to the collection of consent and notification and follow-up of serious adverse events.

The potential risks of the study are considered to be minimal and are addressed in the protocol and consent form. A written consent will be obtained by clinical practitioners from each participant. The trial was registered on the Clinical Trial Registry at ClinicalTrials.gov. Data will be published in peer-reviewed journals and presented at oral.

In accordance with the law, the participants are informed, at their request, of the overall results of the research.

Patient and public involvement
No patient involved.

DISCUSSION
The study started in January 2023 with a 2 years period for inclusions. Six months after the last inclusion, a first set of analysis will be performed to describe BP evolution in the two groups at 2 months post RDN or sham procedure off treatment. The patients and their general practitioner or obstetrician will be kept blind until the end of pregnancy. It is obviously impossible to know when these pregnancies will happen but the study will be closed after a maximum of 5 years after starting and all pregnancies available will be analysed. The results of such preliminary study, if positive, would allow designing and running a powered study to compare RDN to the conventional pharmacological treatment not only in women with chronic hypertension but also possibly in women with previous pre-eclampsia during past pregnancies even if BP has returned to a normal level after delivery.

We think that it is time to consider that pregnancy should not be an obstacle to perform trials that would allow use of evidence-based medical strategies for hypertensive disorders of pregnancy.20

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Contributors PG, MA (hypertension specialists) and LS (obstetrician) have contributed in the conception and design of the study. RB, AC (hypertension specialists) and JG as study coordinator have taken part in designing the study and drafting the article. The department of pharmacovigilance, pharmacy and imaging contribute to review the protocol and develop their respective parts.

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Competing interests LS has been a consultant for Dilatior and Ferring Pharmaceuticals and has received in the past payment for presentations and educational events from Bayer, GlaxoSmithKline, Ferring Pharmaceuticals and Sigvaris. All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


## Supplementary Table. Visits schedule and documented parameters

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<td>Adverse events</td>
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<tr>
<td>HTN therapy escalation (if needed per BP criteria)</td>
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</table>

* : Only for patients randomized to the renal denervation group
*: If CTA > 12 months