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Associations between bacterial infections and blood pressure in pregnancy

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ABSTRACT

Objectives: To test the hypothesis that bacterial infections in pregnancy are related to maternal blood pressure.
Study design: Bacterial infection was assessed using antibiotic usage as a surrogate and its association with blood pressure in pregnancy tested in the Cambridge Baby Growth Study.
Main outcome measures: Antibiotic usage in pregnancy was self-reported in questionnaires. Blood pressure measurements at four time points in pregnancy were collected from the hospital notes of 622 women.
Results: Using all the available blood pressure readings (adjusted for weeks gestation) antibiotic usage was associated with a higher mean arterial blood pressure across pregnancy: antibiotics used 85 (84, 87) mmHg vs. no antibiotics used 83 (83, 84) mmHg (β = 2.3 (0.6, 4.0) mmHg, $p = 9.6 \times 10^{-3}$, from 621 individuals). Further analysis revealed that antibiotic usage was associated with diastolic (β = 2.3 (0.6, 4.0) mmHg; $p = 7.0 \times 10^{-3}$) more than systolic blood pressure (β = 1.4 (−0.9, 3.7) mmHg; p = 0.2). The effect size associated with antibiotic usage appeared to rise slightly after the first trimester.
Conclusions: Bacterial infection in pregnancy, as assessed by self-reported antibiotic usage, is associated with small rises in blood pressure.

1. Introduction

Pre-eclampsia remains a leading cause of maternal and perinatal mortality and morbidity. Its established risk factors include null parity, maternal age > 40 years, multiple pregnancy, extended times between pregnancies, the presence of antiphospholipid antibodies, prior pre-eclampsia in a previous pregnancy or a positive family history, chronic hypertension or gestational hypertension during pregnancy, pre-gestational or gestational diabetes, obesity and use of assisted reproductive technology [1,2]. Less established potential risk factors include infection [3] and consequences of infection such as inflammation. Indeed the usual inflammatory response observed in uneventful pregnancies is enhanced in pregnancies affected by pre-eclampsia [4]. It has been suggested that the link between infection and the development of pre-eclampsia could be at the level of its initiation, due to an increased risk of uteroplacental atherosis (fibrinoid necrosis of the vessel wall with subintimal accumulations of lipophages), and/or its progression, through an increase in the maternal inflammatory response during pregnancy [5].

A number of studies have sought associations between infections in pregnancy and the development of pre-eclampsia. Whilst not all studies have found significant associations [3], most have found a positive association, as supported by subsequent meta-analyses [6,7]. Less is known about potential links between infections and less severe rises in blood pressure in pregnancy. To investigate this we studied antibiotic usage in pregnancy as a surrogate of bacterial infection exposure, plus urinary tract infection (UTI) exposure (the commonest form of bacterial infection in pregnancy), to test the hypothesis that bacterial infection in pregnancy is associated with rises in blood pressure.

2. Materials and methods

2.1. Cohort

The prospective and longitudinal Cambridge Baby Growth Study recruited 2229 mothers (and their partners and offspring) attending ultrasound clinics during early pregnancy at the Rosie Maternity Hospital, Cambridge, United Kingdom, between 2001 and 2009 [8]. All study participants were over 16 years of age and for this study, women who took anti-hypertensive drugs were excluded. Participants who may have had raised blood pressure at certain points during the pregnancy, e.g. during labour, but who did not report anti-hypertensive usage were still included in the study. Fasting blood samples were collected from 1239 participants for the measurement of plasma glucose and insulin

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concentrations around week 28 of pregnancy for the evaluation of insulin sensitivity by Homeostasis Model Assessment (HOMA) modelling [9]. In this cohort, 96.9% of the offspring were of white ethnicity, 0.8% were of mixed race, 0.6% were black (African or Caribbean), 0.8% were East-Asian, and 0.9% were Indo-Asian.

2.2. Antibiotic usage

Each of the study participants were given a printed questionnaire at recruitment to fill in and return once the pregnancy was completed [10]. One of the questions asked "Have you taken any medicine during this pregnancy?" Those women who responded in the affirmative were then asked to complete a table with the following headings: "Name", "Disease", "Daily Dose", "No. of Days" and "Gestational Week(s)". From these questionnaires drugs were categorised into three major dichotomous groups: paracetamol-containing drugs, drugs used to treat indigestion and antibiotics. No account was taken of the number of times that a particular drug was taken, the specific drug that was taken or the doses consumed.

For the purposes of this study only the category based on antibiotic usage was employed. The timings when the antibiotics were reported having been taken were divided into trimesters (first trimester being up to gestational week 12, second trimester being weeks 13–27 and third trimester being from week 28 onwards). Of the 1271 women that filled out questionnaires, 173 (13.6%) reported that they had taken antibiotics during pregnancy and 1098 had not. Of the women that reported having taken antibiotics in pregnancy 51 reported first trimester usage, 68 second trimester and 54 third trimester (some women did not specify the timing when they took antibiotics, whereas some of the others reported taking them in more than one trimester). Specific antibiotic usage was reported as follows: amoxycillin (71 women), cephalexin/cefalexin (16), penicillin (16), erythromycin (15), flucloxacillin (6), clarithromycin (3), augmentin (2), cephradine (2), ampicillin (1), cefaclor (1), cefotaxime (1), ciproflaxine (1), metronidazole (1), trimethoprim (1) and 'antibiotic(s)' (37).

2.3. Urinary tract infections

The most common reason given for taking antibiotics during pregnancy was to treat UTIs. Of the 1271 women that filled out their questionnaires, 53 (4.2%) self-reported that they had experienced UTIs at some point during their pregnancy. Of these women 19 reported having had UTIs in the first trimester of pregnancy, 25 in the second trimester and 14 in the third trimester; some women reported having had UTIs in more than one trimester and some did not disclose when in pregnancy they were infected.

2.4. Blood pressure during pregnancy

Routine blood pressure measurements during pregnancy that had been recorded in hospital notes were collected from a total of 968 women in the Cambridge Baby Growth Study (other hospital notes either not being available to us or the blood pressures not being recorded in the notes) [8]. They were grouped into one of four readings according to the gestational week at which the measurements were taken: (1) at 11.8 (11.5, 12.0) weeks, (2) at 31.4 (31.3, 31.5) weeks and (3) at 37.0 (36.9, 37.0) weeks. The fourth readings were taken during the final 2 weeks prior to parturition (mean 38.8 weeks), parturition occurring at 39.8 (39.7, 39.9) weeks. Blood pressure measurements were available from 622 women for whom self-reported antibiotic usage was available (84 (13.5%) of whom had taken antibiotics during pregnancy). The characteristics of those who we had blood pressure readings for, according to whether they took antibiotics or not are shown in Table 1. There were no significant differences between the groups, although the pre-pregnancy BMI was borderline higher in those who subsequently took antibiotics. In those women where we had blood pressure readings 27 (4.3%) reported that they had had at least one UTI during their pregnancy.

Table 1
Characteristics of those Cambridge Baby Growth Study participants who reported to have taken antibiotics during pregnancy and those that did not in women that we had blood pressure readings from.

Characteristic	Women who reported taking antibiotics during pregnancy (n = 84)	Women who did not report taking antibiotics during pregnancy (n = 538)	p-value
Maternal age (years)	33.4 (32.4, 34.4)	33.6 (33.3, 34.0)	0.7
Parity	1.7 (1.5, 1.9)	1.7 (1.6, 1.8)	1.0
Gestational age at baby's birth (weeks)	39.8 (39.5, 40.1)	40.0 (39.8, 40.1)	0.4
Birth weight of baby (kg)	3.530 (3.433, 3.628)	3.479 (3.440, 3.518)	0.3
Percentage giving birth to males	51.8	51.3	0.9
Pre-pregnancy BMI (kg/m^2)	24.7 (23.7, 25.6)	23.7 (23.3, 24.1)	0.06
Percentage that reported smoking	4.8	2.6	0.3
Percentage with gestational diabetes	11.7	10.9	0.9

The birth weights of the offspring were adjusted for gestational age at birth, sex, parity and maternal BMI before pregnancy.

2.5. Ethics

The Cambridge Baby Growth Study was approved by the local ethics committee, Addenbrooke's Hospital, Cambridge, United Kingdom. All procedures followed were in accordance with the institutional guidelines. Written informed consent was obtained from all the study participants.

2.6. Assays

Blood glucose concentrations were measured using a routine glucose oxidase-based method. Plasma insulin concentrations were measured using a DSL ELISA kit (London, U.K.) according to the manufacturer's instructions.

2.7. Calculations

Mean arterial blood pressure was estimated as twice the diastolic plus the systolic blood pressure all divided by three. The body mass index (BMI) before pregnancy was calculated as the pre-pregnancy body weight divided by the height squared. HOMA S was calculated using the online calculator available at https://www.dtu.ox.ac.uk/homacalculator/ [9].

2.8. Statistical analysis

The associations between antibiotic usage (or UTI) at any time during pregnancy and blood pressure (mean arterial, systolic or diastolic) were tested using general estimation equation modelling, adjusting for weeks of gestation (and sometimes BMI) when the blood pressure readings were taken. Associations at individual time points and between antibiotic use and HOMA S (insulin sensitivity) or between blood pressure and antibiotic use/UTIs in specific trimesters were assessed by linear regression. Values for those women that experienced