**Observational Study NIS Synopsis**

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# Congenital malformations and maternal use of anti-hypertensive medication in the UK

## Observational Study NIS

*Name of Company or Sponsor AZ team or function:* MEOR, GRAPSQA

*Development Phase of the Product (please check a box):*

*[ ] Not Applicable [ ] Pre-development [ ] In-development (including phase) [ X ] Marketed*

# 1. RATIONALE

It is difficult to carry out standard clinical trials on pregnant women and therefore the relation between hypertension and hypertensive treatment options for childbearing women has not been studied as well as one would expect. This study gave us the possibility to look back and study the medications that hypertensive women were taking while pregnant and assess patterns indicating which drug or drug classes may be least harmful to the child.

# 2. OBJECTIVES

The objective of this study was to evaluate diagnoses of congenital malformation in live births or post-partum infant death outcomes in women with diagnosed hypertension or who are treated with anti-hypertensive medication, more specifically ARBs and ACE inhibitors. This evidence is essential to enable safe and more effective use of treatments for hypertensive control among women who may be pregnant.

Aim 1. Assemble a cohort of pregnant women with a hypertension diagnosis and/or treated with Anti-hypertensive medication including but not limited to ARBs and/or ACE inhibitors during the course of the pregnancy.

Aim 2. Once the patient population was identified, mother-child pairs were linked in order to describe characteristics such as age, weight, anti-hypertensive treatment, co-morbidity, and adverse neonatal outcomes.

Aim 3. Analyze the independent association between treatment with ARBs and/or ACE inhibitors and the risk of congenital malformation in live births or post-partum infant death, overall and by morbidity type in the selected hypertensive mothers (sub-population of subjects with diabetes or heart failure for instance).

# 3. METHODOLOGY

The study is a descriptive study, providing information on the characteristics of hypertensive mothers and pregnancy outcomes captured in a primary health care setting and substantiated by the Mother-Baby link, provided by the Clinical Practice Research Datalink (CPRD).

## 3.1 Study Design

This was a descriptive study to assess differences in outcome of congenital malformation in live births or postpartum infant death among hypertensive mothers in the UK.

Women who are hypertensive and pregnant were included in the study; the study period was from January 1, 1997 until December 31, 2014.

### 3.1.1 Data Source / Investigation Site

THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD) this database with primary health care practice information is located in the United Kingdom.

# 4. STUDY POPULATION

The cohort selected consisted of pregnant women (n=50,182) with hypertension as defined by a medical diagnosis based on READ codes, via recorded prescriptions for hypertension, or systolic/diastolic blood pressure levels > 140/90. A study period of 1 January 1997 to 31 December 2014 was used to build this cohort of hypertensive and pregnant women where pregnancy status was identified from CPRD using Read Codes and entity types that indicate a pregnancy outcome.

For the initial descriptive aspect of the study, all hypertensive pregnant women in CPRD GOLD were included, but the main part of the study used the Mother –Baby data linkage to allow further study of mother child pairs with regards to specific adverse outcomes. This data was further linked to the Hospital Episodes Data (HES), the UK ONS Mortality Data, and the Index of Multiple Deprivation (IMD).

## 4.1 Inclusion Criteria

The inclusion criteria consisted of pregnant women with hypertension as defined by a medical diagnosis based on READ codes, via recorded prescriptions for hypertension, or systolic/diastolic blood pressure levels > 140/90 during the following study period from 1 January 1997 to 31 December 2014 and with at least 1 year of information in the CPRD prior to start date.

## 4.2 Exclusion Criteria

Patients with a primary diagnosis for a major malignant disease, or with gestational diabetes and gestational hypertension (pre-eclampsia), were excluded.

# 5. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

## 5.1 Exposure and Covariates

Independent variables of interest, *confounders,* included:

- Age
- Parity
- Duration of disease for hypertension (≤2 yrs, >2-10, ≥10 years) at baseline
- Number of anti-hypertensives medicated concomitantly (1 vs >1 anti-hypertensive drug)
- Gestational period (first trimester, second trimester, and third trimester
- Weight (kg) at baseline for the mother
- Blood pressure mm Hg (Annex D)
- Socio-economic status (index of multiple deprivations)
- Smoking status (ever smoker/ never smoker)

- Glycated hemoglobin HbA1c (mmol/l)

## 5.2 Study Measures (Outcomes)

Fetal adverse outcomes of interest were:

- Main outcomes included malformations, still birth and infant mortality post live birth.
- Secondary outcomes of interest included pre-term birth (less than 38 weeks), low birth weight (401 to 1500 g (very low birth weight [VLBW]) at birth by gestational age, birth weight, and gender), hypoglycemia at birth (plasma glucose level ≤ 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and ≤ 45 mg/dL (2.5 mmol/L) thereafter, hypotension at birth (will be defined as the 10th centile for mean blood pressure within the first 24 hours according to birth weight), any severe, and cardiovascular defects (for instance murmurs and hypoxia).

# 6. STATISTICAL METHODS

## 6.1 General Aspects

Summary statistics (mean, standard deviation, minimum and maximum for continuous data, and counts and percents for categorical data) for each risk factor were generated and displayed for hypertensive subjects. Conditional Logistic Regression was used, in this cross-sectional cohort, to analyze the effect of maternal exposure to anti-hypertensive medication (most importantly ARBS) on the risk of fetal malformation or mortality. This analysis allowed us to estimate the probability of this risk occurring across various anti-hypertensive treatment groups and by pregnancy status (trimester) while also controlling for confounders.

Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Adjusted analyses will include potential confounders.

## 6.2 Sample Size and Power Calculations

Antihypertensive treatment is administered cautiously to women who may be pregnant. Initial feasibility studies indicate that this CPRD Cohort of hypertensive pregnant women will be a population of approximately 50,000.

Our power calculations below were based on Cooper et al (ref 1 in protocol) and Lennestål (ref 4 in protocol). Assuming 80% power and alpha=0.05, it is estimated that 387 patients would be needed per group to show difference. Our feasibility estimates, based on our cohort of 50 182 women exposed to antihypertensive drugs, indicate that 963 women may be taking an ACE inhibitor at some point during pregnancy and are available for analyses (these estimates are prior to mother-baby linkage).

## 6.3 Results

Final numbers included in study post linkage.

| Summary | Mothers | Pregnancies | Babies |
|---|---|---|---|
| Overall Count | 34 701 | 43 155 | 43 831 |

No differences were noted across antihypertensive medication status in women with a history of hypertension. Negative outcomes were similar across treatment status indicating the proportion of mothers who experienced an outcome of malformation or death post live births may not vary by antihypertensive treatment. A major limitation to this result may be our inability in the CPRD to capture spontaneous abortions throughout the full pregnancy term per mother.

| Antihypertensive Medication Status | TOTAL BABIES IN GROUP | BABIES WITH AN ABNORMALITY | PERCENTAGE |
|---|---|---|---|
| Mother on anti-hyp drug during pregnancy | 5995 | 441 | 7,36 |
| Mother on anti-hyp drug in year prior to pregnancy, but not during pregnancy | 8076 | 570 | 7,06 |
| Not on anti-hyp during pregnancy or in the year before | 29760 | 2123 | 7,13 |
| | 43831 | 3134 | |

# 7. STUDY CONDUCT

## 7.1 Study Procedures

Information on Investigator sites is not applicable for this NIS conducted retrospectively in a primary health care database.