

# Preeclampsia and birthweight by gestational age in singleton pregnancies in Flanders, Belgium: a prospective study

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## Summary

**Purpose:** Recent studies have questioned the relationship between low birthweight and hypertension in pregnancy, especially in term pregnancies. We aimed to analyse the influence of chronic hypertension, preeclampsia, gestational hypertension and superimposed preeclampsia on birth weight in singleton pregnancies at different gestational ages.

**Methods:** Between January 1, 2001 and December 31, 2002 data on hypertension (subdivided in chronic hypertension, preeclampsia, gestational hypertension, superimposed preeclampsia and eclampsia) were collected prospectively for all deliveries in the region of Flanders, Belgium. Multiple pregnancies and patients with diabetes were excluded from analysis. Multiple linear regression was performed to construct a model for the prediction of birthweight and to determine the contribution of hypertension.

**Results:** Hypertension was diagnosed in 5,284 of 111,007 (4.8%) singleton pregnancies, and of these 647 had chronic hypertension (0.6% of the total group), 2,253 (2%) gestational hypertension, 2,244 (2%) preeclampsia and 140 (0.1%) superimposed preeclampsia.

Birthweight less than 2,500 g was most frequent in the preeclamptic group and less frequent in case of gestational hypertension, but in all hypertensive groups it was statistically more frequent compared to the normotensive pregnancies. Before 26 weeks' gestational age the presence of any kind of hypertension did not influence birthweight. From 26 weeks on preeclampsia contributed to a lower birthweight. Gestational hypertension resulted in a lower birthweight between 28 and 34 weeks, but not before or after this period. Superimposed preeclampsia only had an effect between 32 and 34 weeks and chronic hypertension only marginally contributed to birthweight. A relation with both a high birthweight (> 4000 g) and birthweight < 2500 g was found in term gestational hypertension and preeclampsia.

**Conclusion:** At an early gestational age (less than 26 weeks) hypertension is not a significant factor influencing birthweight. Uncomplicated chronic hypertension is not an important factor determining birthweight but preeclampsia is. Gestational hypertension influences birthweight in a limited period between 28 and 34 weeks of gestational age. When hypertensive pregnancies reach term they tend to result both in more babies weighing < 2,500 g and > 4,000 g.

**Key words:** Preeclampsia; Hypertension; Pregnancy; Birthweight; Fetal growth.

## Introduction

Hypertension complicates 5-10% of pregnancies and constitutes the most frequent medical disorder in pregnancy. Babies born to hypertensive mothers have an increased risk of intrauterine growth retardation, but some recent reports have questioned this and have even suggested a relation to higher birthweight in term pregnancies [1-4].

The aim of the present study was to determine the contribution of hypertension in pregnancy and its different forms [chronic hypertension, superimposed preeclampsia, preeclampsia and gestational hypertension] on birthweight at different gestational ages.

## Materials and Methods

For the purpose of this study a questionnaire on hypertension was introduced in the system of data collection on deliveries in Flanders, Belgium between January 1, 2001 and December 31, 2002. The Flemish Center for Perinatal Epidemiology collects data on all deliveries in the region of Flanders (Northern part of

Belgium) covering over 99% of all deliveries in the region. Only deliveries after 22 weeks of gestational age are registered.

For the purpose of this study chronic hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg and/or diastolic  $\geq 90$  mmHg before 20 weeks' gestational age (no data are available on hypertension persisting after delivery), gestational hypertension was hypertension that newly developed after 20 weeks, preeclampsia was considered if proteinuria (more than 1+ on stick or more than 300 mg in a 24-hour urine collection) was present and superimposed preeclampsia was defined as preeclampsia developing in a patient with preexisting disease such as chronic hypertension or renal disease. The presence or absence of significant proteinuria was also registered as an independent item. As multiple pregnancy and diabetes are strong factors influencing birthweight but also influencing the incidence of preeclampsia we considered them as confounding and excluded patients with multiple pregnancy and/or diabetes from further analysis. For each delivery the following data were available: maternal age, gestational age, parity, fetal sex, the use of artificial reproductive technology and birthweight. No data were available on tobacco use, drugs or maternal nutritional status.

Statistical analysis was performed with SPSS11.0. For univariate analyses the chi square test was used; significance was accepted at  $p < 0.05$  and odds ratio (OR) was calculated with a 95% confidence interval when appropriate. Stepwise multiple

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Table 1. — Outcome of pregnancy for different hypertensive disorders compared to the normotensive group..

	Normotensive N = 105,723			Chronic hypertension N = 2,253				Gestational hypertension N = 2,253					Preeclampsia N = 2,244					Superimposed preeclampsia N = 140				
	N	%	N	%	P <sup>1</sup>	OR <sup>2</sup>	95%CI <sup>3</sup>	N	%	P	OR	95%CI	N	%	P	OR	95%CI	N	%	P	OR	95%CI
Maternal age > 40 years	1,548	1.5	30	4.6	<0.001	3.24	2.26-4.66	55	2.4	<0.0001	1.66	1.28-2.16	42	1.9	0.113	1.28	0.94-1.72	7	5	0.001	3.53	1.65-7.54
Maternal age < 20 years	2,521	2.4	6	0.9	0.015	0.38	0.18-0.86	40	1.8	0.06	0.74	0.55-1.01	38	1.7	0.033	0.71	0.52-0.97	1	0.7	0.195	0.29	0.04-2.12
Nulliparity <sup>4</sup>	48,223	45.6	332	51.3	0.004	1.25	1.08-1.46	1,437	63.8	<0.0001	2.07	1.90-2.25	1,667	74.3	<0.0001	3.36	3.06-3.69	79	56.4	0.01	1.51	1.10-2.15
Gestational age < 37 weeks	6,025	5.7	81	12.5	<0.0001	2.33	1.66-2.96	170	7.5	<0.0001	1.34	1.15-1.56	596	26.6	<0.0001	5.54	5.06-6.06	38	27.1	<0.0001	6.13	4.23-8.89
Birthweight < 2,500 g	4,863	4.6	288	12.8	<0.001	3.01	2.39-3.87	187	8.3	0.0051	1.85	1.60-2.14	579	25.8	<0.001	6.54	5.98-7.16	30	21.4	<0.001	5.61	3.75-8.38
Birthweight < 2,500 g at gestational age 38-42 weeks	1,045	2.1	13	2.85	0.005	1.01	1.00-1.02	58	5.5	<0.001	1.03	1.02-1.05	84	9.9	<0.0001	1.06	1.05-1.08	4	6.9	0.02	1.00	0.99-1.01
Birthweight > 4,000 g	9,304	8.8	192	8.5	0.77	0.96	0.73-1.26	160	7.1	0.005	0.80	0.68-0.94	94	4.2	<0.0001	0.46	0.38-0.57	8	5.7	0.194	0.63	0.31-1.28
Birthweight > 4,000 g at gestational age 38-42 weeks	4,428	9.5	28	10.3	0.73	1.00	0.99-1.01	78	7.5	0.04	0.99	0.98-1.00	47	5.3	<0.0001	5.54	5.06-6.06	38	27.1	<0.0001	6.13	4.23-8.89

<sup>1</sup>p value in chi-square test as compared to normotensive; <sup>2</sup>OR odds ratio; <sup>3</sup>95% CI 95% confidence interval of the OR; <sup>4</sup>nulliparity: the actual pregnancy is the first to result in birth at more than 22 weeks' gestational age.

linear regression was performed to construct a model to predict birthweight at different gestational ages. Factors included were parity, gestational age, different forms of hypertension (included as "dummy variables"), fetal sex (as "dummy variables"). As the overall relationship between gestational age and birthweight is non-linear when considering the complete period from 22 to 42 weeks, and we wanted to know at what gestational age hypertension influences birthweight, the analysis was performed in 2-week blocks from 22 weeks on (i.e., 22 and 23 weeks, 23 and 24 weeks, 24 and 25 weeks and so on).

## Results

A general overview of pregnancy outcome for the different groups is given in Table 1. In the period studied there were 111,007 pregnancies included, 7,584 were excluded because of diabetes and/or multiple pregnancies. Some kind of hypertension was diagnosed in 5,284 (4.8%), and of these 647 had chronic hypertension (0.6% of the total group), 2,253 (2%) gestational hypertension, 2,244 (2%) preeclampsia and 140 (0.1%) superimposed preeclampsia. Maternal age over 40 was more frequent in all hypertensive groups except preeclampsia while maternal age < 20 years was less frequent in chronic hypertension and preeclampsia but not in gestational hypertension and superimposed preeclampsia. Nulliparity was more frequent in every hypertensive group. There were no differences in the use of artificial reproductive technology (artificial insemination, in vitro fertilisation, hormonal stimulation) between groups except for intracytoplasmatic sperm injection which was more common in women with chronic hypertension (10/647 (1.5%) vs 478/105,723 (0.4%) in the normotensive group;  $p < 0.0001$  in the  $\chi^2$  test (OR 3.41, 95% CI 1.83-6.32).

In all hypertensive groups more babies weighing less

than 2,500 g (irrespective of gestational age) were born and birth was more frequent at less than 37 weeks' gestational age. In term pregnancies there were more babies with a birthweight < 2,500 g, but significance was not reached for superimposed preeclampsia. When considering gestational age 38-42 weeks, there was no over-representation of babies with a high birthweight (> 4,000 g) in chronic hypertension and superimposed preeclampsia, but in gestational hypertension and preeclampsia there were marginally more infants with a birthweight > 4,000 g.

Stepwise multiple linear regression to construct a model for birthweight including gestational age, parity, maternal age, preeclampsia, superimposed preeclampsia, chronic hypertension and gestational hypertension (as dummy variables) resulted in the following model with all factors being significant at  $p < 0.05$ : birthweight = - 3385.75 + 168.53 (gestational age in weeks) + 42.86 (parity) - 152.78 (preeclampsia) + 2.87 (maternal age in years) - 41.67(gestational hypertension) - 55.57 (chronic hypertension) - 99.46 (superimposed preeclampsia) - 61.7 (fetal sex).

Preeclampsia, gestational hypertension, chronic hypertension and superimposed preeclampsia are mutually exclusive and have a value of 0 if not present and a value of 1 if present. Fetal sex is 0 for girls and 1 for boys. Adjusted R<sup>2</sup> for the model is 0.33 suggesting that only 33% of the variation in birthweight is predicted by this model.

To discern from what gestational age on and until what gestational age hypertension influences birthweight, we performed an analysis in 2-week blocks. The two-week period was chosen because, especially in the earlier gestational ages, there were insufficient patients per week.

Analysis of the 2-week block from 28-30 weeks

showed for instance that birthweight was significantly lower in preeclampsia but not in chronic hypertension, gestational hypertension or superimposed preeclampsia: birthweight =  $-2977.78 + 142.45$  (gestational age in weeks) +  $49.13$  (parity) -  $146.37$  (preeclampsia) -  $266.47$  (gestational hypertension) with preeclampsia and gestational hypertension = 0 if not present and = 1 if present; p-values for excluded variables in the model are: chronic hypertension 0.36; fetal sex 0.25, and superimposed preeclampsia 0.55. The adjusted  $R^2 = 0.21$  meaning that the model actually explains only about 21% of the variance in birthweight between 28 and 30 weeks. These calculations demonstrated that for gestational age < 26 weeks hypertension did not influence the model but only 138 babies (13 with hypertension including 2 with chronic hypertension and 11 with preeclampsia, no superimposed or gestational hypertension and 125 non-hypertensive patients) were born at this age. From 26 weeks on preeclampsia makes a significant difference lowering birthweight, gestational hypertension makes a difference from 28 weeks on, and superimposed preeclampsia only between 32 and 34 weeks. Although chronic hypertension contributed to the general model, after subdivision in 2-week blocks, there was no single period in which patients with chronic hypertension demonstrated significantly lower birthweight.

## Discussion

The incidence of hypertension in our population is 4.8%, somewhat lower than expected but this is most probably due to the exclusion of two major subpopulations, namely diabetics and multiple pregnancies, who both have a high risk for preeclampsia. Excluding diabetes specifically excludes part of the patients with superimposed preeclampsia. This study does provide information on birthweight but not on actual intrauterine growth as only babies that are born are studied, irrespective of any causal relationship between preterm birth and a hypertensive disorder. Only part of the variation in birthweight can be explained by our data. We lack information on known factors influencing birthweight such as maternal smoking behaviour, use of drugs, maternal nutritional status, maternal habitus (weight, weight gain, body mass index). Possible interactions between these factors, hypertension and birthweight can not be studied by our data. Smoking reduces the incidence of preeclampsia but when combined it is not clear whether the effect on birthweight is simply additive or synergistic [5, 6].

Chronic hypertension when not developing into superimposed preeclampsia, does not seem to be a relevant factor influencing birthweight; gestational hypertension and preeclampsia can be considered as two stages of a progressive disease, demonstrated by the earlier and more pronounced effect of preeclampsia on birthweight.

Although fetal growth can be restricted by preeclampsia, most infants born to women with preeclampsia have a weight appropriate for their gestational age [4, 5] and contradictory results have been obtained on the relation-

ship between the severity of the hypertensive disease in pregnancy and the amount of growth restriction [1, 5]. We can not confirm the finding of Xiong *et al.* that babies born to mothers with preeclampsia at term have fetal growth similar to that of babies born to normotensive mothers and have increased rates of both small-for-gestational-age and large-for-gestational-age neonates [4, 9]. Both in a Canadian and a Chinese population more babies with high birthweight (4,000-4,200 g) have been reported [1, 7]. It is possible that the exclusion of diabetic mothers contributes to this discrepancy as they tend to have both more hypertension in pregnancy and babies with a higher birthweight. The present study supports the results as described by Vatter *et al.* [3] suggesting a U-shaped association with birthweight for preeclampsia diagnosed around term and an L-shaped association for preterm preeclampsia, but the relationship is not clear-cut nor present at very early gestational ages (< 27 weeks).

## Conclusion

This study demonstrates a lower birthweight for preeclamptic patients from 26 weeks' gestational age on. A relation with higher birthweight for term hypertension was demonstrated. We found marginally more term babies weighing > 4,000 g in gestational hypertension and preeclampsia. Uncomplicated chronic hypertension only marginally contributes to a lower birthweight, while the most important factor for chronic hypertension is probably that it is a predisposing factor for superimposed preeclampsia. Hypertensive disorders can explain only a relatively small part of the variance in birthweight.

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