Upsala J Med Sci 83: 97–102, 1978

Studies on Toxaemia of Pregnancy with Special Reference to Blood Pressure

II. Results after 6–11 Years' Follow-up

H. ÅBERG, L. KARLSSON and S. MELANDER

From the Department of Internal Medicine and the Department of Obstetrics and Gynaecology, University Hospital, Uppsala, Sweden

ABSTRACT

One hundred and fifty women with a diagnosis of toxaemia of pregnancy treated in the Department of Obstetrics and Gynaecology, University Hospital, Uppsala between 1964 and 1968 were investigated. One hundred women were still living in the area in 1975 and thus could be re-studied. The participation rate was 100% in this group. After this follow-up period of 6–11 years 17 women were hypertensives at the investigation and 12 were already on antihypertensive therapy. The incidence of hypertension was thus 29%. The toxaemic women who had developed hypertension showed a higher frequency of a family history of hypertension as well as of cardiovascular lesions than the toxaemic women with normal blood pressures at follow-up. At the time of the toxaemia the future hypertensive women ($n=29$) had a higher blood pressure on admission, as well as a greater body weight, than the women who were normotensive at the follow-up investigation. Forty-six of the 100 re-studied women were taking contraceptive pills. Seven developed hypertension while 'on the pill'. Four of these became normotensive after discontinuating the pill.

INTRODUCTION

In Part I of this report (1) the incidence of toxaemia of pregnancy and some characteristics of a series of women with this disorder were described. The main purpose of these studies on toxaemic women was to investigate the behaviour of the blood pressure (BP) at delivery and after some years of follow-up.

The literature reflects conflicting views on the late prognosis of toxaemia with regard to the BP development (2–6). The reason for this is probably the difficulties encountered in diagnosing toxaemia of pregnancy. The combination of hypertension, proteinuria and oedema—the three criteria for the diagnosis of toxaemia—is not a well-defined one. Oedema, for instance is present in 40% of pregnant women with essential hypertension (7). Proteinuria is also much more common amongst pregnant women with the latter disorder (8).

It is thus easily understood that some materials are very heterogeneous and cannot uncritically be compared with one another. For the purpose of the present study, however, the essential matter is not so much the diagnosis of toxaemia but, rather, what happens to a woman with hypertension during pregnancy as regards future hypertension.

MATERIAL

The material comprised all women with a diagnosis of pre-eclampsia or eclampsia treated in the Department of Obstetrics and Gynaecology, University Hospital, Uppsala between 1964 and 1968. The criteria for diagnosis and a survey of the fulfilment of these various criteria were presented in Part I (1). All diagnoses during the period under study were checked by one of the authors (S. M.) at the time of the diagnosis. He was not aware at that time, however, of the purpose of the present study.

In all, 150 women were given the diagnosis toxaemia of pregnancy. Eleven of them had eclampsia. The average annual incidence of toxaemia was 0.9% (1).

In 1975 a letter was sent to these women inviting them to participate in a health examination survey conducted at the Department of Medicine, University Hospital, Uppsala. The investigation was carried out between April and

Table I. *A review of the patients with toxaemia of pregnancy ($n=100$) after 6–11 years of follow-up*

BP groups	n	Age (y) Mean±S.D.	Weight (kg) Mean±S.D.	Height (cm) Mean±S.D.
Normotensives	71	33.6±4.6	67.4±16.9	164.2±5.5
Hypertensives	29	39.9±7.6 $p<0.001$	81.5±18.2 $p<0.001$	163.6±5.6 n s

Table II. *A review of the blood pressures (BP) in a group of women (n=100) 6–11 years after they had had toxaemia of pregnancy*

BP groups	BP, mmHg		Pulse rate beats/min
	Supine (mean±S.E.M.)	Erect (mean±S.E.M.)	(mean±S.E.M.)
Normotensives	129.8±1.4/81.7±0.8	127.7±1.4/ 85.5±0.8	77.7±1.5
Hypertensives, untreated	156.6±5.4/97.8±1.8	156.6±5.6/100.6±1.9	79.1±3.8
Hypertensives, treated	144.2±4.8/92.5±2.5	136.1±5.2/ 95.6±2.7	74.2±3.6

May 1975 and was performed in the afternoon, except that some of the laboratory investigations were carried out separately in the morning with the women fasting.

Out of the original 150 women 100 were invited to the examination. The participation rate was 100% of those invited. In some cases repeated invitations both by letter and phone had to be made. Of the remaining 50 women about half had moved from the city and as many could not be traced within the study period.

Those women who had BP≥160/95 were considered as hypertensives, as also were those already on antihypertensive drugs (HT group). Some data on the population examined are summarized in Table I.

METHOD

The health examination survey comprised a physical examination, some laboratory investigations (Fig. 1) and a questionnaire on family and personal medical histories as well as on obstetrical–gynaecological data, including the use of oral contraceptives. The subjects were examined by the same physician (L. K.).

The BP was recorded on the right arm, using a mercury manometer (wall model). The diastolic pressure (DBP) was recorded when the sounds had completely disappeared (Korotkoff phase 5). The BP was read to the nearest 5 mmHg mark and was measured after 10-min rest and after 2-min in the erect position. As previously mentioned a subject with a supine BP of ≥160/95 mmHg was considered to be hypertensive.

Conventional methods were used for calculation of the mean value, standard error of the mean (S.E.M.) and standard deviation (S.D.). Significance of differences between mean values was estimated by Student's *t*-test (2-tailed test).

RESULTS

Blood pressure

Seventy-one of the re-examined women were normotensive. Seventeen women had become hypertensive according to the definition given above. In addition, 12 were already on antihypertensive therapy. Four of these 12 women had a BP lower than 160/95 mmHg. Three women were being treated with β-blocking agents only, 4 were having this treatment in combination with saluretics and/or hydralazine, 3 were on saluretics only and the remainder were having both hydralazine and a saluretic. The BPs and pulse rates in each group are shown in Table II. The incidence of hypertension in this material after a mean of less than 10 years was 29%.

Laboratory investigations

Some characteristics of the three groups—normotensives, untreated hypertensives and treated hypertensives are presented in Table III. The only significant difference between them was that the treated hypertensives had a higher serum urate level than both the untreated hypertensives and the normotensives. This was of course an effect of the saluretic therapy. In spite of the small number it should be noted that there were 3 subjects with a positive urinary glucose test among the hyper-

Table III. *Results of laboratory investigations at the time of follow-up in the three groups of patients with previous toxaemia of pregnancy: I normotensives, II untreated hypertensives, and III treated hypertensives (mean±S.D.)*

Groups	*n*	Blood				Serum				
		Haemoglobin (g/l)	Hematocrit (%)	ESR (mm/h)	Bicarbonate (mmol/l)	Na (mmol/l)	K (mmol/l)	Ca (mmol/l)	Urate (μmol/l)	Creatinine (μmol/l)
I	71	132.3±10.3	39.5±2.6	11.3± 8.1	23.8±1.5	140.9±2.3	3.98±0.32	2.44±0.10	183.6±57.7	70.6±12.6
II	17	136.1±6.7	39.9±1.8	15.7±10.2	23.6±1.3	140.7±1.7	3.89±0.24	2.45±0.08	196.7±42.8	65.7± 7.6
III	12	134.4±13.5	40.3±2.8	21.8±18.5	24.7±1.1	139.8±2.3	3.88±0.47	2.44±0.06	251.4±70.8	83.3±36.1

	In all
Blood	Hemoglobin
	Hematocrit
	Sedimentation rate
	Serum urate
	Serum creatinine
	Serum potassium
	Serum sodium
	Serum bicarbonate
	Serum calcium
Urine	Albustix
	Clinistix
	Sediment
	In hypertensives also
	Blood sugar
	Triglycerides (Fasting)
	Cholesterol

Fig. 1. The laboratory investigations performed at the follow-up examination.

tensives, as against one among the normotensives, who were almost three times as numerous. With regard to serum cholesterol, triglycerides and fasting blood sugar in the hypertensive women, no special trend was observed.

Hereditary aspects

In Table IV it can be seen that half (14/29) of the hypertensive women had known hypertension in their families. The corresponding proportion for the normotensives was less than one-third (23/71). This difference is not significant ($\chi^2=2.23$). In another comparison the occurrence of relatives with hypertension, myocardial infarction, cerebrovascular lesions and diabetes was 75% (53/71) in the normotensive group. However, these disorders were recorded 21 times in 17 untreated hypertensives and in 10 of the 12 treated hypertensives. Only 6 of the mothers and sisters of the 100 women with toxaemia had had toxaemia of pregnancy.

Urine			
Albustix (*n*)		Clinistix (*n*)	
Trace	Positive	Trace	Positive
4	6	1	–
1	2	–	–
2	1	1	2

Contraceptive pills

Of the 100 women re-examined, 46 had taken contraceptive pills after the pregnancy with toxaemia (Table V). Seven developed hypertension while 'on the pill', but 3 of these 7 remained hypertensive in spite of discontinuating the pill. Other reasons for discontinuation were much more frequent. Thus more than one-third of the women on the pill increased in weight to such a degree that they did not want to continue with the medication.

Predictability of developing hypertension

A comparison was made between the 29 women who developed hypertension within the period under study and the rest of the toxaemia material ('normotensive' group), at the time of the pertinent toxaemic pregnancy. As seen in Table VI, some differences were found. With regard to BP, the future HT group had a higher BP on admission than the normotensive women. Still more impressive is the difference in maternal weight in the two compared groups, the group with HT having a significantly higher average weight than the normotensive group ($p<0.01$). The same difference was also true for foetal weight ($p<0.05$).

A few points should be stressed concerning Table VII. There was a greater preponderance of primiparae over multiparae in the normotensive than in the HT group. A striking finding was that there was not a single case with eclampsia in the HT group. Finally, there was no difference in the symptoms recorded.

DISCUSSION

All series of women with toxaemia of pregnancy are afflicted with one disturbing factor—the heterogeneity of the material. Some authors are therefore more prone to discuss the hypertensive states of pregnancy than different subdivisions (9). However, the important task in the present study was to carry out a long follow-up of women with hypertension during pregnancy with regard to their BP situation. Only two-thirds of the original group of patients could be re-investigated. This is not surprising, as women of these child-bearing ages often move from place to place. This is especially true in Sweden today, with its rather marked instability of the labour market. It is important, however, to know whether this reduction of the original material could have influenced the results. Since

Table IV. *A review of diseases and/or death in parents, sisters and brothers of the toxaemic women (n=100), divided into groups according to their blood pressure (BP) at the time of follow-up*

HT=hypertension, MI=myocardial infarction, CVL=cerebrovascular lesion

BP groups	*n*	HT *n*	MI *n*	MI *n* dead	CVL *n*	CVL *n* dead	Diabetes[a] *n*	Toxaemia[b] *n*
Normotensives	71	23	13	6	5	3	12[c]	4
Hypertensives, untreated	17	10	4	4	4	3	3	1
Hypertensives, treated	12	4	3	3	1	1	2[d]	1

[a] All relatives with diabetes counted (all, except one, had maturity onset diabetes).
[b] Mother and/or sister.
[c] Five of them had more than one relative with diabetes.
[d] One of them had more than one relative with diabetes.

the remaining women could not be traced or had moved from the city, there is no reason why these non-participants should differ from the participants in the respects concerned. The situation is not similar to that seen in other health examination surveys where some of the people who are invited do not come to the examination (10). It is a well known fact that these latter individuals are not representative of the population as a whole.

We feel, therefore, that the conclusions drawn in the present study may be considered relevant for the total material of toxaemia of pregnancy according to the definitions used and presented in another communication (1).

The incidence of hypertension (29%) within a mean period of less than 10 years is high. It is difficult to find accurate numbers for comparison. However, one possibility is to use the mean age of the women at this re-examination and make a comparison with the prevalence figure for hypertension from the County health examination survey. In women of the age group 30–40 years ($n=1034$) this figure is 2.2%, using a cut-off limit of ≥105 mmHg in DBP (11). These figures must, however, be viewed against the different limits for diagnosing hypertension. On the other hand similar criteria should have been used for starting therapy in the County survey and in the women under study. These figures are 1.6% and 8%, respectively.

Taking into full account the difficulties encountered in defining the different hypertensive states of pregnancy, there is no doubt that the group of women we have studied comprises a high-risk population and should be under regular control after their toxaemic pregnancy.

There has been much discussion in the literature concerning the relationship between toxaemia of pregnancy and the subsequent development of hypertension. However, most studies have suggested that no such relationship exists. Thus, Chesley et al. (4) reported the same prevalence of hypertension 15 or more years after pregnancy

Table V. *Contraceptive pill intake previously (after the pertinent toxaemic pregnancy but not at follow-up) and at the time of follow-up in various blood pressure (BP) groups*

In case of discontinuation of the pill intake, the reason for this is given

BP groups	*n*	P pills taken after toxaemia	P pills taken at follow-up	Reason for discontinuation: Hypertension	Psychological reason[a]	Weight increase	Others
Normotensives	71	37	10	4	8	6	9[b]
Hypertensives, untreated	17	4	1	1[c]	1	1	1
Hypertensives, treated	12	5	1	2[c]	–	–	2

[a] Headaches, depression, moodiness.
[b] Thrombosis 1, pruritus 1, frightened 3, wanted spiral 1, unknown 3.
[c] Persistent hypertension in spite of discontinuation of contraceptive pill intake.

Table VI. *A comparison between some data at the time of parturition for the women who later developed hypertension (HT group) and data for the women of the total material who did not develop hypertension (normotensive group)*

		BP mmHg (mean±S.D.)		Weight kg (mean±S.D.)	
	n	On admission	Highest recorded at parturition	Maternal	Foetal
HT group	29	165.2±25.1/108.2±12.0	177.9±20.1/116.0±12.8	84.5±14.9	3.475±0.682
Normotensive group	121	155.3±21.2/101.6±11.6	176.3±22.0/118.1±16.0	73.8±14.8	3.099±0.770
		$p<0.05$ $p<0.02$	ns ns	$p<0.01$	$p<0.05$

among women who had had eclampsia as in an unselected control group of the same ages. However, they also found that the death rate was increased considerably in women whose eclampsia occurred after the first pregnancy.

In 594 women who had had toxaemia of pregnancy, Herrick & Tillman (12) found that 30% had hypertension at the end of one year of follow-up and 50% after 3 years. Results in the same direction have been presented by many authors (6, 13).

Chesley et al. (14) have reported the effect of pregnancy on patients with essential hypertension. These authors found a much higher incidence of toxaemia among previous hypertensives than in the population at large. It is therefore easy to understand that the results might be influenced by the fact that we so often lack pre-pregnancy BPs.

An interesting finding was the differences between those women in the toxaemia group who remained normotensives, and the future hypertensives. The women who developed manifest hypertension were heavier at the end of pregnancy, more often multipara than primipara when having the toxaemia, and gave birth to heavier infants. Whether the greater birth weight of the infants only reflects the fact that these hypertensive women more often were multiparas, or is an expression of some metabolic disturbance, is not known.

The future hypertensives also more frequently had a family history of hypertension, myocardial infarction, cerebrovascular disease and diabetes. This family trend, the higher age, and the greater maternal weight stress the possibility of another reason for the late hypertension than the original pre-eclampsia. The material is too small for any long-ranging conclusions. However, the possibility of a latent essential hypertension unmasked by pregnancy in the women who develop hypertension later must be borne in mind.

Contraceptive pills have often been discussed in connection with toxaemic women. Laragh et al. (15) and Woods (16) stated in the same year that contraceptive pills might be the reason for hypertension in some women. In the present series remarkably few women, less than 10%, selected as they were because of earlier toxaemia, had developed hypertension. Out of the re-examined normotensives who had taken contraceptive pills ($n=41$), 4 had developed hypertension which disappeared after discontinuation of the pill.

However, it is important to mention that in fact very few women continued for any length of time on the pill. Many women stopped the pill for various side-effects. It is possible that otherwise more women might have developed hypertension later. On the other hand, Clezy et al. (17) reported that

Table VII. *Some characteristics of the women with hypertension (HT group) at the follow-up examination compared with those of the normotensive group (see p. 99) at the time of the pertinent toxaemic pregnancy*

			Symptoms of toxaemia (%)			
	n	Primipara/ multipara (%)	Headache	Visual disturbances	Headache+ visual disturbances	Eclampsia
HT group	29	37	27	–	10	–
Normotensive group	121	65	29	4	4	9

the change in BP after oral contraceptives seems to come relatively early, after a few months.

In spite of a figure below 10% for hypertension induced by oral contraceptives in this series of toxaemia cases, the possibility of a pill-induced hypertension must be considered.

In conclusion, it is important that women who have had hypertension during pregnancy should be checked regularly. This seems to be of even greater importance when there is a family history of hypertension, diabetes or cardiovascular disease, or when the pregnant woman has had a high body weight and a heavy infant.

REFERENCES

1. Åberg, H., Karlsson, L. & Melander, S.: Studies on toxaemia of pregnancy with special reference to blood pressure. I. Incidence and some characteristic features of the mothers and infants. Uppsala J Med Sci *83:* 29, 1978.
2. Bryans, C. J. & Torpin, R.: A follow-up study of two-hundred and forty-three cases of eclampsia for an average of 12 years. Am J Obstet Gynecol *58:* 1054, 1949.
3. Tillman, A. J. B.: The effect of normal and toxaemic pregnancy on blood pressure. Am J Obstet Gynecol *70:* 589, 1955.
4. Chesley, L. C., Amito, J. E. & Cosgrove, R. A.: Long-term follow-up study of eclamptic women. Am J Obstet Gynecol *101:* 886, 1968.
5. Frithiof, J.: Health control of women with arterial hypertension during earlier pregnancy. Läkartidningen *73:* 225, 1976.
6. Gibson, G. B. & Platt, R.: Incidence of hypertension after pregnancy toxaemia. Br Med J *ii:* 159, 1959.
7. Thomson, A. M., Hytten, F. E. & Billewicz, W. Z.: The epidemiology of oedema during pregnancy. J Obstet Gynaecol Br Commonw *74:* 1, 1967.
8. Beilin, L. J., Redman, C. W. G. & Bonnar, J.: *In* Hypertension: Its Nature and Treatment, p. 99. Ciba, 1974.
9. Greenhill, J. P. & Freidman, E. A.: Hypertensive states of pregnancy. *In* Biological Principles and Modern Practice of Obstetrics, pp. 391–414. W. B. Saunders Company, Philadelphia, London, Toronto, 1974.
10. Tibblin, G.: A population study of 50 year old men. An analysis of the non-participation group. Acta Med Scand *178:* 453, 1965.
11. Hillerdal, O. & Irnell, L.: En praktiskt användbar form av allmän hälsoundersökning. Läkartidningen *66:* 3274, 1969.
12. Herrick, W. W. & Tillman, A. J. B.: Toxaemia of pregnancy. Its relation to cardiovascular and renal disease: clinical and necropsy observations with a long follow-up. Arch Int Med *55:* 643, 1935.
13. Epstein, F. H.: Late vascular effects of toxaemia of pregnancy. N Engl J Med *271:* 391, 1964.
14. Chesley, L. C., Annitto, J. E. & Jarvis, D. G.: A study of the interaction of pregnancy and hypertensive disease. Am J Obstet Gynecol *53:* 851, 1947.
15. Laragh, J. H., Sealey, J. E., Ledingham, J. G. G. & Newton, M. A.: Oral contraceptives. Renin, aldosterone, and high blood pressure. JAMA *201:* 918, 1967.
16. Woods, J. W.: Oral contraceptives and hypertension. Lancet *ii:* 653, 1967.
17. Clezy, T. M., Foy, B. N., Hodge, R. L. & Lumbers, E. R.: Oral contraceptives and hypertension. An epidemiological survey. Br Heart J *34:* 1238, 1972.

Received July 18, 1977

Address for reprints:

Hans Åberg, M.D.
Department of Internal Medicine
University Hospital
S-750 14 Uppsala 14
Sweden