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TREATMENT OF HYPERTENSION IN PREGNANCY WITH β-ADRENOCEPTOR ANTAGONISTS

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Introduction

This report describes results obtained in an on-going study carried out by a multidiciplinary team of nephrologists and gynaeco-obstetricians to investigate the use of β-adrenoceptor antagonists for the treatment of hypertension during pregnancy. A preliminary report of the results has already been published (Dubois & Petitcolas, 1978). The results included here are based on 121 patients (125 pregnancies) who were treated with β-adrenoceptor antagonists during pregnancy, pindolol was used in 38 cases, atenolol in 31 and acebutolol in 56.

Methods

Monitoring of clinical status and laboratory tests were perfomed on a monthly basis once the diagnosis of hypertension had been confirmed.

Monitoring by the nephrologists included body weight, blood pressure levels in the recumbent and then the upright position, heart rate and laboratory values (plasma uric acid and creatinine levels, 24 h urinary protein concentration, and when necessary uroculture analysis). Obstetric surveillance included the monitoring of foetal growth with an ultrasonographic investigation at each consultation.

Cardiotachymetric tracings were obtained prior to labour. Amnioscopy was performed at the onset of labour and during delivery. Continuous cardiotocography was systematically performed throughout labour and delivery. Status of the neonate at birth was assessed by the Apgar score and in many cases a blood sample was taken from the umbilical cord for plasma glucose determination.

Patients

The study population of the pindolol group (38 cases) aged 20 to 44 years. It is beyond the scope of this paper to give a detailed history of patients. Nevertheless, two factors of patient history merit emphasis as they underline the high risk nature of pregnancies in this series. Table 1 summarizes the history of hypertension in our patients for the three groups (acebutolol – pindolol – atenolol).

Seventy patients or 56% displayed a history of hypertension and in previous pregnancies of these women, there were 25 deaths *in utero* and 5 acute complications at delivery (Table 2).

Administration of a β-adrenoceptor blocking drug was considered when blood pressure levels reached 140/80 mm/Hg (Gallery & Hungor, 1979).

Results

β-adrenoceptor blockers were administered to a total of 121 patients with hypertension during 125 pregnancies.

The pindolol group included 38 patients. One received the drug throughout the entire course of pregnancy, in 6 treatment commenced before the sixth week, in 20 between the 14th and 26th week, in 10 between the 26th and 34th week and in one after the 34th week. In most patients the initial daily dose of pindolol (5 mg) sufficed while in 7/38 cases either an increase in the dose of pindolol or addition of a second antihypertensive agent was considered necessary.

The atenolol group included 31 patients. Four women received the drug throughout the pregnancy.

Table 1 History of hypertension

Drug	*Number of cases*	*Prior to pregnancy*	*Recurrent with pregnancy*	*Permanent after onset of pregnancy*	*Total*	*%*
Acebutolol	56	15	8	3	26	46.4
Pindolol	38	13	11	1	25	65.8
Atenolol	31	11	2	6	19	61.3
Total	125	39	21	10	70	56

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For 1 patient, treatment commenced before the 12th week. In 10 cases treatment began between the 12th and 24th week, in 8 cases between the 24th and 32nd week and in 8 cases after the 32nd week. In 27 cases, atenolol was used as monotherapy at doses of 100 or 200 mg/day.

In 4 cases, we had to use other antihypertensive drugs, mainly dihydralazine.

The acebutolol group included 56 patients. Treatment commenced before pregnancy in 3 cases.

In 3 cases treatment began before the 12th week, in 11 cases between the 12th and 24th week, in 15 cases between the 24th and the 32nd week. In 24 cases drug was given after the 32nd week. The daily doses ranged from 200 mg to 600 mg/day.

In 4 cases acebutolol was given together with dihydralazine.

Maternal blood pressure control was good and a satisfactory response was obtained in over 95% of the cases. No statistically significant differences were apparent between the responses to the different antagonists. Tolerance was excellent and in no case was interruption of treatment necessary.

Birth weight Table 3 shows the mean and range of birth weights after treatment with pindolol compared with the other two groups treated with acebutolol and atenolol.

Apgar scores Table 4 summarizes the overall Apgar scores in our series of 125 cases. We did not notice any difference between the three groups with only two children displaying a score under 10 at the tenth minute in the pindolol group.

Resuscitation at birth was rare except in one hypotrophic child born prematurely at 35 weeks. Bradycardia or hypoglycaemia was not a problem in our series even in the children sent to a neonatal intensive care unit. On the other hand, the blood pressure of neonates was not controlled (Dumez *et al.*, 1981).

Malformation Four children in our series of 125 had miscellaneous malformations (3.2%). In fact in three of the four cases, treatment with the β-adrenoceptor blocker was started after the 24th week of pregnancy

Table 2 Complications during previous pregnancies of the same group of women

	Deaths in utero					*Premature*
	Second quarter	*Third quarter*	*Deaths at birth*	*Pre-eclampsia*	*Eclampsia*	*Separation of normal placenta*
Future acebutolol group	2	4	1	1	0	1
Future pindolol group	7	5	0	0	1	1
Future atenolol group	3	3	0	0	0	1
Total 155 pregnancies	12	12	1	1	1	3
		25 deaths				

Table 3 Birth weight

	< 2500 g Number of cases	*2500–2800 g Number of cases*	*> 2800 g Number of cases*	*Mean (g)*	*Range (g)*
Acebutolol	7	5	44 (78.5%)	3160	1680–4040
Pindolol	3	6	29 (76.3%)	3375	1415–5240
Atenolol	10	4	17 (54.8%)	2745	1000–3900
Total (125 infants)	20	15	90 (71%)		

Table 4 Agpar scores

		< 8 at 5 min *Number of cases*	< 10 at 10 min *Number of cases*
Acebutolol	56 cases	7	2
Pindolol	38 cases	10	2
Atenolol	31 cases	3	3
Total	125 cases	20	7

and could thus not be considered responsible for any malformation. The only case of malformation noticed was a vesico-ureteral reflux in a second full term pregnancy after pindolol in a mother with asymetrical segmented renal hypoplasia. In summary, no teratogenic effect was seen in this study.

Discussion

Hypertension in the course of pregnancy is a particularly serious event (Gallery *et al.*, 1979). Numerous subsequent complications have been attributed to HT, including repeated abortions, intrauterine foetal death, prematurity and foetal growth retardation (Friedmen, 1976). Retroplacental haematoma is more frequently encountered in pregnancies complicated by HT, although the role of HT as a causative factor in such cases is currently open to question. Accordingly, appropriate measures must be taken to reduce high blood pressure levels during pregnancy, with however the attending risk of disturbed foetal development and possible side effects of the drugs used in this respect. Until recently, α-methyldopa (Redman *et al.*, 1976), hydralazine or clonidine have been preferred by obstetricians and internists in the management of hypertensive pregnancies. Use of these drugs over many years has confirmed their good tolerance in this indication.

Given the widespread use of β-adrenoceptor blockers to treat HT in young adults, it is not surprising that many women begin their pregnancy while taking these drugs (Gladstone *et al.*, 1975). In such cases, β-adrenoceptor blocker therapy maintained in the course of pregnancy has led to stable normal blood pressure levels, consistent foetal growth and term delivery of normal babies. Based on these preliminary findings we decided to use β-adrenoceptor blockers to treat cases of hypertensive pregnancy (Dubois & Petitcolas, 1978).

However, on a theoretical basis many objections have been raised as to the appropriateness of β-adrenoceptor blocker therapy in these conditions. Untoward uterine contractions have been suggested as a primary inconvenience of these drugs (Reed *et al.*, 1974). The presence of adrenoceptors in the uterus led to the fear that β-adrenoceptor blockade would induce abortion or premature labour. However, animal studies by Wansbrough *et al.* (1969) have shown that this effect of β-adrenoceptor blockade does not occur in the gravid uterus. The results of our study in 125 pregnancies confirm the data reported by Wansbrough *et al.* (1969).

For obvious reasons of medical ethics our study did not include a placebo control group. Furthermore, the three different drugs used were not randomly assigned. However, the three treatment groups were relatively homogeneous, thus allowing certain conclusions to be drawn. Although the data were not strictly identical in all cases, blood pressure control was not significantly different when the three treatment groups were compared. Conversely, a marked difference was found regarding birth weight. In this respect, birth weight was very similar after acebutolol and pindolol treatment whereas the mean birth weight of the babies born to mothers after atenolol therapy was significantly lower. Despite these findings, the foetal prognosis was not worse in the atenolol group with respect to Apgar scores or the necessity of neonatal intensive care. The finding that bradycardia was more pronounced in the mothers on atenolol therapy allows us to postulate that an excessively reduced maternal heart rate may have led to decreased vascular supply to the placenta. This hypothesis merits confirmation by systematic determination of placental blood flow during pregnancy. Accordingly, our current therapeutic attitude is to avoid the use of atenolol in the initial phase of pregnancy and to give acebutolol or pindolol.

The improvement of foetal prognosis in these high risk pregnancies is such (1 intrauterine death and 2 miscarriages in 125 pregnancies *v* 25 foetal deaths in 155 hypertensive pregnancies without β-adrenoceptor blockade) that β-adrenoceptor blocker therapy should be largely recommended under the condition that strict monitoring, especially echography, be performed.

Since maternal and foetal blood levels of β-adrenoceptor blockers are similar, the occurrence of foetal malformations related to maternal drug therapy merits discussion. The single intrauterine death in our series was that of a hypotrophic, but otherwise normally constituted foetus. As discussed above, among the four neonates presenting a malformation, only one case (vesico-ureteral reflex) was born to a mother who had received β-adrenoceptor blocker treatment during the very early stages of embryogenesis. In this case, the eventual responsibility of the maternal drug ingestion remains to be elucidated.

In conclusion, the results of this series of 125 hypertensive pregnancies treated with β-adrenoceptor blockers underline the following points:
1 β-adrenoceptor blockade allowed good maternal blood pressure control, 95% of the patients displaying less than 140/90 mmHg at the time of delivery (Redman *et al.*, 1976);
2 the tolerance of β-adrenoceptor blocker therapy was excellent (no interuption due to side effects);
3 foetal blockade had very little or no effect on the course of foetal growth.

However, it must be emphasized that every high risk pregnancy, including those complicated by hypertension, requires rigorous clinical echographic and laboratory monitoring by a medical team trained in this field.

Birth of children in these conditions should be conducted in a specialized maternity unit in order to achieve additional improvement of the maternal and foetal prognosis in hypertensive pregnancies treated with β-adrenoceptor blocking drugs.

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