First year of life after the use of atenolol in pregnancy associated hypertension

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SUMMARY We describe the results of a prospective study in which 120 women who developed hypertension in the last trimester of pregnancy were randomly allocated in double blind manner to atenolol or placebo. The mean duration of treatment was five weeks. The only difference between groups during the neonatal period was in respiratory distress syndrome, mainly related to spontaneous premature labour, which occurred in six placebo group babies but in none from the atenolol group. Fifty five children from each group have been followed to 1 year of age. All in the atenolol group are developing normally but one child from the placebo group is brain damaged. These findings do not suggest any short or medium term paediatric complications after the use of beta blockers in pregnancy.

Beta adrenoceptor antagonists have become widely accepted in general medical practice. Their introduction to obstetrics, however, has been accompanied by concern about a wide range of adverse effects largely affecting the fetus and neonate. These drugs have been implicated in the production of growth retardation of the fetus and have had ascribed to them a considerable range of neonatal problems including hypoglycaemia, hyperbilirubinaemia, bradycardia, respiratory depression, and death.2-8 The precise relation between these complications and drug administration was difficult to evaluate because of the anecdotal or retrospective nature of observations in patients who had major disorders of pregnancy.9 We have recently completed a placebo-controlled evaluation of the beta blocker atenolol in women with pregnancy associated hypertension10 and describe here the findings of paediatric follow up to 1 year of age.

Methods

One hundred and twenty women who developed a blood pressure of between 140/90 and 170/110 mmHg on two occasions 24 hours apart during the last trimester of pregnancy were randomly allocated in double blind manner to treatment with atenolol or placebo. The maximum dose of atenolol was 200 mg per day and the average duration of treatment was five weeks. No other antihypertensive medication was prescribed. All babies were admitted to the special care nursery where they had a detailed clinical examination including measurement of weight, length, occipitofrontal circumference, triceps and subscapular skinfold thickness, together with assessment of gestation by the Dubowitz method.11 The results of biochemical, haemodynamic, and pharmacokinetic measurements made during this period have previously been reported.10,12 Infants were subsequently seen at 3, 8, and 12 months of age when a Denver development screening test was performed and growth indices were recorded. At all stages of assessment the investigator performing the evaluation was unaware of treatment category.

Data are presented as mean (standard deviation) and analysis is by intention to treat. Continuous variables recorded in the neonatal assessment were compared by unpaired two sided t test and in the subsequent paediatric follow up by repeated measures analysis of variance. Categorical variables were compared by analysis of contingency (X²).

Results

There were no major congenital malformations in either group. Two babies from the placebo group had abnormalities on clinical examination at birth: one congenital dislocation of the hip and one patent ductus arteriosus. Four babies had abnormal examinations in the atenolol group: two had congenital dislocation of the hip and two minor glandular
hypospadias. In all cases the abnormalities resolved without medical intervention. Clinical indices at
birth are shown in Table 1.
Respiratory distress syndrome requiring ventilation
occurred in six babies from the placebo group
but in none from the atenolol group (P<0.05). The
reasons for delivery in these six babies were
spontaneous premature labour (4), caesarean section
for fulminating pre-eclampsia (1), and caesarean
section because of spontaneous premature labour
and bad obstetric history (1).
Fifty five babies from each group attended for
follow up examination through to 1 year of age.
Clinical examination was normal by 12 months in all
children who had defects identified at birth. Three
children from the placebo group had less than a
normal score on the Denver development screening
test. Two were graded as 'doubtful' at 8 months but
were classified 'normal' at both 3 and 12 months.
One of these was born at term but was below the
10th centile for weight and length and had bradycar-
dia for the first 12 hours of life. The second was born
at 39 weeks' gestation after induction of labour
because of maternal hypertension, and showed signs
of cerebral irritation for two days. The third child
was definitely abnormal at all three follow up visits.
She was born by caesarean section after sponta-
nous premature labour at 35 weeks, was below
the fifth centile for weight, length, occipitofrontal
circumference, and was slow to establish respira-
tion, and was nursed in oxygen for 48 hours. Clinical
evaluation at 12 months of age confirmed the
presence of a spastic quadripleasia with a severe
pseudo-bulbar palsy. All children in the atenolol
group were graded as normal on Denver develop-
ment screening test at all stages of follow up. The
remaining clinical indices at 3, 8, and 12 months of
age are shown in Table 2. There were no further
differences between the groups.

### Discussion

Maternal morbidity and mortality now represent
rare complications of hypertensive pregnancy and
therapeutic intervention is directed largely at the
fetus. There has been increasing use of anti-
hypertensive drugs in all forms of pregnancy hyper-
tension during recent years. Among the various
drugs used, methyldopa has been shown to be
effective in lowering blood pressure but safe for
the fetus but maternal side effects necessitated
stopping treatment in 14.5% of women. Beta
blockers have been shown to have similar efficacy
to methyldopa in lowering blood pressure but have
been held responsible for a wide range of fetal and
neonatal adverse effects. Since beta blockers are
used only in pregnancies having a major complica-
tion, usually severe hypertension, it can be very
difficult to differentiate drug effects on the fetus
from those caused by the disease. Such difficulties
are overcome by a placebo controlled and double
blind design as used in this study.

We have previously described the absence of
adverse biochemical effects of atenolol in the
neonatal period. The further data presented here
provide no support for a harmful effect of beta
blockers on the fetus or neonate, with both acute
and long term clinical problems being concentrated
in the placebo group. The largest single aetiologi-
cal factor in morbidity was spontaneous premature
labour, accounting directly or indirectly for five
cases of severe respiratory distress syndrome and
the one case of chronic disability. It seems unlikely
that a beta-1 adrenoceptor antagonist such as
atenolol would directly influence uterine motility,
and the most reasonable inference to draw is that

### Table 1  Clinical indices at birth (values mean (SD))

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<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Atenolol group</th>
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</thead>
<tbody>
<tr>
<td><strong>Length (cm)</strong></td>
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<tr>
<td>3</td>
<td>48.6 (3.0)</td>
<td>48.6 (2.7)</td>
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<td>8</td>
<td>68.9 (2.6)</td>
<td>68.7 (2.1)</td>
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<tr>
<td>12</td>
<td>72.4 (2.4)</td>
<td>72.7 (2.3)</td>
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<tr>
<td><strong>Occipitofrontal circumference (cm)</strong></td>
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<tr>
<td>3</td>
<td>40.8 (1.3)</td>
<td>40.5 (1.2)</td>
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<td>8</td>
<td>45.0 (1.4)</td>
<td>44.6 (1.2)</td>
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<tr>
<td>12</td>
<td>46.8 (1.2)</td>
<td>46.6 (1.4)</td>
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<tr>
<td><strong>Triceps thickness (mm)</strong></td>
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<td>3</td>
<td>6.8 (1.2)</td>
<td>6.9 (1.2)</td>
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<tr>
<td>12</td>
<td>8.5 (1.3)</td>
<td>8.6 (1.2)</td>
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<tr>
<td><strong>Subscapular thickness (mm)</strong></td>
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### Table 2  Clinical indices at 3, 8, and 12 months of age (values mean (SD))

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<tr>
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<tr>
<td><strong>Weight (kg)</strong></td>
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<tr>
<td>3</td>
<td>5.59 (0.76)</td>
<td>5.72 (0.76)</td>
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<td>8</td>
<td>8.07 (0.89)</td>
<td>8.37 (0.86)</td>
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<tr>
<td>12</td>
<td>9.58 (0.97)</td>
<td>9.64 (1.19)</td>
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<tr>
<td><strong>Length (cm)</strong></td>
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<tr>
<td>3</td>
<td>60.2 (3.0)</td>
<td>59.8 (2.6)</td>
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<td>8</td>
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<td>66.7 (2.1)</td>
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poor blood pressure control was responsible for the premature labour.

These findings relate to a consecutively recruited series of patients attending the obstetric unit of a district general hospital. They serve to emphasise the importance of good blood pressure control in relation to pregnancy outcome. These data, however, do not suggest that beta blockers used during the last trimester are likely to be associated with major fetal, neonatal or paediatric adverse effects.

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References

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