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LETTER TO THE EDITORS

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Non-lethal fetal toxicity of the angiotensin receptor blocker candesartan

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Angiotensin receptor blockers are potent antihypertensive drugs with very few side effects [1, 2]. No association has been documented between use of angiotensin receptor blockers during the first trimester of gestation and congenital defects. However, there are several reports of malformations and physiologic disturbances, mostly with lethal outcome, in infants exposed to these drugs during the second and third trimesters, as recently reviewed [3, 4]. We report the adverse long-term sequelae noted in an infant following maternal treatment with an angiotensin receptor blocker.

A 39-year old woman on treatment with candesartan cilexetil 16 mg once a day [5] for mild essential hypertension became pregnant but the drug was not discontinued. At 31 weeks a male boy weighing 1.65 kg was delivered by cesarian section. The physical examination disclosed climb contractures, skull hypoplasia with microcephaly (head circumference 0.265 m) and moderately underdeveloped calvarial bones. The child developed immediate respiratory distress (treated with oxygen, exogenous surfactant and mechanical respiratory support), arterial hypotension (treated with dopamine and epinephrine), and moderate oliguria (creatinine up to 281 μmol/l, urea up to 15.6 mmol/l and a pathologically increased urinary protein to creatinine ratio of 739 mg/mmol; upper reference 50). His conditions improved during the second week of postnatal life. However, a tendency towards arterial hypertension (mean blood pressure 75–80 mm Hg; upper reference 68) was noted, requiring treatment with the calcium channel blocker amlodipine once a day during 6 weeks. Routine chromosome analysis revealed a normal male karyotype.

The boy is currently 34 months of age. Body weight is 11.1 kg (−2.8 SDS), length 0.901 m (−1.5 SDS), head circumference 0.481 m (−2 SDS) and blood pressure slightly elevated (approximately 110/70 mm Hg; upper reference 106/66) and the calvarial bones normally developed. His cognitive and especially his linguistic development are moderately retarded. The physical examination is otherwise normal. Plasma creatinine (36 μmol/l) and urea (6.0 mmol/l) are normal. The urinary protein to creatinine ratio is slightly increased (29 mg/mmol, upper reference 20). Renal ultrasound study demonstrates rather small hyperechogenic kidneys and loss of corticomedullary differentiation.

In conclusion during pregnancy the use of drugs that block the renin–angiotensin–aldosterone system, namely angiotensin receptor blockers [3, 4] and converting enzyme inhibitors [4, 6], is strongly cautioned against. Infants surviving the exposition to these agents during the second and third trimesters tend to a chronic kidney disease and a developmental delay. A corresponding long-term follow up is warranted.

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