Angiotensin receptor blockade in diabetic women of childbearing potential: an acceptable risk?

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
DIRECT	Diabetic RETinopathy Candesartan Trials
RAS	Renin–angiotensin system

Around 10% of all pregnancies are complicated by hypertension, which represents the most common medical disorder of pregnancy. As opposed to pregnancy-induced hypertensive disorders, such as pre-eclampsia/eclampsia and gestational hypertension, chronic hypertension precedes pregnancy (most commonly, essential hypertension) or develops before the 20th week of gestation, complicating approximately 3% of pregnancies [1]. Although associated with an increased risk of superimposed pre-eclampsia, pregnancies in otherwise healthy women with uncomplicated mild essential hypertension generally have a very good prognosis. In the absence of evidence to support a role for specific blood pressure targets or specific antihypertensive drugs to reduce the risk of pre-eclampsia, the goal of antihypertensive treatment in hypertensive women of child-

bearing potential is not different from that in other hypertensive patients and is aimed at reducing overall cardiovascular risk. In fertile women, however, the choice of antihypertensive medication is primarily dictated by the desire to minimise adverse fetal effects, particularly so in women actively planning a pregnancy. To this end, inhibitors of the renin–angiotensin system (RAS) are generally contraindicated because of their clearly established teratogenic potential during the second and third trimester [2]. The teratogenic potential of these inhibitors in early pregnancy is less well described and, paired with evidence supporting a specific therapeutic effect of RAS inhibition in clinical conditions such as diabetic nephropathy [3], raises the question of whether the use of RAS inhibitors may be justified in specific patient groups if pregnancy is not actively sought.

In this context, in this issue of *Diabetologia*, Porta et al. report on pregnancy outcomes in normotensive women with type 1 diabetes who were exposed to the angiotensin receptor blocker candesartan or placebo as part of the Diabetic RETinopathy Candesartan Trials (DIRECT) [4]. Over a 4 year period a total of 208 pregnancies occurred in 178 women, 86 of whom were in the candesartan arm. Although it was not possible to determine the exact number of patients taking study medication (either placebo or candesartan) during the first trimester, more than half of the patients were likely to have been exposed. Importantly, study medication was discontinued in all patients before the end of the first trimester, thereby excluding the possibility that any teratogenic effects that may have occurred in this study were related to exposure during the second or third trimester. Compared with women exposed to placebo, those who received candesartan had similar delivery outcomes

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(full-term, premature, miscarriage rates and others). Similarly, no difference was observed between placebo and candesartan treatment with regard to fetal outcomes, including the number of stillbirths and ‘sick babies’. The only congenital malformation, in the form of a ventricular septal defect, occurred in the placebo group. From their analysis the authors concluded that the risk of fetal consequences might not be high if exposure to candesartan is restricted to the first trimester.

Whilst it was not the primary focus of the study, the investigators are to be commended for having included pregnancy report and outcome forms in the DIRECT trial series, allowing relatively precise assessments of the time of conception, exposure to study medication and assessment of pregnancy outcomes and child status. In the absence of prospective controlled clinical trials aimed primarily at assessing the fetal risk associated with various antihypertensive treatment regimens, data derived from clinical trials such as DIRECT add relevant and practical information.

Several aspects have to be taken into account when interpreting the study results. These include (1) the relatively small total number of women who were actually exposed to candesartan, as appropriately acknowledged by the authors; (2) the fact that both investigators and participants were made aware of the appropriate action (e.g. withdrawal of medication) if menstrual period did not occur and pregnancy was anticipated, which is perhaps less likely to occur outside of a clinical trial environment, thereby potentially increasing the risk of exposure to the drug late into or beyond the first trimester; (3) the exclusion of type 1 diabetic patients with microalbuminuria or diabetic nephropathy, who have a different risk profile and in whom intensified antihypertensive therapy may be of particular relevance to reduce adverse pregnancy outcomes [5]; and (4) that the analysis was restricted to women with type 1 diabetes and excellent blood pressure control, which is different from the scenario typically encountered in non-diabetic women of childbearing potential, in whom angiotensin receptor blockers are primarily prescribed to lower elevated blood pressure, which is itself associated with increased fetal risk [6].

The therapeutic dilemma is particularly evident in women with type 1 diabetes, given the evidence from previous trials with regard to the specific beneficial effects of RAS inhibition on diabetes complications such as diabetic nephropathy. Accordingly, the authors raise the question of whether young diabetic women with hypertension or early diabetic nephropathy should be denied treatment with angiotensin receptor blockers solely on the grounds of potential fetal exposure in case of pregnancy.

Irrespective of the potential benefits of such treatment for the patient’s own health, it is desirable to enter pregnancy in a state of optimal health to ensure the highest

likelihood of a positive outcome for both mother and child. This includes more general aspects such as a healthy lifestyle (not smoking, physical activity, maintaining a normal weight, etc.) but also appropriate management of pre-existing risk factors, common ones being hypertension and diabetes. Although it is desirable to avoid exposure to most drugs, at least during specific times in pregnancy, this has to be balanced against the need to achieve adequate glycaemic and blood pressure control, highlighting the importance of pregnancy planning and careful counselling before and during pregnancy. Indeed, both diabetes [7] and hypertension [6] have been associated with an increased teratogenic risk, making it even more difficult to ascertain the extent to which reported adverse fetal outcomes are causally associated with the use of drugs, at least in the first trimester, and particularly so for inhibitors of the RAS.

Achieving adequate blood pressure control is one of the most important strategies for reducing or minimising overall cardiovascular risk. This obviously includes women of childbearing potential, with additional implications for pregnancy outcomes. Whilst all major classes of antihypertensive drugs effectively reduce blood pressure, inhibitors of the renin–angiotensin system are often used as a first-line treatment because of their favourable side effect profile and excellent data with regard to patient adherence and persistence, which might be of particular relevance in younger patients. Aside from this, there is no compelling evidence for their specific use in uncomplicated hypertension, making drugs with a negligible teratogenic potential, such as methyldopa, the preferred choice if pregnancy is planned or has occurred [1, 5]. In this scenario, the use of RAS inhibitors can hardly be justified and should be avoided.

The situation may be different if comorbidities exist for which there is compelling evidence for the specific use of inhibitors of the RAS in women of childbearing potential, such as those with diabetic nephropathy [3, 5]. If no pregnancy is planned and adequate advice and monitoring is provided to ensure timely cessation in case of pregnancy, the use of RAS inhibitors may appear to be reasonably safe [4]. Indeed, another very recent study reporting the outcomes of 91 pregnancies (including 24 women with type 2 diabetes) with exposure to either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers in early pregnancy also failed to detect an excess risk of congenital abnormalities [8]. However, it is of concern that one of the largest cohort studies, which included more than 29,000 infants in the USA, reported major congenital malformations in 7.1% of infants exposed to ACEIs during the first trimester, as opposed to a rate of only 2.0% in infants exposed to antihypertensive drugs other than ACEIs and 2.6% in infants not exposed to antihypertensive drugs

at all [9]. In this regard it also remains elusive as to whether withholding RAS inhibition for the limited period of time during which a pregnancy is actively planned and carried out will alter the maternal outcome with regard to the progression of diabetic nephropathy.

Ultimately, it will be up to the treating physicians to make the decision of whether or not treatment with RAS inhibitors should be commenced in women of childbearing potential. This decision will have to be based on the evidence supporting their use in a given clinical scenario (e.g. diabetic nephropathy) after thorough consideration of the patient's personal circumstances and the possibility that a potential pregnancy may go undetected far into the first trimester or beyond. The current report by Porta et al. [4], despite its limitations, perhaps provides some reassurance that the fetal risk might not be excessively high if RAS inhibition is stopped at least upon early detection of pregnancy. Based on the currently available data, if pregnancy is actively planned the use of RAS inhibitors does not appear to be justified under any circumstances.

Perhaps merely a Panglossian view, recent advances in non-pharmacological strategies to control blood pressure by means of radiofrequency ablation of renal sympathetic nerves, which has been proven to safely and effectively reduce blood pressure in hypertensive patients who are resistant to conventional drug treatment [10], may offer an attractive novel approach to the therapeutic dilemma of hypertension in women of childbearing potential. Of note, increased efferent renal sympathetic nerve activity is of specific relevance in the pathogenesis of hypertension in the young [11], providing reasonable pathophysiological grounds for such an approach.

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