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Statins are detrimental to human placental development and function; use of statins during early pregnancy is inadvisable

Dear Editor:

The rapid rise in obesity, metabolic syndrome and type 2 diabetes is one of the major healthcare problems of the Western world. Affected individuals are often treated with statins (HMG CoA reductase inhibitors) to reduce circulating cholesterol levels and the risk of developing cardiovascular disease [1]; given the evolving demographic profile of these conditions, such drugs are increasingly prescribed to women of reproductive age.

Cholesterol is essential for normal foetal development and therefore the use of lipid-lowering drugs, including statins, is contraindicated during pregnancy. However, a recent study suggests that the detrimental effects of statins may be restricted to the more lipophilic compounds as there have been no reports of foetal congenital abnormalities in association with the relatively hydrophilic statins, for example pravastatin [2].

The actions of statins are not limited to modulation of cholesterol levels, as inhibition of HMG CoA reductase also interferes with the production of dolichol and isoprenoids; dolichol is involved in the N-linked glycosylation of membrane-targeted glycoproteins, whereas isoprenoids are necessary for the optimal function of numerous intracellular signalling molecules. Previous studies indicate that the insulin-like growth factor (IGF) system – a key system in the control of foetal growth – is particularly sensitive to such modulation by statins [3].

IGFs mediate their effect on foetal growth, at least in part, by promoting normal placental development; thus maternal IGF can enhance the growth, survival and differentiation of the placental trophoblast cell layer [4], which is responsible for maintaining the nutrient/waste exchange barrier between mother and foetus. We therefore investigated if statins affect IGF action in the human placenta, using pravastatin as an example of a hydrophilic statin that is potentially compatible with use in pregnancy and the potent lipohilic compound, cerivastatin, which is no longer clinically available but is known to abrogate IGF effects in other cell models.

We have used an explant model of early pregnancy placental villous tissue that can be maintained in a viable state for several days [4], representing a much more physiologically relevant system for toxicology studies than cell culture. In particular, cell proliferation is maintained, the vectorial relationship between maternal and foetal blood compartments is preserved and test compounds may be supplied to the maternal surface of the placenta to faithfully recapitulate *in vivo* exposure. As expected, both IGF-I and IGF-II stimulated the proliferation of cytotrophoblast within placental explants (Fig. 1). Cerivastatin inhibited the proliferative response to IGF and, importantly, the stimulatory effect of both IGF-I and -II was also abolished by pravastatin ($P < 0.05$; Fig. 1).

These data clearly show that in placenta, the effect of statins is not dependent on their lipophilicity, perhaps because placenta expresses

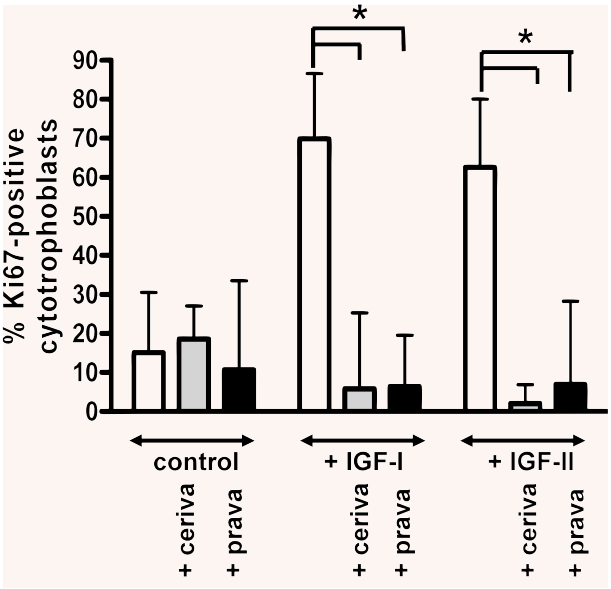

Fig. 1 Cerivastatin and pravastatin abolish IGF-stimulated cytotrophoblast proliferation. Explants of human first trimester placenta (obtained with informed consent and in accordance with Local Ethics Committee approval) were incubated in the absence or presence of cerivastatin (+ ceriva; 50 nM) or pravastatin (+ prava; 250 nM) for 24 hrs before the addition of vehicle, IGF-I (10 nM) or IGF-II (10 nM) and culture for a further 24 hrs. Proliferation was assessed using immunohistochemistry to determine Ki67-positive cytotrophoblasts as a percentage of total cytotrophoblasts. Data were analysed by using the Kruskal–Wallis test and are presented as median ± interquartile of three independent experiments performed in triplicate. *<0.05 versus IGF alone.

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organic anion-transporting polypeptides (OATPs) [5], which are known to enhance active uptake of statins. Whilst hydrophilic statins have not been reported to increase the incidence of foetal malformations, our data suggest that they will have a detrimental effect on placental growth; this is highly likely to result in poor pregnancy outcome, as reduced placental size is associated with impaired nutrient uptake, intra-uterine growth restriction and the accompanying long-term health sequalae. Healthcare professionals should continue to advise women to avoid the use of any type of statin once they plan to start a family or when a pregnancy is suspected or confirmed.

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