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 lipophilic 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

Letter to the Editor

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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 sequelae. 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.

Acknowledgements

KF, JMG, JDA and MW conceived the idea for the study and designed the experiments. KF and LH conducted the experimental work and along with MW, analysed the data. MW and LH prepared the first draft of the paper, which was critically revised by all other authors. All authors had full access to all of the data in the study and all take responsibility for the integrity of the data and the accuracy of the data analysis. KF is supported by a Biotechnology and Biological Sciences Research Council project grant awarded to JDA and MW. The authors gratefully acknowledge Astrazeneca Plc and Bayer Pharmaceuticals Plc for the generous gift of the HMG-CoA reductase inhibitors used in this study. JMG has received honoraria from Astrazeneca Plc and Bayer Pharmaceuticals Plc for presentations relating to the management of cholesterol levels in clinical practice.

Karen Forbes, Lucy M. Hurst,
John D. Aplin, Melissa Westwood
Maternal & Fetal Health Research Group,
University of Manchester, Manchester, UK
J. Martin Gibson
Genomic Epidemiology Research Group,
University of Manchester, Manchester, UK

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