solutions with a sodium concentration between 131 and 154 mmol/l should be administered to children [11]. We argue that the same standards should also be applicable to the neonate just prior to delivery.

We also support an upper limit of 8 mmol/l in the peripartum period [8], as recommended by Barrett *et al*. [12]. They observed less maternal harm and no difference in neonatal outcome when the upper limit was relaxed to 8 mmol/l. This strategy reduced the need for intrapartum glucose and i.v. insulin infusions and their associated complications. Additionally, as it is recognized that the use of an i.v. insulin infusion to obtain tight glycaemic control with a lower limit of 4 mmol/l is harmful, we suggest that the lower limit should be at least 5 mmol/l.

We are aware that the National Institute for Health Research has been asking whether it is actually feasible and ethical to recruit patients and centres to a trial in which parturients with diabetes will be randomized to either permissive or intensive maternal intrapartum glycaemic control [13].

In summary, as there is now overwhelming evidence that using i.v. insulin and dextrose whilst aiming for a capillary blood glucose target of 4–7 mmol/l is associated with harm [1–3,5–12], guidelines for the management of parturient patient with diabetes should now be urgently reviewed to minimize the risk of adverse outcomes. Furthermore, in order to mitigate the risk of maternal hypoglycaemia, we suggest that the use of i.v. insulin is only considered once the capillary blood glucose exceeds 8 mmol/l (rather than 7 mmol/l) and that the lowest acceptable capillary blood glucose whilst on i.v. insulin should be 5 mmol/l (rather than 4 mmol/l). In addition to reduce the risk of maternal and neonatal hyponatraemia, we argue that new guidance should explicitly state that only solutions with a sodium concentration between 131 and 154 mmol/l should be used to run alongside the i.v. insulin infusion.

N. Levy[1], A. Modi[1] and G. M. Hall[2]
[1]Consultant Anaesthesia, Department of Anaesthesia and Peri-operative Medicine, West Suffolk NHS Foundation Trust, Hardwick Lane, Bury St Edmunds, and [2]Emeritus Professor of Anaesthesia, Department of Anaesthesia and Intensive Care Medicine, St George's Hospital Medical School, London, UK

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Pioglitazone and bladder cancer: improving research methods

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In their *Letter to the Editor* [1], the authors asserted that biased and inconsistent studies were included in a meta-analysis by Ripamonti *et al*. [2] Let us clarify that in the cited paper [2] we showed heterogeneity measures, but no pooled estimate has been calculated for any effect measure, exactly for the reason that included studies were, for different reasons, biased or poorly conducted.

IIn the light of this premise, our systematic review showed how no conclusion on the association between pioglitazone

and bladder cancer can be posited, as most studies in this area are affected by different sources of bias, most notably time-related biases. This specific point seems to be ignored by the authors of the *Letter to the Editor* [1], who stated that it is not 'appropriate, as suggested by Ripamonti *et al*., to devote further resources to yet more research into a connection between pioglitazone and bladder cancer'. To justify their assertion, they referred to the results of the Insulin Resistance Intervention after Stroke (IRIS) study [3] and they also invoked more randomized controlled trials on the potential protective effect of pioglitazone on cardiovascular events. However, the IRIS trial was designed to investigate the effects of pioglitazone in people with insulin resistance. People diagnosed with diabetes at baseline were excluded from the trial, as well as people at risk or with a history of bladder cancer. In addition, incident bladder cancer was reported in 12 participants in the pioglitazone group and in eight participants in the placebo group (which, while statistically non-significant, was not exactly a null effect).

Randomized controlled trials like IRIS were mainly designed to assess efficacy, not safety, and certainly not to investigate outcomes such as cancer, which have long latencies. Only properly conducted pharmacoepidemiologic research can lead to a well-pondered answer on the evaluation of the association between pioglitazone and bladder cancer. The assessment of toxicity (especially cumulative exposure) and carcinogenesis might require long follow-up time windows that may not be covered by randomized controlled trials, being only captured by historical and ongoing information provided by automated pharmacoepidemiologic databases. Moreover, even the largest randomized controlled trials cannot attain the statistical power of population-based observational studies.

While pharmacoepidemiologic studies are essential to understand risk factors and pathogenic associations, they may be difficult to conduct, and are frequently exposed to intrinsic limitations as well as to different potential sources of bias. In our systemic review we showed some limitations of those studies, for instance, in terms of limited control of potential confounders such as co-morbidities and environmental factors. Science needs repeatability and replicability, and, especially in the field of diabetes pharmacoepidemiology, studies are characterized by a high degree of heterogeneity, hence only relying upon the conclusions of single studies may obfuscate the possibility of detecting consistent associations, and, in the very end, limit the progress of diabetes care.

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E. Ripamonti[1], L. Azoulay[2,3], M. Abrahamowicz[2,4], R. W. Platt[2,3] and S. Suissa[2,3]

[1]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet – A Medical University, Stockholm, [2]Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada, [3]Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, Montreal, Canada and [4]Centre for Clinical Epidemiology, Royal Victoria Hospital, Montreal, Canada

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