Diabetes

Diabetes therapy and bladder cancer risk

A UK population-based cohort study, published in the *BMJ*, concludes that pioglitazone is associated with an increased risk of bladder cancer in patients with type 2 diabetes.

Using data from the UK Clinical Practice Research Datalink, 145,806 patients newly treated with diabetes drugs between 1 January 2000 and 31 July 2013 were followed until the end of July 2014. The cohort was followed for a mean of 4.7 years and resulted in 689,616 person-years of follow-up. The main outcome measure was incident bladder cancer.

A total of 622 patients were diagnosed with bladder cancer during the study. Statistical modelling was used to estimate hazard ratios (HR) for bladder cancer with adjustment for a large number of confounding factors.

Compared with no thiazolidinedione use, pioglitazone was associated with an increased risk of bladder cancer: 121 vs 88.9 per 100,000 person-years; HR 1.63 (95% CI: 1.22-2.19).

A duration response relation was also seen ($P < 0.01$ for trend) with use of pioglitazone for more than two years associated with a raised risk of bladder cancer: HR 1.78 (95% CI: 1.21-2.64).

Rosiglitazone was not associated with a raised risk of bladder cancer: 86.2 vs 88.9 per 100,000 person-years; HR 1.1 (95% CI: 0.83-1.47). Similarly no duration response relation was seen.

The authors acknowledge that there may be sources of error from retrospective data analysis. Confounding factors such as family history, ethnicity, occupational exposure, diet and exercise may not be controlled for, and the quality of data input may vary. However, the clear difference between the two drugs of the same class suggests a true association between pioglitazone and bladder cancer.

'Additional studies are needed to better understand the biological mechanism behind the possible pioglitazone specific effect on the bladder,' the study authors conclude.

Although most GPs have been aware of the possible link, and have acted to counsel patients on the drug, the research evidence linking pioglitazone with bladder cancer has been contradictory.

It is not easy for frontline GPs to review the evidence for themselves when the debate involves statistical analyses of huge retrospective data sets. In practice, we should ensure that any patients who still take pioglitazone are aware of the continuing debate about the risks of bladder cancer, and leave the drug for specialist initiation only. We should continue to be vigilant for bladder cancer in patients who have ever taken pioglitazone.

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Tuccori M, Filion KB, Yin H et al. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ* 2016;352:i541

Obstetrics and gynaecology

Does alcohol consumption reduce fertility?

Drinking in moderation does not appear to have an adverse effect on a woman's ability to conceive, a prospective cohort study from Denmark has found.

A total of 6,120 women, aged 21-45 years, who were trying to become pregnant and not receiving fertility treatment were followed up. Participants completed a baseline questionnaire and bimonthly follow-up questionnaires for 12 months or until they became pregnant.

The researchers used a statistical model to estimate fecundability ratios representing the cycle-specific probability of conception among women exposed to alcohol divided by that among non-drinking women. A fecundability ratio below one indicated reduced fertility for women exposed to alcohol compared with those not exposed.

They also assessed the association between time to pregnancy and total alcohol consumption.

In total, 4,210 (69%) of the 6,120 participants achieved a pregnancy during the follow-up period.
At baseline, median alcohol intake was 2.0 standard measures of alcohol per week. (A standard measure was taken as 330 ml regular beer, 120 ml wine or 20 ml spirits).

Compared with no alcohol use, the adjusted fecundability ratios for consumption of one to three, four to seven, eight to 13, and 14 or more measures of alcohol a week were: 0.97 (95% CI: 0.91-1.03), 1.01 (95% CI: 0.93-1.10), 1.01 (95% CI: 0.87-1.16), and 0.82 (95% CI: 0.60-1.12), respectively.

Compared with no alcohol intake, the adjusted fecundability ratios for women who consumed only wine (≥ 3 measures), beer (≥ 3 measures), or spirits (≥ 2 measures) were 1.05 (95% CI: 0.91-1.21), 0.92 (95% CI: 0.65-1.29), and 0.85 (95% CI: 0.61-1.17), respectively.

The results did not show a reduction in fertility at lower levels of consumption (1-13 measures a week). The highest level (≥ 14 measures a week) was associated with an 18% reduction in fecundability compared with no alcohol use, although the confidence interval was wide.

There were no appreciable differences in the associations between beer and wine consumption, while the association between consumption of spirits and reduced fecundability was only slightly stronger.

While women who drink moderately may not have to achieve abstinence in order to maximise their fertility, ongoing consumption must be balanced against the possible harm of drinking during an early or unknown pregnancy. Those drinking more heavily, or binge drinking, while trying to conceive should be advised to reduce consumption.

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Mikkelsen EM, Riis AH, Wise LA et al. Alcohol consumption and fecundability: prospective Danish cohort study. *BMJ* 2016;354:i4262