Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

Addiction
Dr Jez Thompson
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Cardiovascular disease
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Diabetes
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Mental health
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Obstetrics and gynaecology
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Urology

Does vasectomy increase the risk of prostate cancer?

Vasectomy may be associated with a small increase in absolute risk of prostate cancer, the findings from a large cohort study in the United States suggest.

A cohort of 49,405 men taking part in the Health Professionals Follow-Up Study, run by Harvard University, was followed up from 1986 to 2010. During this period 12,321 men (25%) had vasectomies. The men were aged between 40 and 75 at baseline.

The study authors, acknowledging the weakness of a cohort study (i.e. it is able to demonstrate association but not causation because of the potential presence of confounding factors), aimed to allow for a variety of potential confounders in their statistical analysis. These included age, BMI, exercise levels, smoking, diabetes, family history of prostate cancer and history of PSA testing.

During the study period, 6,023 men were diagnosed with prostate cancer and 811 died from the disease.

The risk of being diagnosed with prostate cancer was 12.4% in those who had vasectomies, compared with 12.1% in those who did not – this represents a 0.3% increase in absolute risk of prostate cancer in men who had a vasectomy, and a relative risk (RR) of 1.10 (95% CI:1.04-1.17).

The risk was also elevated for high-grade (Gleason 8-10) disease RR 1.22 (95% CI:1.03-1.45) and lethal disease (distant metastases or death) RR 1.19 (95% CI:1.00-1.43).

One of the strongest predictors of a prostate cancer diagnosis is whether the man has had a PSA test, either because of symptoms or opportunistically/via a screening programme. Therefore, the increased risk of prostate cancer in the vasectomy group might be explained if this group of men were more likely to engage with healthcare and therefore be more likely to have had a PSA test.

The authors therefore looked at a subcohort of 13,901 'highly screened' men. In this group, 3,740 (27%) had had a vasectomy. Vasectomy was not associated with an increase in total prostate cancer incidence or with risk of low-grade or localised prostate cancer. It was, however, associated with an increase in high-grade and Gleason 7 cancers, although the difference did not reach statistical significance.

Lethal prostate cancer was seen in 56% more men who had undergone vasectomy (RR 1.56). However, because of the low incidence of lethal prostate cancer, 1.6% over 24 years, this increase in relative risk represents only a very small increase in absolute risk.

Overall, the study found a 10% increase in relative risk of prostate cancer, a 22% increase in risk of high-grade cancer (Gleason 8 to 10 at diagnosis), a 20% increase in risk of advanced prostate cancer and a 19% increase in risk of prostate cancer with distant metastasis or that causes death.

This is a high quality study, well designed, with large numbers of men followed up for a long period. It is not, however, a prospective, randomised, controlled trial and therefore cannot demonstrate causation. The absolute risk of developing prostate cancer, even if the study is correct, is small, but not insignificant. The finding that more men undergoing vasectomy had PSA tests does raise the question of whether this influenced results, even allowing for the statistical analysis of this.

The authors conclude: 'The decision to opt for a vasectomy remains a highly personal one in which the risks and benefits should be considered.'

This paper attracted a huge amount of interest in the lay press and will undoubtedly lead to GPs being questioned by men considering a vasectomy in the future and also by those who have had the procedure in the past.

GPs need to be aware of this small increase in absolute risk over a 24-year follow-up and arm patients with the facts to help them make a decision as to whether they wish to proceed with a vasectomy.

DR JON REES

● **Siddiqui M, Wilson KM, Epstein MM et al. Vasectomy and risk of aggressive prostate cancer: a 24 year follow up study. *J Clin Oncol* 2014 Jul 7. pii:JCO.2013.54.8446 (Epub ahead of print)** »

Diabetes

Which eating patterns are most effective for weight reduction in type 2 diabetes?

Eating two larger meals a day is more effective than consuming the same amount as six smaller meals in patients with type 2 diabetes who are trying to lose weight, the findings of a crossover study suggest.

The Prague-based study population comprised 54 patients (29 men) with type 2 diabetes of more than one year's duration. They had all been treated with oral hypoglycaemic drugs. Participants' BMI ranged from 27 to 50 kg/m^2 and HbA_{1c} 6.0-11.8%, average 7.2%. The mean age was 59.4 years and mean duration of diabetes 8.1 years.

The study design was a single centre, randomised, open, crossover trial. After a run-in period of a month, during which patients learned how to use pedometers, glucometers and food diaries, the patients were randomised to the two meals a day group, or the six meals a day group. After 12 weeks of the diet, the groups crossed over to the opposite regimen. Initially 27 patients were assigned to each of the two groups. There were four dropouts in the original six meals a day group and three in the other group. The results were analysed on an intention to treat basis.

The patients ate meals designed to give a standard caloric reduction based on each individual's resting energy expenditure. Alcohol was limited to one drink a day for women and two a day for men. Participants were asked not to change their exercise habits during the study. One half of each group, chosen at random, were provided with all their meals for the duration of the study, while the other half prepared their own food. Medication was not adjusted, except when hypoglycaemia occurred.

Measurements were taken at weeks 0, 12 and 24. As well as physiological recording of height, weight and waist circumference, blood pressure and heart rate, several biochemical markers were used to assess the response to the differing regimens. These included fasting glucose, C-peptide, immunoreactive insulin, isoglycaemic-hyperinsulinaemic clamping, and proton magnetic resonance spectroscopy to assess hepatic fat content.

Both regimens saw favourable changes in the measured parameters, but the twice daily meal regimen was consistently more successful.

Weight fell by 2.3 kg (95% CI: 2.0 to 2.7) in the six meals a day group, and by 3.7 kg (95% CI: 3.4 to 4.1) in the two meals a day group. BMI and waist circumference showed similar patterns.

Fasting plasma glucose fell by 0.47 mmol (95% CI:0.36 to 0.57) in the six meals a day group, and by 0.78 mmol (95% CI: 0.68 to 0.89) in the two meals a day group. HbA_{1c} decreased significantly but comparably with both regimens. The decrease in hepatic fat content strongly mirrored the reduction in fasting blood glucose.

The more sophisticated tests of insulin resistance such as immunoreactive insulin and C-peptide showed a similar pattern of greater positive effect from the reduced number of daily meals.

The authors conclude that for patients with type 2 diabetes on weight-reducing diets, fewer daily meals are more effective in achieving physiological changes, and these are mirrored by improved biochemical measurements.

Although the crossover trial is a strong study design, the authors did not feel the results could be extrapolated to the real world of general practice, because of the short duration of the study, and the provision of a high proportion of the participants' meals.

This study may lend some support to the idea of fasting between larger meals, rather than frequent small meals, as a healthy lifestyle choice.

The most difficult element of the study to replicate in general practice is to calculate the optimum dietary intake for each patient.

DR MATTHEW LOCKYER

● **Kahleova H, Belinova L, Malinska H et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. *Diabetologia* 2014;57(8),1552–60**

Mental health

Combination treatment only of benefit in severe depression

The addition of cognitive therapy to antidepressant treatment increases the likelihood of recovery from major depression, but only in those with severe non-chronic depression, an American secondary care study has found.

A total of 452 patients with either chronic (duration ≥ 2 years) or recurrent DSM-IV major depression were recruited from outpatient clinics. Of these 225 were randomised to receive antidepressant treatment alone and 227 to combination therapy.

Antidepressant treatment was prescribed using a detailed sequential algorithm. Cognitive therapy was provided using the Beck treatment manual. Treatment was continued for a maximum of 42 months until patients had achieved recovery.

Remission was defined using the Hamilton Rating Scale for Depression (HRSD score ≤ 8) and a measure of functional impairment. Recovery was defined as six months without relapse following remission.

Overall, 72.6% of those treated with combination treatment achieved

recovery compared with 62.5% of those treated with antidepressants alone, hazard ratio 1.33 (95% CI:1.06-1.68); NNT = 10). There was no significant difference in remission rates.

An HRSD cut-off score ≥ 22 was used to define the threshold between low- and high-severity depression. Only patients with severe non-chronic depression derived significant benefit from combination treatment, 81.3% vs 51.7%, HR 2.34 (95% CI: 1.54-3.57; NNT = 3).

The dropout rate was lower in the combination treatment group (18.9% vs 26.8%). It has been suggested that the benefit of adding cognitive therapy results from greater adherence to treatment rather than a genuine therapeutic effect.[1]

The HRSD is a clinician-administered depression rating scale that has been regarded as the gold standard tool for measuring depression severity.

However, there is no consensus as to how HRSD scores should be interpreted. The American Psychiatric Association (APA) severity bandings are: none (0-7), mild (8-13), moderate (14-18), severe (19-22) and very severe (≥ 23). The NICE severity bandings are: none (0-7), subthreshold (8-13), mild (14-18), moderate (19-22) and severe (≥ 23).[2] The cut-off used in this study does not quite correspond to the NICE boundary between moderate and severe.

Recovery was defined merely as a period of six months without the recurrence of major depression. It has been suggested that the definition should be much more stringent i.e. absence of depressive symptoms which impair functioning plus psychological wellbeing plus no need for ongoing therapy.[3]

NICE provides separate guidance for depressed patients with and without a chronic physical condition. Combination treatment is recommended for both moderate and severe depression in the absence of a chronic condition, and for severe depression with a chronic condition (Quality statements 6 and 8).[4]

In contrast, the British Association for Psychopharmacology (BAP) guideline recommends combination treatment only for those with severe depression, whether or not they have a chronic condition.[5] This study suggests that the BAP is right and that combination treatment in moderate depression is a waste of valuable resources.

However, there are a couple of caveats. Patients with a first episode of depression were not included in the study, so we do not know whether the results apply to them. Also, only two categories of depression severity were compared 'low severity' depression (HRSD score 14-21) includes both the mild and moderate NICE categories.

It is a mistake to think that we can define a precise point on the continuum of depression severity whereby those on one side of the divide will benefit from added CBT and those below will not.

In clinical practice it is very difficult to determine depression severity accurately. Even with revised cut-off scores, severity questionnaires such as the PHQ-9 are not sufficiently precise and it is doubtful whether they are any better than GPs' clinical judgement.[6]

DR PHILLIP BLAND

● **Hollon SD, DeRubeis RJ, Fawcett J et al. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder. A randomised clinical trial. *JAMA Psychiatry* 2014;doi:10.1001**

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Cardiovascular disease

Spironolactone in heart failure with preserved ejection fraction

Spironolactone did not significantly reduce deaths in patients with heart failure and preserved ejection fraction, however it did cut hospitalisations for heart failure, the TOPCAT study has shown.

This was an international, multicentre, randomised, double-blind trial of patients with symptomatic heart failure and left ventricular ejection fraction ≥ 45%.

A total of 3,445 patients were randomised to receive either spironolactone (15 to 45 mg daily) or placebo. The mean age of patients was 68.7 in both groups.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of heart failure. Mean follow-up was 3.3 years.

The primary outcome occurred in 320 (18.6%) of the 1,722 patients in the spironolactone group and 351 (20.4%) of the 1,723 patients in the placebo group; hazard ratio (HR) 0.89 (95% CI:0.77-1.04; P = 0.14).

However, there was a significant fall in the incidence of hospitalisation for heart failure in the spironolactone group, 206 patients (12.0%) vs 245 (14.2%) in the placebo group; HR 0.83 (95% CI:0.69-0.99, P = 0.04).

In terms of adverse outcomes, spironolactone was associated with increased serum creatinine levels, and a doubling of the rate of hyperkalaemia, 18.7% compared with 9.1% in the placebo group, but reduced hypokalemia. With frequent monitoring, there were no significant differences in the incidence of serious adverse events.

The authors conclude that in patients with heart failure and a preserved ejection fraction, adding spironolactone to existing therapy did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of heart failure.

Mineralocorticoid-receptor antagonists (MRAs) such as spironolactone and eplerenone improve the prognosis for patients with heart failure and a reduced left ventricular ejection fraction. However, it would appear that MRAs are not as effective in those patients with preserved ejection fraction.

Perhaps we can take some encouragement from the reduction in hospitalisations for heart failure as this is a key component in the cost-effective management of this patient group and in an area with little in the way of meaningful therapeutic interventions this trial may at least give us another option.

DR PETER SAVILL

● **Pitt B, Pfeffer MA, Assmann SF et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;370(15):1383-92**

PCUS
Primary Care Urology Society

Inaugural Meeting

Tuesday 18 November 2014, 10am-3pm

10-11 Carlton House Terrace
London SW1Y 5AH

The Primary Care Urology Society (PCUS), led by Dr Jonathan Rees, is now established with registration open for its inaugural one day meeting on 18 November in London.

An online survey of interested healthcare professionals found that 75% of respondents wanted to increase their urology knowledge through the Society by learning with peers and 70% welcomed the opportunity to network with others in a community setting.

The Primary Care Urology Society will provide a forum for healthcare professionals working in primary and community care to discuss and debate practical and topical management issues in urology.

Further details about the PCUS and registration for its first meeting can be found at: **www.primarycareurologysociety.org** All interested healthcare professionals are invited to register.

Obstetrics and gynaecology

Comparing treatments for infertility in women with PCOS

Letrozole appears to be more effective, and associated with fewer maternal side effects, than clomiphene in the treatment of infertility in women with polycystic ovary syndrome (PCOS), a double blind trial has found.

A total of 750 women, aged 18-40 years, with PCOS but without other impediments to fertility were recruited. Modified Rotterdam criteria (anovulation with hyperandrogenism or polycystic ovaries) were used to define PCOS. Participants were randomised to receive letrozole (n = 374) or clomiphene (n = 376).

Blinding was possible as both treatments were given for five days starting early in the follicular phase of the menstrual cycle. The maximum number of treatment cycles was five.

The primary outcome was live birth. The secondary outcomes were ovulation, pregnancy loss, singleton birth and congenital abnormality.

Women given letrozole were more likely to conceive (41.2% vs 27.4%; P <0.001) and to have a live birth (27.5% vs 19.1%), rate ratio 1.44 (95% CI:1.10-1.87; P = 0.007) than those treated with clomiphene. Pregnancy loss rates were similar (31.8% vs 29.1% respectively; P = 0.65).

Women given clomiphene had more twin pregnancies compared with those treated with letrozole but the difference was not statistically significant (7.4% vs 3.4%; P = 0.32). The time to pregnancy and duration of pregnancy were similar.

Two serious adverse events were recorded in women given letrozole (ruptured corpus luteum cyst and ovarian cyst) and one in women given clomiphene (ovarian torsion).

Five infants were born with significant congenital abnormality four of whom (3.9%) were conceived following letrozole treatment: cerebral palsy with hydrocephalus; spina bifida with imperforate anus; hemimegalencephaly with partial cerebral dysgenesis; and one case of ventricular septal defect. The one (1.5%) anomaly associated with clomiphene was atrial septal defect with ventricular septal defect and pulmonary stenosis. Although the difference between the groups was not statistically significant given the group size a potential difference cannot be ruled out, the researchers caution.

PCOS is the most common cause of anovulatory infertility in women. The standard first-line treatment to induce ovulation is clomiphene which selectively blocks the action of oestrogen at the level of the hypothalamus. The aromatase inhibitor letrozole, which blocks oestrogen production at the level of the ovary, appears to be more effective and associated with fewer adverse effects.

Letrozole, better known as an adjuvant treatment for breast cancer, does seem to have real potential in the treatment of women with PCOS and sub-fertility. However, questions about teratogenesis will need to be resolved before it can be recommended for regular use.

'Further study with larger numbers of infants is needed to clarify the safety and teratogenic risks with letrozole relative to those with other infertility therapies,' the study authors conclude.

DR CHRIS BARCLAY

● **Legro RS, Brzyski RG, Diamond MP et al for the NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 2014;371:119-29**

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