Higher risk of hospitalization for twins born after fertility treatment

Twins born as a result of assisted reproductive technology are more likely to be admitted to neonatal intensive care and to be hospitalized in their first 3 years of life than spontaneously conceived twins, according to new research (Hansen et al, 2009).

Although it was already known that assisted reproductive technology twins are at higher risk of problems such as low birth weight and premature delivery than singletons around the time of their birth, there has been conflicting evidence about whether assisted reproduction itself is responsible for adding to the number of problems seen in assisted reproductive technology twins.

Michèle Hansen, Telethon Institute for Child Health Research, Perth, Western Australia

Researchers in Australia and the UK looked at perinatal outcomes and hospital admissions for all twin children born in Western Australia between 1994 and 2000, whether as a result of assisted reproductive technology or spontaneous conception.

Michèle Hansen of the Telethon Institute for Child Health Research, Perth, said: 'We found that twins conceived following assisted reproductive technology treatment had a greater risk of adverse perinatal outcome, including preterm birth, low birthweight and death, compared with spontaneously conceived twins of unlike sex. Assisted reproductive technology twins had more than double the risk of perinatal death compared to unlike sex spontaneously conceived twins, although the risk was similar to that of all spontaneously conceived twins, including identical twins.'

The group reported that assisted reproductive technology twins:

- Stayed longer in hospital than unlike sex spontaneously conceived twins at the time of birth: an average of 12 days compared with 8 days
- Were four times more likely to be admitted to neonatal intensive care than unlike sex spontaneously conceived twins, and were more likely to be admitted to hospital during the first 3 years of their life.

Ms Hansen continued: 'Couples undergoing fertility treatment should be aware that, in addition to the known increased perinatal risks associated with a twin birth, assisted reproductive technology twins are more likely than spontaneously conceived twins to be admitted to neonatal intensive care and to be hospitalized in their first 3 years of life.

'We don't know the reason for the increased risks ... and preliminary analysis of specific diagnoses does not provide any answers.

'The underlying causes of parental infertility and/or components of the assisted reproductive technology procedure may be increasing the risks of adverse outcome, and increased concern about children born after a long period of infertility may also be contributing to their increased risk of hospitalization.

She concluded: 'Estimates of the cost of an assisted reproductive technology twin delivery should take into account these increased risks, and, in order to reduce the problems associated with twin births, clinicians and couples should consider the benefits of opting for single embryo transfer.'

Stephen Pinn

Hansen M, Colvin L, Petterson B, Kurinczuk JJ, de Klerk N, Bower C (2009) Twins born following assisted reproductive technology: perinatal outcome and admission to hospital. *Hum Reprod* May 20. (Epub ahead of print)

Sleeping through dialysis is a better medical strategy for patients

Three times a week overnight haemodialysis sessions offer a viable alternative to conventional shorter daytime dialysis in patients with irreversible kidney disease – particularly in dialysis clinics where there are constraints on time and resources.

Reporting in the *Clinical Journal of the American Society of Nephrology*, Dr Joanna Powell of the Western Infirmary, Glasgow, outlined new data in which the health of patients who received long overnight haemodialysis sessions (6–7 hours) was compared to those who received conventional haemodialysis during the day (4–5 hours) (Powell et al, 2009).

She and her colleagues observed that during 10 years of study, 146 patients in their clinic chose long overnight haemodialysis (approximately 11% of their dialysis population). The mean age at the time of starting long overnight haemodialysis was 51.8 years (range 30 to >70 years), with 74.7% having functional arteriovenous fistulae. The median duration of continuous long overnight haemodialysis was 1.6 years.

Overnight therapy was well tolerated, with only one-third of patients converting back to conventional dialysis after an average of approximately 2 years – mostly because of personal preference than for medical reasons.

In a direct comparison of 106 patients (equal numbers for long overnight haemodialysis and conventional haemodialysis), those who underwent long overnight haemodialysis had lower rates of anaemia (increased haemoglobin and a trend towards a lower erythropoietin index) and reduced levels of urea in their blood (increased urea reduction ratio).

Dr Powell added that previous studies have found that long overnight haemodialysis also reduces blood pressure, blood phosphate levels and risk of premature death compared to conventional haemodialysis.

The researchers concluded that long overnight haemodialysis is a practical way for clinics to offer longer dialysis sessions that are well tolerated by most patients with kidney disease.

Stephen Pinn

Powell JR, Oluwaseun O, Woo YM et al (2009) Ten years experience of in-center thrice weekly long overnight hemodialysis. *Clin J Am Soc Nephrol* (e-pub ahead of print 21 May) http://cjasn.asnjournals.org/cgi/content/abstract/CJN.06651208v1

PPIs lower benefit of clopidogrel in stent patients

New data suggest that proton pump inhibitors (PPIs) reduce the benefits of clopidogrel in patients who have undergone coronary stenting.

Proton pump inhibitors can interfere with enzymes in the liver that metabolize clopidogrel, reducing its anti-clotting effects, said Society for Cardiac Angiography and Interventions president-elect Dr Steven Bailey. A statement from the Society follows the largest trial to date examining the outcomes of patients who are taking clopidogrel and a proton pump inhibitor.

Dr Steven Bailey, president-elect of the Society for Cardiac Angiography and Interventions

Results from the Clopidogrel Medco Outcomes Study were presented during the Society for Cardiac Angiography and Interventions's annual scientific sessions held in Las Vegas, USA.

Investigators found that patients taking both clopidogrel and a proton pump inhibitor experienced a 50% increase in the combined risk of hospitalization for myocardial infarction, stroke, unstable angina, or repeat revascularization. Specifically, patients who took a proton pump inhibitor faced:

- A 70% increase in the risk of myocardial infarction or unstable angina
- A 48% increase in the risk of stroke or stroke-like symptoms
- A 35% increase in the need for a repeat coronary procedure.

The study included 16 690 patients taking clopidogrel for a full year following coronary stenting. Patients enrolled in the study took proton pump inhibitors for an average of 9 months.

The overall event rate for the cohort without proton pump inhibitors was 17.9% (a composite of risk of hospitalization for myocardial infarction, stroke, unstable angina or repeat revascularization); the entire cohort taking the different proton pump inhibitors had a 50% relative increase over the control group.

The event rates for individual proton pump inhibitors (all statistically significant compared to the no-proton pump inhibitor control group) were as follows:

- Lansoprazole 24.3%
- Esomeprazole 24.9%
- Omeprazole 25.1%
- Pantoprazole 29.2%.

The Society for Cardiac Angiography and Interventions recommends that while more research is needed, clinicians treating post-stent patients on dual-antiplatelet therapy should consider prescribing an H2 blocker or antacids instead of a proton pump inhibitor, in view of the high risk for adverse events shown in this study.

Stephen Pinn

Twice-weekly regimen for maintenance of eczema

Tacrolimus monohydrate (Protopic ointment) is already licensed to treat moderate and severe eczema (atopic dermatitis), often involving the treatment of flares as and when they occur. It is now also approved for twice-weekly application to previously affected skin to prevent these exacerbations and prolong flare-free periods in tacrolimus-responsive patients.

Clinical studies have shown over 40% of patients with moderate to severe eczema remaining flare-free for at least 1 year. Flares place an enormous burden on patients. About 55% of these patients worried about the onset of their next exacerbation and they spent on average over a third of the year (136 days) with their eczema in flare.

Approval of the twice-weekly regimen of tacrolimus was based on sub-analysis of the results from two phase III studies conducted in 524 adults and children in 13 European countries (Bieber, 2008; Thaçi et al, 2008). Once patients had responded to twice-daily treatment of their flares with tacrolimus ointment, continuing treatment to previously affected areas with a twice-weekly regimen significantly reduced the number of flares compared to a flare treatment-only regimen.

'Helping patients to reduce the number of flares they experience will lift many of the burdens patients face,' said Dr Sakari Reitamo, Hospital for Skin and Allergic Diseases, Helsinki University Central Hospital, Finland.

Bieber T (2008) Mechanisms of disease: atopic dermatitis. *N Engl J Med* **358**: 1483–94

Thaçi D, Reitamo S, Gonzalez Ensenat MA et al (2008) Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* **159**: 1348–56

Telemonitoring could 'radically' change care in heart failure

Management of heart failure is most effective when tailored to the individual patient's needs, said Professor John Cleland from the University of Hull, speaking at Heart Failure Congress 2009. Telemonitoring could help to change this situation, but service evolution would be needed to make this work.

Dietary treatment of gestational diabetes

The results of a small Australian study, published in *Diabetes Care*, show that prescribing a low glycaemic index diet for women with gestational diabetes mellitus can reduce the number of women needing insulin without compromising pregnancy outcomes.

Effect of telmisartan on renal outcomes similar to placebo

The *Annals of Internal Medicine* reported a multicentre, multinational study comparing telmisartan and placebo in 5927 adults with known cardiovascular disease or diabetes with end-organ damage who cannot tolerate angiotensin-converting enzyme inhibitors. Telmisartan's effects on major renal outcomes were similar to those of placebo.

Study assesses risk of cervical intraepithelial neoplasia recurrence

Long-term risks of invasive cancer and recurrence of severe cervical intraepithelial neoplasia are higher among women previously treated for cervical intraepithelial neoplasia than those with no cervical intraepithelial neoplasia diagnosis, according to data from a large, retrospective cohort study published in the *Journal of the National Cancer Institute*.

The study was undertaken because information on the long-term risks of subsequent cervical intraepithelial neoplasia or invasive cancer among women previously treated for the disease is limited. More information on long-term risks is needed to help guide long-term follow-up of these patients.

To determine such risks, Dr Joy Melnikow, of the Center for Healthcare Policy and Research at the University of California, Davis, and colleagues retrospectively identified a cohort of 37 142 women who were treated for cervical intraepithelial neoplasia 1, 2, or 3 from 1986 to 2000, and compared them with a cohort of 71 213 women with no previous cervical intraepithelial neoplasia diagnosis. Both groups were under active surveillance through 2004.

The researchers found that risk for subsequent cervical intraepithelial neoplasia or cervical cancer was associated with initial cervical intraepithelial neoplasia grade, treatment type and age. The risk of invasive cervical cancer and cervical intraepithelial neoplasia 2/3 recurrence was highest for women who were older than 40 years, previously treated for cervical intraepithelial neoplasia 3, or treated with cryotherapy.

The highest rates of cervical intraepithelial neoplasia recurrence were seen in the first 6 years after treatment in the cervical intraepithelial neoplasia cohort, with a majority of those identified in the first 2 years. Recurrence rates for cervical intraepithelial neoplasia 2 or 3 during this 6-year period ranged from 2.3% in the lowest risk group to 35% in the highest risk group.

Overall incidence of cervical cancer in the cervical intraepithelial neoplasia group was 37 cervical cancers per 100 000 woman-years compared with six cervical cancers per 100 000 woman-years among women who had not been previously diagnosed.

In an accompanying editorial, Dr Edward J Wilkinson, of the University of Florida College of Medicine in Gainesville, points out that these results support evidence that active surveillance has value in identifying most incidences of cervical intraepithelial neoplasia 2/3 recurrence and early stages of cervical cancer.

'[T]his work provides evidence that women with cervical intraepithelial neoplasia who have undergone treatment need long-term surveillance after their therapy and remain at some risk for cervical intraepithelial neoplasia as well as for cervical carcinoma for 20 years or more,' Dr Wilkinson concluded.

Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A (2009) Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *J Natl Cancer Inst* **101**: 721–8

Wilkinson E (2009) Women with cervical intraepithelial neoplasia: requirement for active long-term surveillance after therapy. *J Natl Cancer Inst* **101**: 696–7

MRI shows natalizumab promotes remyelination in multiple sclerosis

A study using advanced MRI (magnetic resonance imaging) technology has found that natalizumab (Tysabri) promoted regeneration and stabilization of damage done to the myelin sheath. Damage to the myelin sheath causes the symptoms of multiple sclerosis.

Natalizumab is the first approved multiple sclerosis therapy with reported data suggesting that some of the signs of disease progression can be stopped. The strong efficacy profile demonstrated in clinical trials is enhanced further from these data and may help redefine success in multiple sclerosis.

The effect of natalizumab on lesions and normal appearing brain tissue in relapsing multiple sclerosis was evaluated with a Voxel-Wise (VW) imaging method using magnetization transfer ratio (MTR). VWMTR is a powerful instrument for monitoring multiple sclerosis disease activity and effectiveness of therapeutic interventions in patients with multiple sclerosis.

The imaging study, which included 110 subjects, used VWMTR to measure lesions and normal brain tissue. The study showed that natalizumab promoted remyelination when compared to those receiving interferon beta-1a IM and normal controls.

In the study, 62 multiple sclerosis patients who received natalizumab were followed for 12 months together with 26 multiple sclerosis patients who received interferon beta-1a IM and 22 age-matched and sex-matched normal controls.

For each subject, baseline and follow-up MTR volume maps were placed in a common halfway-space. The resulting Voxel-Wise subtraction map was then enhanced via threshold-free cluster enhancement algorithm, and a significance threshold was determined based on subject-specific Monte Carlo simulation. Supra-threshold volumes (95th percentile) were quantified for both areas of increasing (remyelinating) and decreasing (demyelinating) MTR voxels, which represent a volume value.

There was no significant difference in decreasing VWMTR normal appearing brain tissue volume over the follow-up between natalizumab-treated and normal control groups. Relapsing-remitting patients on both therapies showed higher remyelination potential and less evident demyelination than relapsing secondary progressive patients.

'What we have seen in these MRI data suggest that Tysabri may have the capacity to repair and possibly restore some of the damaged myelin sheath that protects nerve fibres. Results from this study support the continued investigation of the potential effects of Tysabri on this process,' said lead investigator Dr Robert Zivadinov, of the Jacobs Neurological Institute in Buffalo, NY.

Zivadinov R, Dwyer MG, Bergsland N et al (2009) Natalizumab (Tysabri) promotes remyelination in patients with multiple sclerosis. a voxel-wise magnetization transfer imaging case-control study. Poster presentation. American Academy of Neurology 25 April–2 May

HEART RHYTHM SOCIETY
BOSTON, MASSACHUSETTS, 13–16 MAY

Defibrillator benefit in MI survivors: 8-year data

The long-term survival benefit of implantable cardioverter defibrillator in patients surviving a myocardial infarction (MI) has been demonstrated in new 8-year follow-up data from an international study.

Reporting at the annual scientific sessions of the Heart Rhythm Society, Dr Ilan Goldenberg said that in the original MADIT-II (Multicenter Automatic Defibrillator Trial II) trial, there was a 31% reduction in the risk of death among 1232 myocardial infarction survivors with implantable cardioverter defibrillators and optimal pharmacological therapy compared to optimal pharmacological therapy alone (P=0.016). At that time, however, the mean follow-up was only 20 months.

The new data represent an 8-year follow-up of MADIT-II, designed to evaluate the long-term consequences of primary implantation of a cardioverter defibrillator.

Dr Goldenberg, of University of Rochester Medical Center, New York, USA, reported that the new analysis confirmed a sustainable benefit over time, including:

- A significant reduction in the number needed to treat with an implantable cardioverter defibrillator in order to save one life (from 17 in the original MADIT-II study to just six at 8-year follow-up, P<0.001)
- A 41% relative reduction at 4 years for implantable cardioverter defibrillator patients (hazard ratio 0.59, P<0.001)
- A 37% reduction at 8 years (hazard ratio 0.63, P<0.001), and even 29% from years 4–8 (hazard ratio 0.71, P=0.02).

It was reported at the meeting that in the EU alone, sudden cardiac death claims an estimated 325 000 lives a year, that sudden cardiac death accounts for half of all cardiac-related deaths, and that more than half of sudden cardiac death victims have no prior symptoms.

It was also said that although about 95% of sudden cardiac death victims die before reaching hospital, approximately 95% of lethal ventricular arrhythmias are effectively terminated if implantable cardioverter defibrillator treatment is initiated within the first few minutes following arrest.

Stephen Pinn

International call for more catheter ablation research

A call to action for more research to be undertaken into catheter ablation in the field of ventricular arrhythmia has been issued in a joint consensus document from the European Heart Rhythm Association and the US Heart Rhythm Society (Aliot et al, 2009).

The consensus document provides an up-to-date review of indications, techniques and outcomes of catheter ablation for treatment of ventricular arrhythmias, a technique now being offered to increasing numbers of patients.

'In the last few years there has been a substantial evolution of techniques for catheter ablation in ventricular arrhythmia. We hope this document will help identify the areas in catheter ablation that require further research, and encourage clinicians to embark on more clinical and registry studies,' says Etienne Aliot, the European co-chair from Nancy, France. 'It is only by conducting more clinical trials and registries that we can begin to get an idea of exactly how catheter ablation fits into the whole ventricular arrhythmia treatment paradigm including implantable cardiodefibrillators and antiarrhythmic drugs.'

The document – authored by 20 leading European and US electrophysiologists – recognizes that there are still 'very limited' data establishing the long-term impact of catheter ablation on morbidity and mortality.

Unanswered questions highlighted include:

- The long-term efficacy of catheter ablation
- The comparative success rates of drug and ablative therapies
- Can ablation slow the progression of ventricular remodelling in structural heart disease?
- Definition of patients with different underlying cardiac and non-cardiac diseases.

Aliot EM, Stevenson WG, Almendral-Garrote JM et al (2009) EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias. *Europace* **11**: 771–817

Psychotropic drugs may increase risk of sudden death

Common psychotropic medications, such as antipsychotics, antidepressants and benzodiazepines, may contribute to an increased risk of sudden death during an acute coronary event, according to a prospective case-control study. The study compared psychotropic medication use in heart attack survivors and victims of sudden cardiac death.

Led by Dr Jussi Honkola, at the University of Oulu, Finland, this prospective sub-study of Finnish Genetic Study of Arrhythmic Events (FinGesture) compared the medications of 321 sudden cardiac death victims caused by an acute coronary event as confirmed by a medicolegal autopsy, with 609 patients surviving acute myocardial infarction. Medication histories were examined from autopsy records and interviews with the victims' relatives.

Victims of sudden cardiac death more frequently used medications compared to heart attack survivors including: antipsychotics (10.9% *vs* 1.4%), antidepressants (7.4% *vs* 3.0%) and benzodiazepines (18.4% *vs* 5.0%). The study also found more frequent use of beta blockers and aspirin among acute myocardial infarction survivors than those who experienced sudden cardiac death.