



IMPACT NETWORK

*Interdisciplinary Maternal Perinatal
Australasian Clinical Trials Network*

Satellite Meeting of the

12th ANNUAL PSANZ CONGRESS

Gold Coast 19-20 April 2008

I M P A C T NETWORK

of the Perinatal Society of Australia and New Zealand



Saturday 19th April 1330–1700 and Sunday
20th April 0830-1300 2008

Gold Coast Hospital, Education Centre, 108 Nerang St, Southport

**PROGRAM INFORMATION AND
ABSTRACTS**

Welcome to the IMPACT Workshop pre PSANZ Congress 2008

Saturday 19 April 2008 & Sunday 20 April 2008

The Interdisciplinary Maternal Perinatal Australasian Clinical Trials Network (IMPACT NETWORK) brings together researchers, practitioners, clinicians, and professional health workers throughout Australia and New Zealand collaborating in a common goal: the improvement of maternal and perinatal health through the promotion of well designed randomised controlled trials (RCTs). Established in 1995 as a subcommittee of the Perinatal Society of Australia and New Zealand (PSANZ), IMPACT is committed to promoting the conduct of high quality trials and also to ensuring all trials results are disseminated and used to inform a clinical practice.



This workshop is predominately dedicated to providing participants with a forum to discuss issues in the conduct of perinatal clinical trials; to assist researchers in the development of new trials through participant input into design and logistics; and implementation into practice of what is already known from the results of high quality RCT's and Cochrane systematic reviews.



IMPACT NETWORK WORKSHOP PROGRAM



Saturday 19th April and Sunday 20th April, 2007

Satellite meeting of the 2007 Perinatal Society of Australia and New Zealand Congress

Venue: Education Centre - Gold Coast Hospital (stands adjacent to the Hospital)
Little High St, Southport

PROGRAM

DAY 1: Saturday 19th April

Registration 1230 –1300		
1330 – 1340	Welcome and Introduction	Jonathan Morris and Caroline Crowther
1340 - 1500	Session 1: Current Research Barriers & Getting Research Into Practice	
1340-1400	○ WOMBAT Activities	Philippa Middleton
1400-1420	○ Research Culture – recruitment predictors	Kate Levett
1420-1440	○ Smoking cessation	Debra Oag
1440-1500	○ ANZSA	Vicki Flenady
1500 – 1530	Afternoon tea	
1530-1700	Session 2: Abstracts	
1530-1545	○ The Australian Placental Transfusion Study	Jonathan Morris on behalf of APTS
1545 -1600	○ PLUTO	Mark Kilby
1600-1615	○ PeriKOOL	Chris East
1615-1630	○ DAME	Gillian Opie
1630-1645	○ Fetal cerebral artery Doppler RCT	Jodie Dodd
1645-1700	○ Dietary and Lifestyle – GDM	Caroline Crowther

PROGRAM

DAY 2 Sunday 20th April

08?-0830	Welcome	
0830-1045	Session 1: Abstracts	
0830-0845	WOMBAT	TBA
0845-0900	WOMBAT	TBA
0900 -0915	Sugar Babies	Deborah Harris
0915- 0930	Dietary and Lifestyle – overweight or obese to limit weight gain during pregnancy – an RCT	Jodie Dodd
0930-0945	Epidural effect ability of neonate to effectively breastfeed	Mary-Ann Davey
0945-1000	A-Steroid – planned RCT	Caroline Crowther / Philippa Middleton
1000 -1015	RCT of Caseload Midwifery	Donna Hartz
1015-1030	Study in preparation (no abstract)	Robyn Maude
1030-1100	Morning tea	
1100-1230	Session 2:	
1100-1120	Introduction	Jonathan Morris
1120-1140	Research Gaps	Philippa Middleton
1200-1230	Panel Discussion – setting National Research Priorities.	Jonathan Morris

Wrap up and close

Dinner:

Don't forget, we are holding the combined IMPACT/WOMBAT/Perinatal Mortality Group/ANZSA dinner at Mario's Restaurant, Broadbeach.

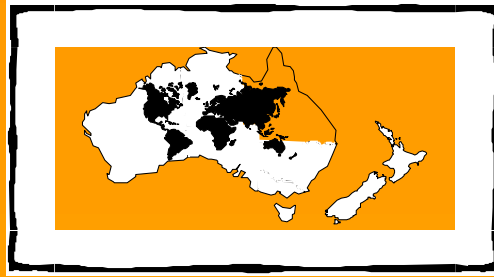
Venue: Marios Restaurant
 Address: Oasis Shopping Centre
 Victoria Ave, Broadbeach Mall
 Time: 7:15 pm

Fully Licenced

+ BYO wine only (\$4 per head corkage)

\$30.00 per head set package – platter style

For further information please visit: <http://www.mariosrestaurant.com.au>



I M P A C T

(Interdisciplinary Maternal Perinatal Australasian Clinical Trials) Network

ABSTRACTS

(in order of program)

WOMBAT Support for Multicentre Trials – Overview of current activity

Caroline Crowther, Philippa Middleton, Rebecca Tooher.

Discipline of Obstetrics and Gynaecology, The University of Adelaide on behalf of the WOMBAT Collaboration

Email: philippa.middleton@adelaide.edu.au

Background: The WOMBAT (Women and Babies Health and Wellbeing – Action Through Trials) promotes and support randomised trials in maternal and perinatal healthcare. One of the ways it does this is to assist trialists to achieve recruitment targets and support multicentre trials by promoting the need for additional collaborating centres. The WOMBAT Collaboration maintains a register/database of maternal and perinatal trials which is available via the WOMBAT website (www.wombatcollaboration.net.au). At March 1 2008 there were 138 trials listed in the database, including 82 maternal/perinatal and 56 neonatal. Currently there are 14 new trials in the WOMBAT database that are not yet recruiting (11 maternal/perinatal and 3 neonatal) and 47 trials that are currently recruiting (27 maternal/perinatal and 20 neonatal).

Multicentre trials: Of the 20 multicentre trials not yet or currently recruiting, at least six trials (five maternal/perinatal trials and one neonatal) are looking for additional collaborating centres. This presentation will outline the research questions and inclusion criteria for the trials seeking additional centres. For example:

- the PPROMT (Preterm Prelabour Rupture of the Membranes Trial) is comparing expectant care with immediate delivery for women with PPROM between 34 and 36⁺⁶ weeks of gestation. To date PPROMT has enrolled 333 women (from a recruitment target of 1800).
- The PROGRESS (Progesterone After Previous Preterm Birth for the Prevention of Neonatal Respiratory Distress Syndrome) Trial is examining the impact of vaginal progesterone on the incidence of RDS. Eligible women are between 13 and 26⁺⁶ weeks gestation with a previous preterm birth with spontaneous onset of labour or following cervical incompetence or PPROM. The PROGRESS trial has enrolled 207 women (from a target of 982).
- BOOST-II (Benefits of Oxygen Saturation Targeting) is comparing two different ranges of arterial oxygen saturation (85% - 90% and 91% to 95%). Eligible infants must be less than 28 weeks gestation and less than 24 hours old. The recruitment target for BOOST-II is 1200.
- The TWINS (Timing at Birth) Trial is comparing elective delivery at 37 weeks with standard management. The recruitment target for TWINS is 576 and current recruitment stands at 142.

Discussion: We are seeking feedback about how to recruit more centres for these and other trials and to discuss methods of optimising recruitment for multicentre trials.

Site Specific Predictors of Recruitment

Levett, K¹, Roberts, C¹, Simpson, J², Morris, J¹.

¹Kolling Institute of Medical Research, University of Sydney, Sydney, Australia

²University of Sydney, Sydney, Australia

Email: klevett@med.usyd.edu.au

Background:

A major concern for clinical trials is the efficiency of recruitment by individual sites. This ongoing, trial sub-study aimed to identify site-specific predictors of recruitment.

Methods:

The PPROMT Trial is an international, multi-centre, RCT of expectant versus immediate delivery of pregnancies complicated by preterm prelabour rupture of the membranes. The main outcome was recruitment rate per 1000 births. Factors potentially predictive of recruitment comprised three broad themes: ethics and regulatory approval times; characteristics of site investigators; and indicators of research culture in collaborating obstetric sites. Data were analysed using contingency tables and categorical analysis.

Results:

At June 2007, 26 of 36 approved centres had recruited at least one woman. Recruitment rates ranged from 0.15 to 6.6 / 1000 births (mean 1.46/1000 births). The factors associated ($p < 0.05$) with a lower than average recruitment rate included delays due to negotiation of Clinical Trial Agreements; Investigator non-response to offer of phone in-servicing, implementation of clearly defined systems of recruitment and an average email response time of > 5 working days. Research culture features of lack of a dedicated trial-coordinator and delayed monthly Consort Statements. Importantly, time to ethics approval (> 3 months) and time to first recruit (> 3 months) were not predictive of recruitment rates.

Conclusions:

Characteristics of the site investigator were the best predictors of recruitment rate. Delays in obtaining ethical approval, or initiating recruitment, do not necessarily indicate that a centre will be a poor recruiter. It may be effective to focus resources on sites with enthusiastic, engaged investigators.



international
stillbirth alliance
ANZSA is the ANZ regional
office of the International
Stillbirth Alliance.
www.stillbirthalliance.org



Reducing stillbirth and improving care for affected families through high quality research, clinical practice improvement and raising public awareness.

ANZSA (s) on research gaps and implementation of research into practice.

Julianne Brown, Jodie Dodd, Vicki Flenady, Adrienne Gordon, Heather Jeffery, James King, Phillipa Middleton, Katie Panaretto, Jonathan Morris on behalf of ANZSA.
www.stillbirthalliance.org/anz

Each year around 2500 infants are stillborn in Australia and New Zealand; a rate of 7.5/1000 births. The high proportion of unexplained deaths, the often suboptimal investigation as to the causes and contributing factors surrounding the death and the limited available research limit the potential for future prevention. Similar to model of the SIDS campaign, collaborative action is needed to address the problem of stillbirth.

The ANZ Stillbirth Alliance (ANZSA) brings together key organisations and individuals to focus on stillbirth prevention through the conduct of high quality research, audit and improvements in maternity care. ANZSA has grown from the work of the Perinatal Society of Australia and New Zealand (PSANZ) Perinatal Mortality Group and collaboration with other organisations which are now also members of ANZSA. These are: SIDS and Kids, Stillbirth and Neonatal Death Support Inc, the Stillbirth Foundation Inc.; the Royal Australasian and New Zealand College of Obstetrics and Gynaecology; the Australian College of Midwives Inc.; SANDS New Zealand; and Bonnie Babes.

Achievements to date

ANZSA was established with seeding funding from the Commonwealth Department of Health and Ageing, Canberra in June 2007. Through additional funding from the Stillbirth Foundation, ANZSA is undertaking a literature review to identify clinical practice and research gaps towards reducing stillbirth. Research gaps will be identified in collaboration with the WOMBAT Collaboration. Regional coordinators have been identified and teams are being established. An educational program to increase the uptake of the PSANZ Perinatal Mortality Audit Guidelines has been developed.

SCORPIO Educational program

The SCORPIO method of teaching includes 6 stations of 25 minutes and a maximum of 6 people per station. The six stations address the key recommendations of the PSANZ Perinatal Mortality Audit guidelines. This educational program is suitable for midwives, doctors and nurses providing maternity and newborn care at the time of a fetal or neonatal death. Participants will be taken through key aspects of the PSANZ guidelines in practical teaching sessions to assist them in undertaking best practice in perinatal audit and bereavement support for women and their families.

Research gaps for stillbirth prevention

Existing Cochrane reviews in pregnancy and childbirth will be reviewed to identify implications for research using the WOMBAT methodology: www.wombatcollaboration.org

The Australian Placental Transfusion Study

Jonathan Morris on behalf of the Australian Placental Transfusion Study Group

Background. Over 3,500 babies are born <30 weeks gestation in Australia annually. Compared with babies born at term, they have up to a hundredfold greater mortality and morbidity, and survivors have tenfold greater risk of disability with lifelong cognitive, behavioural and educational difficulties, coupled with near normal life expectancy. Reducing this burden is a major priority. Three convergent streams of evidence, much of it published by members of our group, provide strong biological plausibility for the idea that placental transfusion may benefit preterm babies. *Evidence from Cochrane Reviews.* Our Cochrane Reviews show no evidence that current cardio-vascular interventions reduce preterm mortality or morbidity. However, our Cochrane Review of 11 RCTs in 494 babies <37 weeks (including 2 APTS pilot studies) shows that placental transfusion decreases adult blood transfusions, and intra-ventricular haemorrhage (IVH) [RR 0.54 (0.37, 0.78)], necrotising enterocolitis (NEC) [RR 0.61 (0.43, 0.88)] and late onset sepsis [RR 0.61 (0.43, 0.88)]. *Evidence from echocardiography.* It is well established that low cerebral and systemic blood flow predispose to brain injury and necrotising enterocolitis. APTS members were the first to propose measurement of superior vena cava (SVC) flow by echocardiography as an index of systemic and cerebral blood flow. In over 20 papers describing early neonatal haemodynamics, we showed that up to a third of very preterm babies have low systemic flow on the first day; and that this is independently related to IVH, NEC, and death and disability at 3 years. Low flow is relatively resistant to inotropes, but usually responds to volume expansion with fluids. Volume expansion with placental blood at birth may therefore improve systemic flow and prevent brain and gut injury. *Evidence from haematology/ immunology:* Adult blood transfusions may predispose to retinopathy, and cord blood is rich in haematopoietic progenitor and stem cells. Placental transfusion may thus reduce retinopathy and enhance bone marrow function and immunocompetence against infection. *Why is more evidence needed now?* Many urge that placental transfusion be introduced now. Against this, effects in babies <30 weeks gestation are still unknown; and delaying resuscitation in very preterm babies by 30–60 seconds might increase hypothermia, asphyxia and adverse outcome. A reliable RCT is essential before the window of opportunity closes. We will include a sub-study with echocardiography to identify effects on low SVC flow, and on subgroups that may not benefit.

Research Plan. Babies born <30 weeks gestation to consenting mothers are randomly assigned by phone to early (<10 sec) clamping or placental transfusion, which is performed in two steps. These are (A) *Delayed clamping:* if possible, babies are held for 30–60 seconds below the placenta, to avoid back flow; (B) *Milking:* When the first step is complete, or if it was not possible, the cord is clamped and cut as long as possible. The baby goes to the neonatal team, who untwist, then milk the cord at resuscitation. This maximises placental transfusion, ensuring all get some placental blood.

Outcomes. 1,440 babies yields >90% power ($2p = 0.05$) to detect an 8% reduction in absolute risk of death or hospital morbidity, or >80% power for a similar reduction in death or severe disability. A substudy of 250 babies has >80% power ($2p = 0.05$) to detect a 7% reduction in low SVC flow.

Significance. This simple, low cost procedure may reduce – but could increase – death and disability in Australia and in developed, indigenous and developing communities worldwide. Large-scale randomised evidence is urgently needed before it is translated into practice and affects millions of babies long term. Groups in the US and Japan conducting similar RCTs have agreed in principle to pool their results in a prospective meta-analysis, in a future project, which would enhance power to detect even smaller differences reliably. Support for the APTS trial will therefore confirm Australia's role as a leading sponsor of innovative, international perinatal research.

PLUTO: Percutaneous Shunting in Lower Urinary Tract Obstruction Randomised Controlled Trial.

M D Kilby, K S Khan, R K Morris.

Dept. of Fetal Medicine, Birmingham Women's Hospital, University of Birmingham, BIRMINGHAM, UK, B15 2TG.

Primary objective:

- To determine if intrauterine vesico-amniotic shunting for fetal bladder outflow obstruction, compared to conservative, non-interventional care improves pre-natal and perinatal mortality and renal function.

Secondary objectives:

- To determine if shunting for fetal bladder outflow obstruction improves perinatal morbidity
- To determine the long-term effects of shunting with respect to: a) development of chronic renal failure, need for dialysis and/or transplantation b) development of incontinence (bladder dysfunction) c) disability free life year (incorporating assessment of cognitive development, quality of life, micturition and general health).
- To determine if improvement in outcomes is related to prognostic assessment at diagnosis, and if possible, derive a prognostic risk index.
- To maintain a prospective non-randomised registry of patients with lower urinary tract obstruction as part of a comprehensive cohort design.
- To ascertain the influences on the decision making of women with respect to opting for termination of pregnancy, randomisation (patient acceptability of trial) and to determine acceptability of the intervention to parents.
- To determine clinicians' prior beliefs about the effectiveness of shunting and to analyse trial results from a Bayesian perspective.
- To determine the cost-effectiveness of vesico-amniotic shunting compared to conservative management.

Design: A multi-centre randomized controlled trial embedded within a comprehensive cohort study, including evaluation of patient acceptability and cost-effectiveness analysis.

Setting: Tertiary referral units for fetal medicine in the UK and international.

Population: Pregnant women with singleton, male fetus with isolated lower urinary tract obstruction. Fetuses with additional major structural or chromosomal anomalies are excluded.

Sample size: A minimum of 150 pregnancies to the randomised trial (75 to each arm) to detect a difference of 20% in perinatal mortality with 80% power ($p < 0.003$).

Methods: Following an initial ultrasound diagnosis of fetal bladder outflow obstruction, eligibility and baseline characteristics will be confirmed including standard assessments of renal function, a detailed ultrasound examination to exclude other co-existing anomalies and ideally fetal karyotyping. Eligible mothers will receive an explanation of the diagnosis, prognosis, and treatment options for the condition and rationale for the trial. There will be no eligibility criteria relating to liquor volume at diagnosis allowing us to look at both a good and poor prognosis group. If the mother consents to participation, the fetus will be randomized to receive either a fetal vesico-amniotic shunt or continue with conservative management without a shunt. A minimum of 150 pregnancies will be randomized from both the UK and international centres. The primary outcome measures are perinatal mortality and serum creatinine at 6 weeks of age. Secondary outcome measures include bladder and renal function, termination and miscarriage rates and resource usage. Initial follow-up of secondary outcomes will continue to one year of age. Long-term follow-up of continence and assessment of childhood development and quality of life is planned at five years. Alongside the trial assessment of Bayesian priors, patient acceptability studies and economic analysis will be performed. In order to obtain the large number of pregnancies necessary for the reliable evaluation of surgical intervention for congenital bladder outflow obstruction, the trial will need the participation of UK and international centres. To make this practicable, the trial procedures will be kept simple, simple entry procedures, the use of standard local diagnosis and monitoring regimens (with few additional hospital visits or tests to be performed above those done as part of standard care), minimizing documentation and using secure web based data collection methods.

Main outcome measures: The main outcome measures will be perinatal mortality rates and renal function at 4-6 weeks and a composite outcome measure (incorporating assessment of cognitive development, quality of life, micturition and general health).

Estimated completion date: 2018

PeriKOOL: Cooling for perineal pain relief: A potential randomised trial

East C, Forster D, Nagle C, Maguire R, Moffat K, Savage T.
University of Melbourne, Royal Women's Hospital, Melbourne.
ANZTRN 12607000557437

Background

Perineal trauma is common following childbirth and may be present with a so-called "intact" perineum, as well as following tears or episiotomy. It can be very painful, which may reduce the woman's mobility and impact on her ability to care for her baby. Cooling treatments are commonly offered as a means of short-term pain relief.

Effectiveness of cooling treatments: The recent Cochrane systematic review (East et al 2007) identified seven RCTs, which were generally of poor quality. Briefly, these demonstrated that: ice packs improved perineal pain relief 24-72 hours after giving birth compared with no treatment: women preferred cold gel pads BUT reported no difference between pain relief from ice packs or cold gel pads; there was a limited effect on oedema and bruising; and there were no difference in activities of daily living or breastfeeding. Many important issues were not addressed by the RCTs. No studies reported the use of a systematic approach to soft tissue injury as used for other body regions, for example, **R**est, **I**ce, **C**ompression and **E**levation / being **H**orizontal (R.I.C.E./H.).

Current hospital practice is for an ice pack to be applied to the perineum in the Birth Suite, with the woman instructed to reapply ice packs as required. Women with third and fourth degree tears are reviewed by the physiotherapists, who incorporate the regime of R.I.C.H., whereby the woman is encouraged to rest, apply ice packs that are held in place (compressed) with firm fitting pads/underwear and to lie horizontal at times where she would otherwise sit up.

We therefore propose an RCT to compare two forms of cooling treatments:

- Standard practice
- R.I.C.H.

Hypothesis: The use of R.I.C.H. will result in a 25% reduction in women's self-reported perineal pain within 24 hours of childbirth, compared with standard treatment.

Estimated sample size: 25% reduction from 51% with moderate to severe pain in standard care group to 39% in R.I.C.H. group: 440 women in each group (allow 10% loss to follow up by 6 weeks, power 80%, alpha 0.049); stratified by parity, mode of birth; degree of trauma. This will also have power to detect a 10% difference in breastfeeding rates at 6 weeks.

Inclusion criteria: Vaginal birth (normal or assisted); written informed consent; perineal trauma – nil, 1st or 2nd degree tear, episiotomy; English speaking.

Exclusion criteria: 3rd or 4th degree perineal trauma; contraindications to cooling therapy; increased background risk of venous thromboembolism.

Outcome measures: some or all assessed at: 24 hours; 24-72 hours; 3-5 days; 6-14 days postpartum. Self-reported perineal pain, pain associated with activities of daily living, perineal oedema, perineal bruising, maternal exhaustion, use of additional perineal analgesia; attending to baby, side effects of perineal cooling therapy severe enough to discontinue treatment, breastfeeding, perineal healing, maternal views and experience with perineal analgesia. Further evaluation at 6 weeks and 6 months postpartum: incontinence, dyspareunia, breastfeeding, postnatal depression.

Significance: Results of this RCT would enable a more evidence-based approach to use of cooling treatment for relief of perineal pain following childbirth.

Study status: Not yet commenced.

Diabetes & antenatal milk expressing (DAME): a proposed RCT

Della Forster,^{B, C} Kerri McEgan,^A Gillian Opie,^A Anita Moorhead,^B Catharine McNamara,^A Susan Walker,^A Lisa Amir,^{B, C} Rachael Ford,^B Deb Boyce.^A

^A Mercy Hospital for Women, Melbourne, Australia; ^B Royal Women's Hospital, Carlton, Victoria, Australia; ^C Mother & Child Health Research, La Trobe University, Melbourne, Australia.

Background: Newborn infants of women with diabetes are at increased risk of hypoglycaemia and often admitted to special care nurseries for monitoring and treatment. If an infant's blood glucose is low and the mother unable to breastfeed/provide sufficient expressed breast milk, infants are usually given formula (or occasionally intravenous glucose), despite the strong evidence of the short and long term health benefits of exclusive breastfeeding from birth. Some hospitals encourage women with diabetes to express colostrum before birth; yet there is limited evidence for this practice. We have completed a pilot study to establish the feasibility of conducting an adequately powered randomised controlled trial (RCT) to evaluate antenatal expression of breast milk by women with diabetes. Forty women with diabetes/gestational diabetes requiring insulin were recruited to the pilot and encouraged to express colostrum twice a day from 36 weeks gestation. Expressed colostrum was frozen for the baby's use after birth. Of the data currently available: volumes of colostrum expressed range from 5 to 181 mls; total days expressing from 4 to 30; and total number of expressions 7 to 56. Women were generally pleased to have participated. Cardiotocography (CTG) was undertaken after the first expressing episode and in no case did the fetus show any sign of distress. Women's blood sugar levels were measured following the first three expressions with no evidence of a decrease related to expressing. Uptake to the pilot was 35-40%.

Methods: We plan to conduct a two-arm, unblinded RCT at two (and possibly more) sites to establish whether antenatal expressing for women with diabetes (requiring insulin) decreases the number of infants of these women who require supplementary artificial feeding in the first 24 hours of life compared with the infants of women receiving standard care. Secondary aims will be: to establish whether antenatal expressing for diabetic women (requiring insulin) has the potential to decrease the number of these infants requiring admission to a special care nursery and the number requiring an intravenous glucose infusion; to increase the proportion of infants breastfeeding at 6 and 12 weeks postpartum; and to explore a range of other factors such as volumes of colostrum obtained, infant blood glucose levels in the first 24 hours postpartum, fetal wellbeing associated with the first episode of expressing (assessed by CTG), and maternal satisfaction and views – measured by questionnaire at recruitment and prior to postnatal discharge home (around day 3, 6 weeks, 12 weeks). An economic evaluation will be included.

Sample size calculations will be based on the proportion of infants of women requiring insulin in pregnancy in the two proposed study sites who receive artificial formula in the first 24 hours of life. An audit of 44 medical records at site A demonstrated that 60% (26/44) of infants of women requiring insulin in pregnancy received artificial formula in the first 24 hours postpartum. We aim to decrease this by 20% therefore need a sample size of 107 per trial arm (214 total, with 80% power, 95% confidence). We anticipate little loss to follow up for the primary outcome, so have allowed 10% overall, ie our sample size will be 238. An audit of site B underway and we will reassess power calculations if appropriate.

Inclusion criteria: 1) Any woman between 34 and 36 weeks gestation with a singleton pregnancy in a cephalic presentation, attending the study sites for pregnancy care as a public patient, with pre-existing or gestational diabetes (requiring insulin), and planning to breastfeed. 2) English-speaking. **Exclusion criteria:** women with: a previous history of spontaneous preterm birth; any history of antepartum hemorrhage; a placenta praevia (even in the absence of any antenatal bleeding); an unknown or classical CS scar or greater than 1 LSCS scar; and if there is suspected fetal compromise or a known fetal anomaly.

For discussion: We are interested in feedback regarding our choice of primary and secondary outcomes; inclusion/exclusion criteria; and envisaged issues.

Fetal middle cerebral artery Doppler velocimetry to determine the timing of second and subsequent fetal blood transfusions in the treatment of fetal anaemia secondary to red cell alloimmunisation: A randomised trial.

Dodd JM¹, Ryan G², Windrim RC²

1. Discipline of Obstetrics and Gynaecology, The University of Adelaide
2. The Department of Maternal Fetal Medicine, Mt Sinai Hospital and The University of Toronto, Toronto, Canada

Background: Red cell alloimmunisation affects 0.1 to 0.6% of all live births. Treatment of fetal anaemia with intrauterine fetal blood transfusion has been associated with survival rates in excess of 90%, but involves an invasive procedure, with recognised complications.

Recently, reports have emerged utilising Doppler ultrasound to measure the fetal middle cerebral artery (MCA) peak systolic velocity (PSV) to determine the timing of second and subsequent transfusion procedures. Cohort studies reporting the use of fetal MCA PSV in this setting yield conflicting results.

Hypothesis: The use of fetal MCA PSV measurements in the fetus who has undergone one blood transfusion for fetal anaemia secondary to red cell alloimmunisation will reduce the number of invasive procedures required for fetal blood transfusion without increasing the risk of adverse outcomes for the infant related to alloimmunisation.

Study Design: An international, multicentre randomised, controlled trial.

Inclusion Criteria: Women with fetal anaemia secondary to red cell alloimmunisation (due to any antibody alone or in combination) as indicated by the need to have performed a single intrauterine fetal blood transfusion.

Treatment Schedules: Women randomised to the *Timing of Transfusion by MCA-PSV Group* will have weekly ultrasound determination of the fetal MCA PSV, with a serial upward trend with values greater than 1.5 MoM being considered indicative of the need for subsequent fetal transfusion.

Women randomised to the *Timing of Transfusion by Prediction of the Fall in Fetal Haemoglobin Group* will have subsequent fetal blood transfusions timed according to accepted criteria, based on an estimated fall in haematocrit of 1% per day following intravascular transfusion.

Outcomes: The primary study outcome is

- **adverse outcomes for the infant related to alloimmunisation.**

The secondary study outcomes are

- procedure related complications;
- adverse outcomes for the woman and her infant;
- maternal quality of life and well-being; and
- costs of health care.

Sample Size: For women eligible for this trial, the best estimate of the incidence of the primary outcome is 25.0%. To reduce this by 35% to 16.25% (alpha 0.05; power 80%), we will need to recruit 714 women to this trial.

Study Status: This trial is currently in the planning stage and will commence recruitment October 2008.

Dietary and lifestyle advice, and treatment for women with borderline gestational diabetes.

Crowther CA¹, McPhee AJ², Hague W¹, Baghurst P³, Dodd JM¹, Robinson JS¹

1. Discipline of Obstetrics and Gynaecology, The University of Adelaide
2. Department of Perinatal Medicine, Women's and Children's Hospital
3. Discipline of Public Health, The University of Adelaide

Background: Treatment of pregnant women with mild gestational diabetes (previously termed impaired glucose tolerance) is beneficial, with improved health outcomes for women and their infants.

There is currently a lack of high quality information available as to whether similar treatment for women with borderline gestational diabetes (positive oral glucose challenge test and normal oral glucose tolerance test) is associated with greater benefit than harm.

Hypothesis: Dietary and lifestyle advice, and treatment for women with borderline gestational diabetes on screening for gestational diabetes will reduce the incidence of large for gestational age infants, reduce the risk of death or serious health outcomes for the infant, and reduce the risk of serious health outcomes for women.

Study Design: A multicentre, randomised controlled trial.

Inclusion Criteria: Women with a singleton pregnancy between 24⁰ and 34⁰ weeks gestation, who have a positive oral 50 gram glucose challenge test (OGCT) and a normal oral 75 gram glucose tolerance test (OGTT), who provide written informed consent.

Treatment Schedules: Eligible women (positive OGCT, normal OGTT) will be randomised to either the **Routine Care Group** who will receive their routine pregnancy care by the attending obstetric team; or to the **Intervention Group** who will receive dietary and lifestyle advice, blood glucose monitoring and treatment as necessary.

Outcomes: The primary study outcome is

- **Incidence of large for gestational age infant** (defined as infant birthweight above the 90th centile for gestational age and infant sex);
- **Death or serious health outcome for the infant;** and
- **Serious health outcome for the woman.**

Sample Size: For women eligible for this trial, the best estimate of the incidence of the primary outcome is 13.7%. To reduce this by 35% to 8.91% (alpha 0.05; power 90%), we will need to recruit 1,916 women to this trial.

Study Status: This trial has commenced recruitment January 2008.

DAY TWO ABSTRACTS

Sugar Babies Study: A Randomised Controlled Trial

DL Harris^{1,3}, PJ Weston¹, M Battin^{2,3}, JE Harding³

1 Newborn Intensive Care Unit, Waikato District Health Board, Hamilton

2 Newborn Services, Auckland City Hospital, Auckland

3 Liggins Institute, University of Auckland, Auckland

Background: Neonatal hypoglycaemia (low blood sugar level) is a common problem and the only known common preventable cause of brain damage in the newborn period. It is a common reason for admission to the Newborn Intensive Care Unit. Oral carbohydrate is first line treatment for low blood sugar levels in the conscious diabetic child or adult. However, Waikato Newborn Intensive Care Unit is the only unit in Australasia to use dextrose gel for the management of hypoglycaemia. Two small unpublished studies have examined the use of dextrose gel. One reported reversal of hypoglycaemia following 0.5ml/kg dose, whereas the other reported no change in blood glucose levels using 1ml/kg dose, but a reduction in the volume of milk taken in the subsequent feed. Therefore, the role of dextrose gel in the management of hypoglycaemia remains unclear.

Hypothesis: That 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycaemia.

That intermittent blood glucose monitoring does not detect all episodes of hypoglycaemia.

Trial design: Randomised, placebo controlled, double-blinded study in hypoglycaemic near-term and term babies, comparing the incidence of treatment failure in babies randomised to receive either 40% dextrose gel or a placebo vehicle gel.

Methods: Term or near term babies at risk of hypoglycaemia will be recruited, if possible before birth. A continuous glucose sensor (CGMS® System Gold™, Medtronic, Minimed®, Northridge, USA) will be inserted as soon as feasible after birth. If hypoglycaemia is diagnosed (blood glucose level <2.6mM) the baby will be fed and randomised to receive either 40% dextrose gel or a placebo gel. If a baby remains hypoglycaemic following two doses of gel 30 minutes apart, on-going management will be according to usual practice.

Outcomes: The primary outcome is treatment failure, defined as a blood glucose level < 2.6mM 30 minutes after the second of two treatment attempts.

Secondary outcomes include: time taken to achieve an interstitial glucose level >2.6mM for >1 hour; incidence of recurrent hypoglycaemia after an initial successful treatment; admission to the neonatal intensive care unit; frequency and total volume of formula administered in the first 48 hours; rate of full breast feeding at two weeks of age

Sample size: In 2006 56% of at risk babies became hypoglycaemic, and 20% of these remained hypoglycaemic after two doses of dextrose gel. 109 babies in each group will allow us to detect a treatment failure rate with placebo gel of 35% (one tailed alpha=0.05, beta=0.2).

Dietary and lifestyle advice for women who are overweight or obese to limit weight gain during pregnancy: A randomised trial.

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Background: Obesity is a significant health problem for pregnant women. Estimates suggest that approximately 35% of women aged 25-35 are overweight or obese.

Well documented risks associated with obesity during pregnancy and childbirth include hypertension and pre-eclampsia, gestational diabetes, infection, thromboembolic disease, need for induction of labour, caesarean section and perinatal death. Risks for infants born to women who are overweight or obese include macrosomia, need for admission to the neonatal intensive care unit, preterm birth, and jaundice or hypoglycaemia requiring treatment.

There is more limited information about effective interventions that may improve health outcomes for this group of women and their infants.

Hypothesis: Implementing a package of dietary and lifestyle advice to overweight and obese women during pregnancy will reduce the risk of infants born large for gestational age.

Study Design: Multicentred randomised, controlled trial.

Inclusion Criteria: Women with a live singleton pregnancy, between 10⁺⁰-20⁺⁰ weeks who are obese or overweight (body mass index greater than 25kg/m²).

Treatment Schedules: Women randomised to the dietary and lifestyle intervention group will receive a comprehensive intervention to limit weight gain in pregnancy that includes a combination of dietary, exercise and behavioural strategies. Women will be referred to a research dietician for dietary advice consistent with current Australian dietary standards, designed to minimise weight gain during pregnancy to less than or equal to 5kg. Women will be provided with information about exercise during pregnancy, and encouraged to make changes to their lifestyle.

Outcomes: The primary study outcome is

- **Infant large for gestational age**

The secondary study outcomes are

- **Other adverse infant health outcomes;**
- **Maternal morbidity from pregnancy complications & adverse outcomes;**
- **Maternal quality of life and well-being;** and
- **Costs of health care.**

Sample Size: For women eligible for this trial, the best estimate of the incidence of large for gestational age infants 13.3%. To reduce this by 27% to 9.7% (alpha 0.05; power 80%), we will need to recruit 2574 women to this trial.

Study Status: This randomised trial will commence recruitment April 2008.

Does fentanyl in epidural analgesia affect the ability of the neonate to effectively breastfeed?

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Aim: To increase the proportion of primiparae who fully and directly breastfeed their babies at 2 weeks.

Background: Personal anecdotal observation for the last few years that some babies have a disorganised suck that appears to be associated with epidural analgesia. This may be related to the use of opiates (fentanyl) in the epidural. Anaesthetists report no/negligible fentanyl in cord blood so reject the association. But fentanyl is lipophilic, and my hypothesis is that it remains in the neonatal brain and is slowly excreted. The effect on sucking is thus relatively prolonged, and enables bad habits to establish, so women decide to wean, or to express and feed with expressed breast milk. Torvaldsen et al. found an association between epidural analgesia and breastfeeding problems (Torvaldsen, Roberts, Simpson, Thompson, & Ellwood, 2006). A RCT of women who had successfully breastfed a previous baby found that those who had fentanyl in their epidural were more likely to wean than those who had an epidural that did not contain fentanyl (Beilin et al.).

Design: Double blind randomised controlled trial.

Inclusions: Primiparae who intend to breastfeed and who are at least 30 weeks pregnant at recruitment.

Exclusions: Preterm birth, conditions that would interfere with breastfeeding e.g. cleft palate; baby admitted to NICU (?SCN); inability to understand English; recreational maternal opiate use.

Recruitment: late in pregnancy at antenatal visits; asked to agree to randomisation if they have epidural analgesia, but no obligation to preferentially use epidural

Intervention: Randomised at recruitment and given study ID. If epidural is required, ampoule matching the ID is used. OR randomised only to group A or group B, and ampoule with unique ID and labelled A or B is used (more open to error); OR randomised at time of request for epidural, and ampoule with the unique ID number is used. Anaesthetist administers drug in the same way as at present, with (ideally) same quantities, same appearance. If not possible, might need to be single blind (or semi blind), but likely to influence outcomes.

Primary outcome: exclusive, direct breastfeeding at 2 weeks

Secondary outcomes: pain relief (VAS change pre- & post?); satisfaction with pain Rx; time to effective analgesia; exclusive BF at 6weeks or 3 months; CS; instrumental birth; attachment problems; any formula in hospital; any successful attachment in hospital; prolonged immobility following epidural; respiratory involvement

Issues for discussion: anaesthetist buy-in; protocol for epidural anaesthesia; SCN admissions; age of primary outcome measurement (as early as possible to match established measures); making up & dispensing of study medication (? Pharmacist or drug company collaborator); timing of randomisation; measurement of time taken from epidural administration to effective pain relief;

A-STEROID: Child health outcomes at 2 years' corrected age after antenatal exposure to either dexamethasone or betamethasone: a planned randomised controlled trial.

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Background: Antenatal corticosteroids given to women at risk of preterm birth substantially improve neonatal health and childhood neurosensory disability. Dexamethasone and betamethasone are both recommended and widely used but it is not clear which drug is more effective.

Aim: To determine whether antenatal exposure to dexamethasone compared with betamethasone given to women at risk of preterm birth at less than 34 weeks gestation increases the rate of survival free of neurosensory disability in their children at 2 years corrected age.

Existing evidence: Evidence from non-randomised studies is conflicting and little evidence of relevance to this question is available from the Cochrane review of antenatal corticosteroids (Roberts et al 2006). A new Cochrane systematic review (Brownfoot et al 2008) includes nine trials comparing dexamethasone with betamethasone. This review shows few significant differences between the two drugs, except for intraventricular haemorrhage where dexamethasone shows a lower risk compared with betamethasone. None of the trials included in the review had sufficient power or length of follow-up to assess the relative effects of the two drugs on child health and Brownfoot et al 2008 conclude that high quality randomised trials are needed.

Summary of proposed RCT protocol: We are planning a multi-centre trial recruiting women with a singleton or twin pregnancy, at less than 34 weeks gestation. The treatments will be either 11.4 mg betamethasone or 12 mgs dexamethasone (both given as two intramuscular injections 24 hours apart. The primary outcome will be death (stillbirths and deaths from liveborn infants) or neurosensory disability (which includes cerebral palsy, blindness, deafness and developmental delay) at two years. **Discussion:** We are particularly seeking feedback about the primary outcome, sample size calculations and also whether other centres are willing to participate in a trial such as this.

References

Brownfoot F, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2008.

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A randomised controlled trial of caseload midwifery.

Chief Investigators: Prof Sally Tracy, Prof Michael Chapman, Prof Michael Peek, Dr Mark Tracy
Prof Caroline Homer and A/Pr Sue Kildea.

Associate Investigators: Prof Maralyn Foureur, Prof Pat Brodie, Prof Nicy Leap and Prof Jane Sandall

PhD Students: Donna Hartz and Helen Cooke

Background: There is concern about the rising levels of caesarean section in Australia and some evidence that women may benefit from caseload midwifery care. This randomised control trial will determine whether caseload midwifery care can reduce interventions and is as safe as usual hospital maternity care.

Null Hypotheses

- Caseload midwifery care and routine care for women are similar with respect to rates of intervention, use of analgesia, mode of birth and cost.
- Caseload midwifery care and routine care for women are similar with respect to the rates of neonatal morbidity, perinatal mortality, maternal morbidity and maternal health consequences.

Aim: To compare the outcomes and costs of caseload midwifery care compared to standard or routine hospital care for childbearing women through a randomised controlled trial.

Design: A clinical trial method is to be utilized. Pregnant women will be randomly allocated to caseload midwifery care versus routine care during pregnancy according to a post-consent method using accepted concealment measures endorsed by the NH&MRC. We aim to recruit a total of 1950 women. Following attrition estimated at (30%), if 750 women or more remain in each of the intervention and control arms, the study will have the power (with 80% power; alpha 0.05) to detect a difference in caesarean section of 29% to 22.9%; instrumental birth rates 11.0% to 6.8%; and rates of admission to neonatal intensive care of all neonates from 9.9% to 5.8% (712 in each arm). The study has not been powered to detect infant or maternal mortality, however all deaths will be reported. . Secondary outcomes will include rates of smoking cessation (eg 14.8% to 9.9% needing 747 in each arm) and breastfeeding initiation and duration.

Study Design: This trial has received a National Health and Medical Research Council Project Grant and recruitment will commence in mid 2008. Currently ethics protocols are being refined for submission to area health services and a pilot site is being negotiated to test the research methods and protocols.



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