

Stillbirth Foundation Australia Research Newsletter June 2011



stillbirth
FOUNDATION
australia

Little Feet continuing to take big steps... to reduce stillbirth

The longest journeys start with the smallest of steps.

Stillbirth is one of the subjects we, as individuals and as a society, find hard to discuss. But not only is the loss of a child so very difficult to accept, the seeking of answers can almost be harder still. That is why the Stillbirth Foundation Australia invests so heavily in research. We are dedicated to helping find the answers to one of Australia's most puzzling problems.

Since its inception, the Stillbirth Foundation Australia has invested over half a million dollars into researching the causes of stillbirth in Australia, and we continue to release grant funding on a yearly basis. This edition of our newsletter is dedicated to an update of the findings completed by our hard working researchers. We applaud them for their efforts, and every single one of these studies we have funded will enable health professionals to better understand stillbirth.

But for the Stillbirth Foundation Australia, seeking an answer to the problem of stillbirth may be an incredible responsibility however we fund these studies for another reason. The funds we raise are YOUR funds. This is money donated by heartbroken families and friends, all of whom are looking to invest in seeking an answer to their loss. We are honoured to be able to most recently remember babies such as Jast Herder, Evie Angela David, James Smart, Ruby Rose Brown and John Hutchinson amongst hundreds of others, in research programs such as the ones in this newsletter. Donations help us to keep searching, researching and investigating, and each small step gets us closer to answers. It is only by researching into the causes of stillbirth, and openly talking about the puzzle, will we be able to make it go away.

The Stillbirth Foundation Australia is also dedicated to making sure that we keep on talking about stillbirth, in the face of the pain it causes. We want to have these children remembered, honoured and celebrated, and

this cannot happen without open and free discussion about the problem of stillbirth. The most recent report into the numbers of stillbirths was published in the AIHW Mothers and Babies Report. That Report recorded 2,188 stillbirths in Australia in 2008. For every baby who tragically passed from SIDs, another 37 babies were stillborn. But we talk about SIDs, we know about SIDs. We do not know about stillbirth, and we talk about it even less.

The loss of life through stillbirth is significant, and yet sadly overlooked.

You can help us change this. By talking, fundraising and continuing to refuse to ignore the problem of stillbirth, we can prevail.

Please read through our updates on our latest research. Be proud of where your money and time has been invested. And join us in thanking the Stillbirth Foundation Australia's Scientific Assessment Committee who kindly donate their time and expertise to assess the suitability of our research applications - Ms Emma McLeod, Professor Jonathan Morris, Dr Christine Roberts, Professor Brian Trudinger and Professor Euan Wallace.

3031 men died from prostate cancer
2788 adults died from breast cancer
2,188* babies were stillborn
1857 people died from skin cancer
899 women died from ovarian cancer
59 babies died from SIDS

Deaths in Australia 2008 – Australian Bureau of Statistics
* AIHW National Perinatal Statistics Report

The Stillbirth Foundation Australia operates to reduce the incidence of stillbirth in Australia, by:

funding and encouraging research into stillbirth and
increasing public awareness about stillbirth.

little feet taking big steps... to reduce stillbirth



Risk factors for Stillbirth – The Sydney Stillbirth Study



Dr Adrienne Gordon, Dr Camille Raynes-Greenow, Professor William Rawlinson, Professor Jonathan Morris, Professor Heather Jeffery

This is a multi-centre study currently running in eight Sydney Hospitals and assessing risk factors for late pregnancy stillbirth. We focus on late pregnancy as these sadly are the deaths that are more likely to remain unexplained.

It is the most comprehensively designed study of its kind to be conducted and is run by a team of highly experienced and passionate investigators. In depth interviews with the families are performed to assess potential risk factors, investigations for viral infection are taken at the time of delivery and detailed placental examination is performed. Currently we have recruited 77 from a planned total of 100 cases and 141 from a planned total of 200 controls.

Funding from the Stillbirth Foundation Australia has enabled us to employ two part-time research midwives which make this sensitive study possible. Additional funding received in 2010 from the Stillbirth Foundation Australia has helped us to perform detailed analysis of the maternal perception of fetal movements.

All our planned hospitals are now recruiting and importantly the study has been acceptable to bereaved parents with a 72% recruitment rate for families of stillborn babies.

Our team presented two abstracts at the International Stillbirth Alliance held in Sydney in October 2010 based on results to date. The first regarding risk factors reported that significantly more cases were identified as having fetal growth restriction during pregnancy (OR 11.1 95% CI 1.4-89) as well as being small for gestational age at birth (OR 7.4 95% CI 3 -25).

The second described maternal perception of fetal movements and our finding that cases were significantly more likely to report a decrease in the perception of fetal movement as pregnancy progressed (OR 4.9 95% CI 1.9,11.9) whereas control women were more likely to report an increase (OR 1.7 95% CI 1.3,2.4). Importantly 59% of women were not given any specific information regarding fetal movements by their caregiver during their pregnancy.

The Role of Infection and Inflammation in Stillbirths

Prof C.C Blackwell, Prof Ian Symonds, Dr Andrew Carlin

It has been suggested that Sudden Infant Death Syndrome (SIDS) and stillbirths are part of the same spectrum of unexpected infant deaths. Although different bacteria and/or viruses are implicated in these conditions, the constant “thread” is the body’s usually protective response to these infections by the mother and/or baby.

We suggested some of these unexplained deaths are due to the immune system’s “shock like response” (SLR) to infection or toxins. Ethnic groups at high risk of SIDS and stillbirths have genetic markers for strong SLR that could be enhanced by major risk factors for stillbirths (minor infection, smoking and obesity).

The pilot study enabled us to set up infrastructure for assessing risk factors for SLR among stillborn babies and their mothers. This entailed a very long correspondence with the ethics committee and making sure all the team looking after families who experience a stillbirth knew about the study and what was needed.

All this is now in place and the first family has joined the study. In the laboratory, we tested the idea that women with a gene profile for strong SLRs would produce

higher levels of some proteins used to measure responses to infection. We also predicted that the presence of two infections (virus plus bacteria) would switch on stronger responses. The third prediction was that cigarette smoke would reduce the body’s response (IL-10) that helps damp down SLR.

We found that women with the genetic profile for strong SLR produced lower levels of IL-10 and that virus infection and cigarette smoke further reduced this moderating response. Once SLR is switched on in these women, it might be less easily controlled. From the “seed money” for the project, we obtained laboratory evidence that our predictions regarding the effects of genetic and environmental risk factors for stillbirths affect the SLR.

We set up the infrastructure and lines of communication to examine samples from stillborn babies and their mothers to look for “footprints” of SLR and infections.

We are using the data collected to apply to NHMRC for three years of funding to allow us to continue this exciting new line of investigation.





Maternal Sleep Health and Fetal Outcomes

Dr Alison Fung, Assoc Prof Sue Walker and Dr Maree Barnes

Obstructive Sleep Apnoea (OSA) is characterised by repetitive episodes of partial or complete upper airway obstruction during sleep, which lead to low oxygen and high carbon dioxide, and frequent arousals from sleep. The consequences of these events include activation of the sympathetic nervous system and inflammatory pathways. These changes may be responsible for the development of hypertension, metabolic syndrome, type 2 diabetes and increased cardiovascular risk.

The impact of OSA on pregnancy outcomes is less clear, but some studies have suggested an increase in intrauterine growth restriction among women who snore. In this study, we will examine the impact of SDB and OSA on foetal growth and health.

We have recruited over 300 women to the first part of study. They have completed sleep questionnaires and 45 of these women have been approached to take part in Part 2. 10 subsequently declined or delivered preterm and one has excluded because of pre-existing diabetes mellitus. Three are as yet undelivered.

All 10 women considered “low risk” for OSA on questionnaires, have had this confirmed by sleep study. The positive predictive value of the questionnaires has been poor, with only 9 of the remaining 21 “high risk” women, having sleep apnoea on sleep study.

The continuous fetal heart rate monitoring in all women has demonstrated only one patient with decelerations present. This was in a case of OSA, where the baby was subsequently shown to be small for gestational age (SGA) at birth. Despite significant OSA in some of the other patients, the fetal heart monitoring has otherwise been normal.

SGA fetuses have been equally distributed amongst OSA and non-OSA women. However, we have seen a trend towards higher rates of reduced growth in the OSA women, with 33% showing a $\geq 30\%$ fall in customized growth centiles from 32 weeks to birth, compared with only 4.5% in the non-OSA group, $p=0.06$.

As we are nearing completion of recruitment, final data analysis with results will occur shortly.

Free Fetal DNA, Placental Apoptosis and the Predication of Late Stillbirth

Dr Jasjot Kaur, Associate Professor Catherine Hyland, Dr Susan Arbuckle and Clinical Professor Jonathan Hyett

Some late stillbirths may be due to sudden and catastrophic failure of the placenta. We have been investigating whether pieces of fetal DNA that can be identified in a maternal blood test can be used to monitor placental function towards the end of pregnancy. The rationale for this is that previous studies have suggested that the DNA levels reflect the degree of placental breakdown (through a controlled process known as apoptosis). Fetal DNA is also cleared very rapidly from the mother's blood – so a test should give an accurate picture of placental function at the time the blood was taken rather than over a period of weeks.

The study has concentrated on collecting matched maternal blood and placental samples from women having a caesarean section. Sample collection is now complete and we have samples from a range of pregnancies including some that have no obvious complications and others where there have been complications such as high blood pressure or diabetes through the pregnancy.

The analysis of the blood samples is now complete and we have data listing the concentration of free fetal DNA from all mothers. The microscopy work detailing

placental condition (looking for the extent of apoptosis) is underway and should be complete in the next two months. Once data collection is complete we plan to compare the ffDNA levels from maternal blood to the degree of apoptosis seen in the placenta.

Dr Kaur presented some preliminary data at the International Stillbirth Alliance meeting in Sydney last year. Although we did not demonstrate any significant association between ffDNA and placental breakdown at this stage, the numbers available were small and we are now using a second complimentary technique to analyse placental function to check the accuracy of these results.

We are hopeful that the statistics will be completed by the middle of the year and that we will then be able to publish the results.

We would like to thank the Stillbirth Foundation Australia for the support they have offered us, which has enabled us to carry out this work.



PhD Project: The Role of Human Cytomegalovirus in Stillbirth

Stuart Hamilton, supervised by Prof. William Rawlinson and Dr Gillian Scott

I have just completed the first year of my PhD studies funded by the Stillbirth Foundation Australia investigating the role of cytomegalovirus (CMV) infection in stillbirth.

My research is examining the immune response to CMV infection within the placenta and how this response can potentially result in stillbirth. I am also investigating how CMV is transmitted across the placenta, and whether damage caused to the placenta by CMV promotes transfer from mother to baby. I do this in two ways: Firstly, by examining tissue specimens from stillbirth cases; and secondly, by looking at *in vitro* culture models of CMV infection in the laboratory.

My research has shown that placentae from stillbirth babies infected with CMV have elevated pro-inflammatory responses, including increased levels of key proteins, called cytokines. Using our placental culture models, we are now examining further the changes that occur in placental cells and tissue in response to CMV infection and looking into potential intervention and therapeutic strategies. Finding

treatments that will prevent CMV transmission and infection, or reduce the damage caused by CMV-induced pro-inflammatory responses within the placenta, are the ultimate goals of this research.

This work was presented at the International Stillbirth Alliance/ISPID Joint Conference in Sydney, October 2010. Next I will be visiting Nuremberg, Germany in May to present my work at the 13th International Betaherpesvirus workshop. It is very encouraging to have my research selected for oral presentations and awards, and highlights the interest that is being received by scientific and clinical researchers in obstetrics, paediatrics and infectious diseases. I am very pleased to be raising awareness regarding the high number of stillbirths per year with unknown aetiology, the need for more research in this area and the potential links to CMV infection.

I would like to say a big thank you to the Stillbirth Foundation Australia and all its supporters for funding this important research.

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