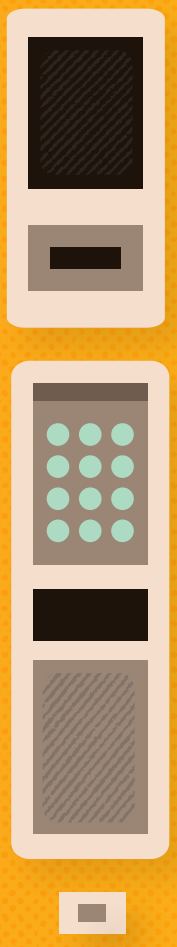

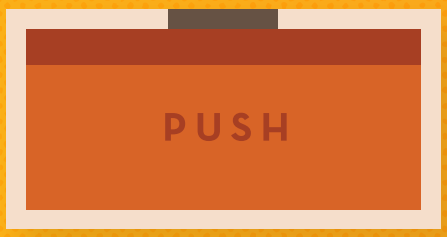


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## Diabetes

## Women's health



## The College



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# From the President

**Prof Steve Robson**
**President**

This issue of *O&G Magazine* deals with one of the most critical public health issues of the day – diabetes. The prevalence of diabetes in our communities continues to increase and the health costs of this non-communicable disease (NCD) seem almost incalculable to me. As always, the team behind *O&G Magazine* have drawn together a stellar group of authors to examine the important aspects of diabetes and its impact on women, in particular, and society in general.

One of the debates with which I have some involvement has been a campaign for a 'sugar tax'. There is good evidence that a mix of community incentives and education around the harmful health effects of consuming processed sugar can yield impressive health results. Unfortunately, as we see so often, there is little political will to follow evidence-based public health principles.

## Out-of-pocket costs

I have been appointed to the Ministerial Advisory Committee on Out-of-Pocket Costs and, by the time you read this column, the group will have had its first meeting. During my Presidential term I have put great effort into issues regarding private practice in our specialty. Surveys and focus groups have been held. The College has hosted meetings with officials from private health insurers (PHIs), indemnity organisations, other craft groups and Australian Government officials. I have also attended meetings with other colleges and societies that have been hosted by the Australian Medical Association (AMA).

Things came to a head early in the new year with the publication in *ANZJOG* of a paper reporting that out-of-pocket costs for maternity care had increased more than 1000 per cent over the last 25 years.[1] The paper provoked a media frenzy and I found myself in a live interview on ABC News that day. I was in the studio with Mark Metherell from the Consumers Health Forum (CHF) and we disagreed at the time. However, I took the opportunity to make friends and spend some time with the CHF team in the hope that we can all work together towards our common goal of improving access to obstetrician-led care for women who aspire to this.

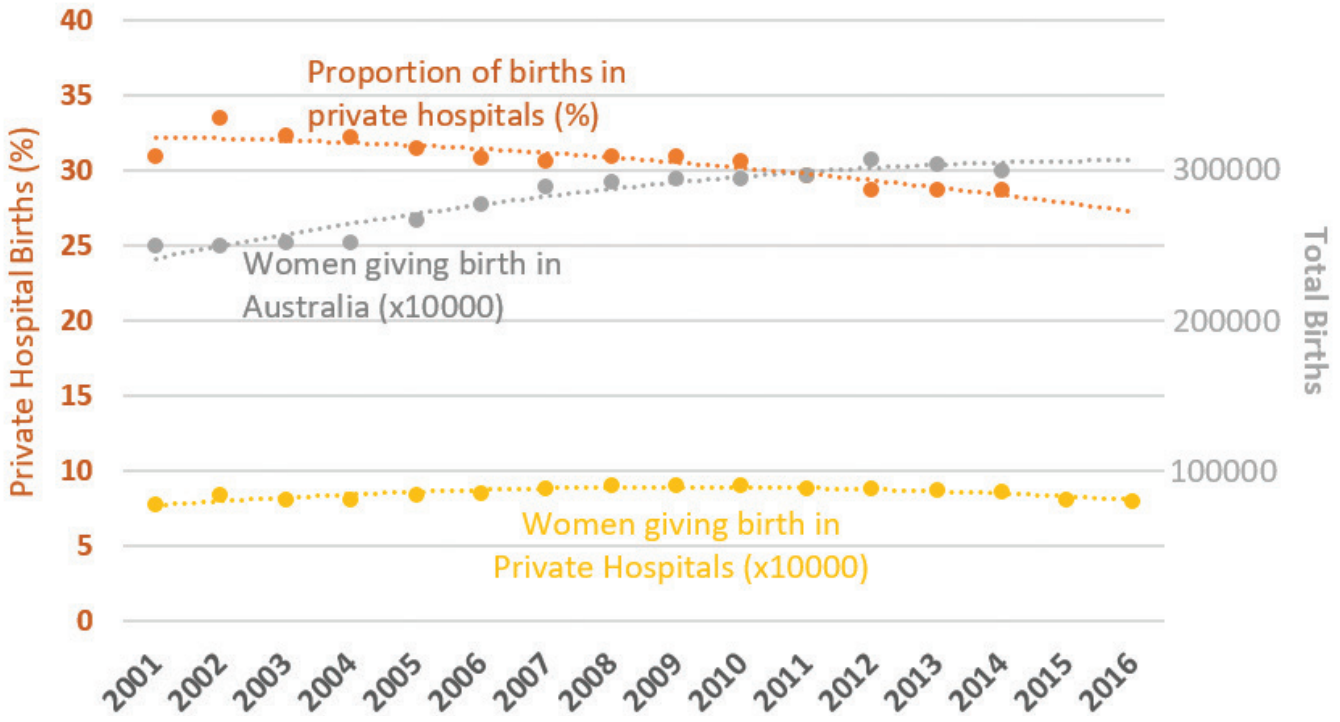
In Australia, we have a balance between the public and private healthcare systems that we should cherish. Looking to the UK, the sometimes beloved National Health Service (NHS) is in a financial struggle that threatens its very survival. Maternity outcomes have prompted a national campaign by the Royal College of Obstetricians and Gynaecologists following revelations that UK stillbirth rates are among the highest in Europe. Across the Atlantic in the USA, where most care is provided in private settings, the rate of maternal death has doubled over the last two decades. These data show that maternal mortality rates are now higher in the USA than in Syria and Iran.[2]

Fortunately, Australia has managed to steer a path between the extremes of all-public NHS-style and all-private US-style healthcare, but there are now tremendous pressures on the private system in Australia. The number of births in private hospitals continues to fall (see Figure 1) and this is a major concern to me. Our own data, obtained from Medicare, show that out-of-pocket costs for private care in Australia have been relatively static, while out-of-pocket costs for antenatal visits have outpaced rises in the consumer price index (CPI). I will report back to you as things progress on this front over the coming year.

## Transvaginal mesh

Since the last issue of *O&G Magazine*, the Australian Therapeutic Goods Administration (TGA) has withdrawn approval for all transvaginal mesh kits. The TGA has also insisted on changes to

**Figure 1.** The proportion of births occurring in private hospitals plotted against the overall numbers of births in public and private hospitals.



the 'instructions for use' (IFU) for mid-urethral tapes. While some products have complied with these instructions, Johnson&Johnson have stopped imports of transvaginal tape (TVT) products through GyneCare, and this is likely to interrupt supply for all of 2018. Although there are other alternatives, this is a major and very retrograde step for the women of Australia and New Zealand.

There is absolutely no doubt that for women with genuine stress incontinence, where proper assessment and counselling has occurred, mid-urethral tapes are a very safe and effective treatment. This is backed by a strong body of evidence.[3] More importantly, other surgical treatments do not yield such good results, are more likely to cause complications and often impose a longer recovery period. It is unequivocal that mid-urethral tapes are an excellent, safe and appropriate treatment for a condition that imposes misery on many women. Unfortunately, politics and populism have overwhelmed a scientific debate to the severe detriment of women.

## The autumn of my term...

By the time you read this column, we will have just wrapped up the National Women's Health Summit, a forum where the 100 most influential leaders in women's health have the opportunity to discuss and address the most pressing women's health challenges facing our nation. Not only was this event an opportunity for the College to demonstrate leadership, it also provided a platform to launch a priorities document as an advocacy tool to ensure women's health stays on the political agenda. This is the second and final year of my Presidential term. Last year was very busy, and, if the Summit is anything to go by, I expect this year to be much the same. Following on from the Summit, I am intending to pursue a body of work on Indigenous women's health, including the appointment of an 'Elder-in-residence' for the College. There is work to do on improving income streams for the RANZCOG Women's Health Foundation, getting the pre-vocational program up and running, and many other projects. I am looking forward to meeting and working with as many of you as possible.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# From the CEO

**Alana Killen**
**CEO**

Members of the College will be aware that the Medical Board of Australia (MBA) has been undergoing a review of the existing CPD registration standard for medical practitioners over the past two years. This review has now been completed and the final report of the Expert Advisory Group has been handed down and may be viewed on the MBA website: www.medicalboard.gov.au/Registration/Professional-Performance-Framework.aspx.
The MBA has accepted the final report on revalidation and its recommendations, including not to adopt the term 'revalidation' as it does not accurately describe the Board's approach. Rather, the MBA is proposing to develop a Professional Performance Framework to support doctors in taking responsibility for their own professional development.

The Five Pillars of the Professional Performance Framework are:

1. Strengthened CPD by:
    - Doing CPD that is relevant to the scope of practice
    - Basing CPD on a personal professional development plan
    - Doing at least 50 hours of CPD per year that includes a mix of:
        i. Reviewing performance
        ii. Measuring outcomes
        iii. Educational activities
2. Active assurance of safe practice, which will include:
    - Identifying practitioners at risk of poor performance and managing that risk
    - Requiring practitioners who provide clinical care to have peer review and health checks at the age of 70 and every three years thereafter
    - Requiring professionally isolated doctors to do more CPD that involves peer review
3. Strengthened assessment and management of medical practitioners with multiple substantiated complaints, which will involve participation in formal peer review of performance.
4. Guidance to support practitioners, which will include:
    - Revising Good Medical Practice: A code of conduct for doctors in Australia
    - Refining existing and developing new registration standards
    - Issuing other guidance as required
5. Collaborations to foster a positive culture of medicine by:
    - Promoting a culture of medicine that is focused on patient safety
    - Working with the profession to reshape the culture of respect
    - Encouraging doctors to:
        i. Commit to reflective practice and lifelong learning
        ii. Take care of their own health and wellbeing
        iii. Support their colleagues
    - Urging governments and other holders of large data to make it accessible to individual practitioners to support practice improvements.

## Supporting our members

RANZCOG has been closely following the 'revalidation' discussion and process to ensure that the transition to the new registration requirements is as seamless and efficient as possible. The MBA has indicated that this transition process is likely to take place over a period of several years, so this enables the College to develop the necessary tools, templates, resources and programs to support our members with the new arrangements. Many of the details have yet to be finalised and will be done in collaboration with the many stakeholders. Questions still to be answered include: which agencies will be responsible for certain activities (for example, identifying practitioners at risk of poor performance, health checks for doctors over 70 years old, peer reviews, remediation); and what will be the role of the medical colleges within this new structure?

## Private practice

Over the past few months, the College has been conducting a number of focus groups to discuss the issues associated with private practice. Following the survey conducted at the end of 2017, it was determined that additional support and advocacy efforts needed to be directed towards this important area of the O&G specialty. It is recognised that many families are electing to discontinue private health insurance, which is placing pressure on the public health system due to increasing demand. The subsequent impact on our members, their practice and future careers needs to be examined and discussed with plans established to manage the changes to the O&G workforce. We rely heavily on information provided by our Fellows regarding type of practice, specialty, subspecialty, hours, location and other relevant information, so your assistance in keeping our data current is greatly appreciated.

## Training Support Unit

Since the launch of the Training Support Unit (TSU) at the College Annual Scientific Meeting in November 2017, the unit has been kept busy with queries and requests from trainees and supervisors. The TSU can support trainees experiencing difficulty in a number of ways: providing support and advice; providing information about existing resources, agencies and organisations; and referring trainees to the College's external assistance program, provided by Converge International. This enables trainees to access:

- Support that is confidential and private
- Up to three sessions of counselling, family assistance and crisis counselling per calendar year (funded by RANZCOG)
- Support that can be tailored to meet individual needs (face to face, telephone or online)
- Services available across Australia and New Zealand

Future plans for the TSU include the appointment of a Supervisor Liaison Officer to provide support and information to those undertaking the critical role of supervising trainees in RANZCOG programs.

# LEADERS IN FOCUS

**Dr Kirsten Connan**
**MBBS (Hons), FRANZCOG, DDU**
**MMedEd (Gender and Leadership)**

This new *O&G Magazine* feature sees Dr Kirsten Connan in conversation with RANZCOG members in a broad range of leadership positions. We hope you find this an interesting and inspiring read.

Join the conversation on Twitter

#CelebratingLeadership @RANZCOG @connankf

## A/Prof Katie Groom
## Researcher and MFM clinician leading in her field

A/Prof Groom began her O&G career in the UK at St Mary's Hospital, Imperial College London. She found quality senior house officer (SHO) opportunities limited in the National Health Service (NHS) and a PhD opportunity presented itself. During this time she fell in love with a Kiwi, and having completed her PhD (examining the potential of COX-2 inhibitors to prevent preterm birth), made the move to New Zealand.

With a newfound passion for clinical research, A/Prof Groom completed her FRANZCOG (2010) and CMFM (2013). She commenced a dual academic and clinical role at National Women's Health, Auckland City Hospital, and the Department of Obstetrics and Gynaecology, University of Auckland.

**What three words best describe your life?**
Challenging, hectic, rewarding.

**Do you see yourself as a feminist?**
Yes, if it's in the setting of equal rights and equal opportunity for men and women. I'm extremely excited by our new female Prime Minister in New Zealand and her pregnancy news left me smiling for days!

**Do you see yourself as a leader?**
I see myself as an evolving leader and I increasingly recognise the gift of leadership as a platform for advocacy. I have to confess, I've had no formal leadership or media training, although Auckland University offers this.

**What current leadership roles do you hold?**
I am currently on the Perinatal Society of Australia and New Zealand (PSANZ) board, chairperson of Interdisciplinary Maternal Perinatal Australasian Collaborative Trials (IMPACT) Network, a board member of the Australian Clinical Trials Alliance (ACTA), chair of the National Executive for the New Zealand ON TRACK Network, a member of the RANZCOG Research Grants Committee, and Chief Investigator of the STRIDER NZAus trial

**What attracted you to clinical research in O&G?**
I think it is invaluable to use evidence to guide management and research is the key to this. I have three goals in my current role: ensure research is a priority for all clinicians, participate in effective clinical trials and update clinicians on current research.

**Have you had formal mentors during your career?**
During my PhD, I had fantastic formal supervisors, but most of my mentors have been informal relationships that have grown from professional roles. Prof Lesley McCowan has been one of my strongest collegiate supporters. I consider her a current mentor.

**What have been your proudest leadership roles?**
I have been appointed to Associate Professor in the Liggins Institute at the University of Auckland.

**What have been your career highlights?**
Completing my PhD and obtaining my MFM subspecialty qualification. Completion of every clinical trial I've been involved in is always such a highlight!

**How do you balance your personal and professional life?**
With difficulty! I have two amazing children and a fabulous husband. We share the parenting and accept lots of help.

A/Prof Katie Groom with her family.

**How do you maintain your resilience in a demanding career?**
I've just returned to clinical work from sabbatical leave, this allowed me some time to remember what motivates me. Maintaining resilience is an ongoing challenge, but I love my job and my engagement with patients and colleagues drives me on a daily basis.

**What do you see for the future of O&G?**
The increasing feminisation of our specialty has both benefits and challenges. We need to increase our conversations about this issue, to ensure our specialty remains attractive and progressive for future trainees.

**What role do you see for the College in the future?**
It would be great to see implementation of a RANZCOG-wide course on cultural competence. This is just starting in New Zealand, but it would be great to see RANZCOG offer this across both countries.

Many New Zealand Fellows feel a divide within RANZCOG between Australia and New Zealand. RANZCOG should strive for collaboration between all members. The tension between private and public sector agendas is challenging for RANZCOG, but again one worthy of further conversation.

**What advice would you give to new trainees?**
Don't rush. Your training years are a unique opportunity. Try all avenues of our specialty, be open to a change in your path and definitely consider a role in academic medicine. Question why we practise the way we do. I'd encourage and advocate that every clinician should be involved in research.

**Are you willing to be contacted for career advice?**
I am very willing to provide advice on clinical research and maternal fetal medicine training.

*I thank A/Prof Groom for her time and valuable comments. She is one of a number of inspiring clinical researchers we have in Australia and New Zealand.*

## Women in O&G leadership within Australia and New Zealand

In 2017, RANZCOG had a female specialist membership of 46 per cent and a female trainee membership of 80 per cent. Women represented 14 per cent of RANZCOG board membership (the same statistic as seen in 2012) and 32 per cent of RANZCOG councillors. Average female leadership was 26 per cent for RANZCOG, 23 per cent for RANZCOG-accredited hospitals and 26 per cent for university O&G departments in Australia and New Zealand. A/Prof Christine Tippett is the only female president since RANZCOG's inception in 1998.

In 2017, women held 23 per cent of leadership positions in RANZCOG-accredited hospitals in Australia and 58 per cent of leadership positions in RANZCOG-accredited hospitals in New Zealand. Within O&G university departments, women held 20 per cent of leadership positions in Australia and 67 per cent of leadership positions in New Zealand.

New Zealand's National Women's Hospital currently has an all-female leadership team, the largest cohort of women in leadership for any O&G hospital in Australia or New Zealand. In 2017, Westmead Hospital was a notable outliner for Australian hospitals with 80 per cent female leadership.

# Guest editorial

**Dr Victoria Rudland**
**MBBS, FRACP, PhD**
**Staff Specialist Endocrinologist**
**Department of Diabetes and Endocrinology**
**Westmead Hospital**

**A/Prof Glynis Ross**
**MBBS, FRACP**
**Visiting Medical Officer**
**Department of Endocrinology**
**Royal Prince Alfred Hospital**
**Senior Staff Endocrinologist**
**Bankstown-Lidcombe Hospital**

Diabetes was first recognised as a National Health Priority Area in 1996. At least one in seven pregnancies in Australia is affected by diabetes. This rate can be as high as one in three pregnancies in some areas. One of the goals of the Australian National Diabetes Strategy 2016–2020 is to reduce the impact of pre-existing and gestational diabetes (GDM) in pregnancy. Areas targeted include pre-pregnancy planning for women with pre-existing diabetes; and appropriate testing, pregnancy management and postpartum care for women with GDM and their offspring.

It is, therefore, pleasing to see that this edition of *O&G Magazine* is dedicated to discussing issues related to the assessment and management of various aspects of diabetes, particularly in pregnancy. In this issue, we are taken on a tour of diabetes, ranging from basic science to research updates, touching on some of the more controversial topics.

GDM has been a much discussed area of obstetric medicine over the past decade, with great debate over whether recommendations from the International Association of Diabetes and Pregnancy Study Groups (IADPSG) for the diagnosis and classification of hyperglycaemia in pregnancy should be adopted locally. The Australasian Diabetes in Pregnancy Society (ADIPS) has largely endorsed the IADPSG recommendations (page 16). However, as Cox and Marnoch (page 14) report, this has not been the case in New Zealand.

The role of the dietitian and recommendations for appropriate gestational weight gain are both reviewed. Pregnancy may be the first time women receive dietary advice, which is increasingly important as rates of overweight and obesity rise. Lester (page 20) addresses barriers to dietary intervention, including patient compliance and access to resources and funding. We are reminded by Poulter and Meloncelli (page 22) that pregnancy provides us with a window of opportunity to change behaviour, as women may be more receptive and motivated during pregnancy. Timely advice (ideally pre-pregnancy or at the first antenatal visit) regarding appropriate gestational weight gain (Institute of Medicine guidelines, page 22), healthy eating and physical activity, is particularly important for women with diabetes.

Various aspects of type 1 and type 2 diabetes are also reviewed in this issue. Schibeci (page 25) takes us on an entertaining tour back to first year biochemistry, where he effectively analogises glucose with a soccer hooligan. Almeida and Mehrotra (page 29) provide a trimester-specific overview of the assessment of the fetus of a diabetic mother. Lee (page 32) reviews the indications for insulin pump therapy in pregnant women with type 1 diabetes, highlighting that women require a diligent personality to proactively manage an insulin pump. Moorhead et al (page 34) review the evidence for antenatal expressing in women with diabetes while Stock (page 38) provides evidence-based advice regarding the timing of delivery for women with pre-existing diabetes or GDM, as it relates to the risk of stillbirth. Finally, the ENDIA group (page 51) summarises the developmental origins and modifiable exposures for type 1 diabetes.

Overall, this edition highlights the breadth of issues relating to diabetes in pregnancy and sheds light on areas requiring future research.

# Screening and diagnosis of GDM in New Zealand

**Dr Stephanie Cox**
**MBChB, FRACP**
**National Women's Health**
**Auckland City Hosptial**

**Dr Catherine Marnoch**
**MBChB, FRACP**
**National Women's Health**
**Auckland City Hosptial**

The prevalence of gestational diabetes (GDM) continues to increase in New Zealand, reaching close to 10 per cent in some populations. In 2013, the New Zealand Ministry of Health commissioned the development of clinical practice guidelines on GDM,[1] with the aim of providing evidence-based national recommendations. The NZ guidelines differ in several areas, compared to recommendations of the International Association of Diabetes and Pregnancy Study Group (IADPSG),[2] which are now supported by the Australian Diabetes in Pregnancy Society, the World Health Organization and the International Federation of Gynecology and Obstetrics (FIGO). We will focus on where NZ guidelines differ from IADPSG, why they differ and the potential issues for women and babies.

## Early screening for undiagnosed pre-existing diabetes mellitus

IADPSG recommends universal early testing, or testing women classified as high-risk, with diagnostic criteria as shown in Table 1. In contrast, the NZ guidelines have opted for universal screening in early pregnancy using only HbA1c. We agree that universal screening is appropriate, due to the increasing prevalence of GDM in our population. HbA1c is the accepted diagnostic test for type 2 diabetes outside of pregnancy[3] and can be easily added to routine antenatal blood tests. The NZ guidelines recommend women with HbA1c ≥ 50mmol/mol (6.7%) be referred to a diabetes in pregnancy service for early care, but women with HbA1c 41–49mmol/mol (5.9–6.6%) be offered dietary and lifestyle advice, followed by a 75g oral glucose tolerance test (OGTT) at 24–28 weeks gestation. Both approaches recognise the rising rates of diabetes in the general population and the importance of recognising overt diabetes in early pregnancy. Benefits of this include: decreasing the risk of congenital anomalies in offspring; detection of diabetes complications requiring treatment during pregnancy; prompt restoration of normal glucose levels with treatment; and appropriate treatment of diabetes after pregnancy.

**Table 1.** IADPSG vs NZ recommendations for early screening for undiagnosed pre-existing diabetes mellitus

| Test | IADPSG | NZ |
|---|---|---|
| Fasting plasma glucose (FPG) | ≥ 5.1mmol/L (GDM) ≥7.0mmol/L (diabetes) | N/A |
| Random plasma glucose (RPG) | ≥ 11.1mmol/L | N/A |
| HbA1c | ≥ 48 mmol/mol (6.5%) | ≥ 50 mmol/mol (6.7%) |

NZ guidelines regarding the management of women with HBA1c 41–49mmol/mol (5.9–6.6%) in early pregnancy have generated considerable local debate. There is little doubt that women with an early pregnancy HbA1c ≥ 50mmol/mol (6.7%) have overt diabetes and should receive care. NZ has chosen a higher cut off (50mmol/mol), compared to other countries (48mmol/L), to align with diagnostic thresholds for diabetes outside of pregnancy. This may lead to under-diagnosis and lends support to the treatment of women with an HbA1c scoring in the high 40s. We would argue that women with an early pregnancy HbA1c 41–49mmol/mol (5.9–6.6%) are a group with increased risk. Providing dietary and lifestyle advice alone, without further support, monitoring or treatment until offering an OGTT at 24 weeks, may mean a missed opportunity to prevent obstetric and neonatal complications. In a 2014 study,[4] women with an early HbA1c of 41–46mmol/mol (5.9–6.4%) who were not treated for diabetes, had significantly increased risks of congenital anomaly, pre-eclampsia, shoulder dystocia and perinatal death, compared with women with an HbA1c of less than 41mmol/mol (<5.9%). Some women do not return for their 24–28 week OGTT and some may have a false negative OGTT, which is more likely in obese women.[5]

Our unit treats women with HbA1c 41–49mmol/mol (5.9–6.6%) in early pregnancy, however, many other units do not and practices differ across NZ. Although these women appear to be at increased risk, it has not yet been established that treating them earlier in pregnancy is effective in reducing this risk. The NZ guidelines opted to wait for more evidence before changing recommendations. Research is ongoing to clarify this issue, with the Pre-diabetes in Pregnancy, Can Early Intervention Improve Outcomes (PINTO) study in NZ and the Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) study in Australia. Proponents for treatment, including us, cite the potential risk reduction of pre-eclampsia, shoulder dystocia and other adverse pregnancy outcomes. Advocates against early treatment cite potential harm from a diagnosis of GDM, such as stigma, pathway shift of obstetric care from low-risk to high-risk and over-medicalisation, as well as the burden of home capillary blood glucose monitoring, dietary modification and clinic visits.

## Screening for GDM at 24–28 weeks

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was a landmark international multicentre trial published in the *New England Journal of Medicine* in 2008.[6] It looked at OGTT results for more than 25,000 women and compared these with rates of GDM-related complications.

At glucose levels of one standard deviation above the mean, but still below contemporary diagnostic levels for GDM, they found increased odd ratios for all their primary outcomes, with the strongest effect on birth weight and cord blood C-peptide. These relationships were continuous and linear, without a clear threshold. The author's conclusion was that even 'mild' dysglycaemia in pregnancy can have an impact on clinical outcomes and that consideration should be given to lowering the diagnostic thresholds.

IADPSG recommended change to a one-step diagnostic process at 24–28 weeks gestation, with a 75g OGTT and diagnostic thresholds based on the HAPO study results.[2] (Table 2)

**Table 2.** IADPSG vs NZ GDM diagnostic glucose cut-offs for 75g OGTT at 24–28 weeks gestation

| OGTT component | IADPSG (mmol/L) | NZ Guidelines (mmol/L) |
|---|---|---|
| Fasting glucose | 5.1 | 5.5 |
| 1 hour glucose | 10 | – |
| 2 hour glucose | 8.5 | 9 |

NZ continues to recommend a two-step process, with a 50g glucose challenge test for women without known risk factors (>11mmol/mol diagnostic, >7.8mmol/L, requiring a follow-up 75g OGTT) and a one-step process with the 75g OGTT for women with risk factors (particularly HbA1c 41–49 mmol/mol 5.9–6.6%). A cost-effectiveness study from 2014 reported the one-step screening strategy would cost NZ$1.38 million more than the two-step screening strategy. Although the authors acknowledged that this approach would miss 12 women with diabetes and 111 women with GDM in their hypothetical cohort of 62,000 women, the additional cost per case detected was high, at NZ$12,460 per case.[7]

The NZ OGGT thresholds remain higher than other Western countries, with a fasting blood glucose greater than 5.5mmol/L, and 2 h>9.0mmol/L. NZ guideline authors cited concerns that emerging new evidence might suggest a change in thresholds again, reducing consistency of practice in NZ, and that the predicted increase in patient numbers would create unsustainable workforce and financial demands.[1]

We are now ten years post-HAPO and eight years on from the publication of the IADPSG guidelines. Recent research has been undertaken, comparing outcomes under the old and new criteria. All of the studies show a significant increase in the number of women diagnosed with GDM, with some reporting up to a three-fold increase.[8,9,10] However, if this cost is mitigated by improvements in maternal and neonatal outcomes, this increase may not represent an unsustainable burden to the system. The St Carlos Gestational Diabetes Study assessed costs, outcomes and cost-effectiveness before and after the adoption of the IADPSG criteria by a tertiary diabetes clinic in Madrid, Spain.[11] The authors found an increase in the rate of GDM (from 10.6% to 35.5%), but also an improvement in pregnancy outcomes, including less gestational hypertension, large for gestational age infants, small for gestational age infants and NICU admissions, as well as lower caesarean rates. Their final analysis showed a cost-benefit of just over €14,000 for each 100 women screened with the new criteria.

In NZ, the Gestational Diabetes Mellitus Study of Diagnostic Thresholds (GEMS) is looking at outcomes by comparing the current NZ and IADPSG criteria. We feel that NZ policy makers need to look at the whole picture of care using the St Carlos study approach. Our concern is that, while NZ waits for more evidence, a generation of at-risk women and babies will have missed out on interventions that could improve their health now and in the future.

If other studies confirm the results of the St Carlos study, then there will be a strong case for NZ to move to the IADPSG criteria. While some fear this may put a strain on already stretched services, in our opinion, the increased number of women diagnosed with GDM could be offset by improvements in outcomes and overall reduction in costs. Current models of care could be reviewed to meet the increased demand, triaging lower risk women to be managed in less costly community settings. What is required is not an approach that ignores some women with GDM, but one which creates innovative ways of managing women appropriately in different settings. In the interim, we encourage all NZ clinicians to offer and support participation in the PINTO and GEMS trials.

We remind NZ midwives, obstetricians and physicians to be aware that women in NZ with pre-pregnancy pre-diabetes and those currently diagnosed with GDM are higher risk compared to international populations. Careful monitoring during and after pregnancy is required.

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# Screening and diagnosis of hyperglycaemia in pregnancy in Australia

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The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) results were published in 2008. Since then, much debate has ensued internationally regarding the best approach to screen and diagnose hyperglycaemia in pregnancy. Here, we discuss the rationale behind the earlier Australian diagnostic criteria for gestational diabetes (GDM) and highlight the main differences between the 2010 recommendations of the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the 2014 guidelines of the Australasian Diabetes in Pregnancy Society (ADIPS) for screening and diagnosis of hyperglycaemia in pregnancy.

Historically, the diagnostic criteria for GDM were based on glucose levels on an oral glucose tolerance test (OGTT) that were associated with an increased risk for diabetes in the mother.[1] The aim of the HAPO study was to assess glucose levels on an OGTT that were associated with adverse neonatal outcomes.[2] In Australia, consensus criteria for the diagnosis of GDM, established in 1991, were designed to standardise the diagnostic approach to GDM, while awaiting further data and international consensus. At the time, individual Australian institutions differed in their assessment of clinical risk factors, glucose loads, test duration and diagnostic thresholds. Using Australian consensus criteria, only one blood glucose level (BGL) needed to be elevated for the diagnosis of GDM, whereas most international guidelines required at least two elevated BGLs to make the diagnosis.

The HAPO study demonstrated a continuous and linear relationship between maternal fasting, one-hour and two-hour BGLs on an OGTT, and increasing frequency of adverse maternal and neonatal outcomes.[2] Importantly, there were no obvious glucose thresholds at which the risks of adverse pregnancy outcomes increased. The results of the HAPO study formed the basis for the 2010 IADPSG consensus guidelines, which were endorsed by a number of international bodies, including the World Health Organization (WHO)[3] and, in Australia, ADIPS[4] and RANZCOG. IADPSG recommended universal testing for hyperglycaemia in pregnancy with a 75g, two-hour OGTT at 24–28 weeks gestation. The 2014 ADIPS diagnostic criteria for hyperglycaemia in pregnancy are summarised in Table 1.

**Table 1.** ADIPS criteria for the diagnosis of hyperglycaemia first detected in pregnancy.

| | Glucose measure | ADIPS criteria |
|---|---|---|
| Gestational diabetes* | Fasting BGL<br>1-hour BGL<br>2-hour BGL | 5.1-6.9mmol/L<br>≥10.0 mmol/L<br>8.5-11.0mmol/L |
| Diabetes in pregnancy* | Fasting BGL<br>2-hour BGL<br>Random BGL<br>HbA1c | ≥7.0 mmol/L<br>≥11.1 mmol/L<br>≥11.1 mmol/L†<br>≥6.5%‡ |

* only one elevated BGL is needed for diagnosis
† in the presence of diabetes symptoms
‡ recommended in remote areas where OGTT is logistically difficult

The majority of the 2014 ADIPS guidelines are consistent with the IADPSG recommendations. ADIPS differs from IADPSG in some of the terminology, as well as in the recommendations for early testing. Women with BGLs in the range for diabetes outside pregnancy are referred to as having 'diabetes in pregnancy' (DIP) by ADIPS and WHO, but as having 'overt diabetes in pregnancy' by IADPSG. It should be emphasised that DIP is an antepartum diagnosis and is not synonymous with type 2 diabetes. A review of local Australian data revealed that when women with 'overt diabetes in pregnancy' attended a follow-up OGTT at 6–8 weeks postpartum, 21 per cent had diabetes; 38 per cent had impaired fasting glucose (IFG) or impaired glucose tolerance (IGT); and 41 per cent had returned to normal glucose tolerance.[5] The ongoing presence of diabetes must, therefore, be confirmed postpartum.

ADIPS also differs from IADSPG with regards to early testing in pregnancy. ADIPS recommends that women with risk factors for hyperglycaemia in pregnancy should be tested early in pregnancy (Table 2). ADIPS recommends that the method of early testing in pregnancy should be based on clinical judgment, local healthcare policy and possible risk stratification, but should ideally be an OGTT. IADPSG recommends early testing only in populations with a high prevalence of type 2 diabetes.

ADIPS and IADPSG also differ in the diagnostic criteria for early pregnancy. The primary aim for early testing is to exclude previously undiagnosed diabetes, in which case, both groups agree that women with BGLs in the DIP range in early pregnancy should receive prompt treatment for hyperglycaemia. However, what is not clear is whether the 24–28 week diagnostic criteria for

Table 2.

ADIPS risk factors for hyperglycaemia in pregnancy[4]

- Previous hyperglycaemia in pregnancy
- Previously elevated blood glucose level
- Maternal age ≥40 years
- Ethnicity: Asian, Indian, Aboriginal, Torres Strait Islander, Pacific Islander, Maori, Middle Eastern, non-white African
- Family history of diabetes mellitus (first degree relative with diabetes mellitus or a sister with GDM)
- Obesity (pre-pregnancy BMI >30kg/m$^2$)
- Previous macrosomia (baby with birth weight >4500g or >90th centile)
- Polycystic ovary syndrome (PCOS)
- Medications: corticosteroids, antipsychotics

GDM are applicable in early pregnancy. This is flagged as an area requiring further research by ADIPS. On the contrary, IADPSG recommend that women with a fasting BGL ≥5.1mmol/L in early pregnancy should be classified as having GDM. This is perhaps one of the most controversial aspects of the IADPSG recommendations. Glucose levels fall during and after the first trimester, so using 24–28 week diagnostic criteria for GDM in early pregnancy may overdiagnose GDM. Zhu et al demonstrated that, of women with a fasting BGL 5.1–5.6mmol/l at their initial antenatal visit and no subsequent treatment, only 37 per cent had GDM at 24–28 weeks gestation.[6] Whether or not the treatment of early GDM, diagnosed by the 24–28 week criteria, is beneficial should be answered by the Australian-led, multicentre randomised controlled trial, Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) study. In the meantime, clinical judgment is required.

In Australia, it is the BGL criteria that have caused debate. However, the greatest impact on the number of women diagnosed with GDM locally has been from the application of the 75g, two-hour OGTT in all pregnant women, instead of using the 50g, one-hour glucose challenge test (GCT) on a select group of women, which missed up to 25 per cent of GDM cases.[7]

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# Gestational diabetes: beyond glycaemia

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Gestational diabetes mellitus (GDM) is by far the most common medical co-morbidity in pregnancy, with rates of 8–30 per cent reported across Australia. It's easy to forget just how much of a 'work in progress' GDM is and feel overwhelmed by the huge numbers of affected women. Since the 1950s, when Pedersen proposed that maternal hyperglycaemia led to fetal hyperglycaemia and an exaggerated fetal response to insulin, the rationale for screening and treating GDM has centred on reducing the risk of fetal macrosomia and its obstetric complications. Recent data has highlighted the importance of GDM as a predictor of future cardiometabolic risks, both for affected women and their offspring,[1] thus providing new impetus for its identification and treatment.

The last ten years have been marked by controversy over the diagnostic criteria for GDM and subsequent treatment targets, with concerns of creeping over-medicalisation and an unnecessarily interventional approach for otherwise low-risk women. The revised International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria (Table 1) have now been adopted by most centres. This is based on an odds ratio of 1.75 for adverse outcomes, compared to the rates seen at mean glucose levels of the HAPO[3] cohort. It is a more evidence-based set of criteria than previously used. These levels are highly sensitive for detecting women at risk of adverse obstetric outcomes, but also detect a significant number of low-risk women, with substantial workforce implications.

The management of GDM is resource intensive, requiring a multidisciplinary approach. Optimising exercise and diet, with self-monitoring of blood glucose levels, is the mainstay of treatment, with the addition of pharmacological agents (metformin and/or insulin) required to optimise glycaemic control in roughly 50 per cent of affected women.

Exactly how low to go remains contentious. To date, there is a paucity of data available to substantiate the implementation of the current low targets outlined in the Australasian Diabetes in Pregnancy Society (ADIPS) position statement (Table 1). For many centres, the additional rate of intervention required is prohibitive.[5] We currently adopt a pragmatic approach, continuing to use the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) targets, although admittedly, with an unofficial tendency to push lower once treatment has been commenced, until more data becomes available.

## Beyond glycaemia

The benefit of screening and subsequently treating GDM extends beyond reducing pregnancy-associated complications. Recent data from the UK[6] and Sweden[7] support that a diagnosis of GDM entails a marked increase in risk of future cardiovascular disease and maternal type 2 diabetes, with rates up to 50 per cent at 20 years. While it is worth noting that in these cohorts, the diagnostic criteria for GDM was far less stringent than it is today (fasting BSL>6.0mmol/L), there is also a significant rise in population rates of obesity and type 2 diabetes. A diagnosis of GDM is a window of opportunity for women to receive education in key lifestyle interventions required to optimise metabolic health.

Children of pregnancies affected by GDM are more likely to be overweight or obese, show greater central adiposity, high blood pressure, insulin resistance and impaired glucose tolerance. These children are at increased risk of developing type 2 diabetes and cardiovascular disease in later life.[1] Maternal dietary re-education and motivational counselling has been shown to reduce rates of GDM, limit weight gain and reduce hypertensive complications. This has potential to benefit subsequent pregnancies and future health in women, and by association their families, who are at a significantly higher risk of obesity, hypertension, and metabolic syndrome. Anecdotally, many women feel better when given the additional impetus to prioritise healthy diet and activity, thus there can be a silver lining to the diagnosis.

## Is metformin a magic bullet?

Where lifestyle intervention is not enough, insulin remains the first-line treatment for GDM in Australia.[8] However, ten years following the publication of

**Table 1.** Diagnostic and interventional targets for GDM

| BGL in mmol/L | IADPSG[2] diagnostic criteria 75g OGTT | 'old' ADIPS criteria 75g OGTT | ADIPS[2] intervention targets | ACHOIS[4] intervention targets |
|---|---|---|---|---|
| Fasting | ≥5.1 | ≥5.4 | ≤5.0 | ≤5.5 |
| One hour | ≥10.0 | – | ≤7.4 | – |
| Two hours | ≥8.5 | ≥8.0 | ≤6.7 | ≤7.0 |

the Metformin in Gestational Diabetes (MiG)[9] study, documenting that metformin is an effective and safe treatment option for women with GDM, metformin is an increasingly used option that may have additional benefits. The long-term effects on offspring exposed to metformin are being carefully monitored, with published outcomes at two years reassuring.[10] There is a particular role for metformin in women who are obese, reluctant to take insulin, or already on large doses of insulin. Mealtime metformin is markedly more effective than would be expected from its pharmacokinetic profile, generally well tolerated and, as seen in MiG, glycaemic targets are achieved much faster than with up-titration of insulin.

Metformin has been shown to have benefits other than the primary indication of insulin sensitisation and reduction of hyperglycaemia in the non-pregnant population. A reduction in overall mortality and bowel cancer risk make it a very compelling first-line agent in type 2 diabetes. It improves fertility in women with PCOS (sometimes unintentionally) and is associated with reduced miscarriage rates when used as part of fertility therapy. This is thought to relate to alterations in anti-angiogenic factors, which may also be associated with a reduction in risk of pre-eclampsia. While this has not yet been directly studied, a very recent meta-analysis comparing insulin to metformin for lowering glucose levels in pregnancy,[11] did show reductions in gestational weight gain and pre-eclampsia in the metformin group. While a formal randomised controlled trial is needed to confirm this, metformin is showing promise as a very useful treatment option in GDM.

## Delivery planning

Timing and mode of delivery in women affected by GDM has seen a significant shift in the goalposts in recent years. Emerging data from paediatric literature emphasises the importance of fetal neurological development right up to term,[12] with a move towards delivery at, or after 39 weeks, seen as best practice. This has led to a more individualised decision-making process, including closer monitoring of estimated fetal weight with ultrasound and enabling a less interventional approach to timing of delivery in women with GDM. At the same time, there has been more widespread use of antenatal corticosteroids right up to 39 weeks for planned caesarean delivery without labour.[13] This necessitates additional planning for glycaemic management of both pre-existing diabetes and GDM. While the benefit of late-term steroids for fetal lung maturation has not specifically been shown in women with diabetes, they are recognised as a high-risk group. Our practice is to give steroids as per usual obstetric indications and up-titrate insulin during that period, using the strategy outlined in Table 2 as a starting point.[14]

**Table 2:** Algorithm for % insulin adjustment during antenatal steroid loading. Adapted from Mathieson.[14]

| Day | Prandial insulin<br><br>(short-acting analogues eg: novorapid) | Nocte insulin<br><br>protaphane |
|---|---|---|
| D1 – first dose steroids | 0% | +25% |
| D2 – second dose steroids | +40% | +40% |
| D3* | +40% | +40% |
| D4 | +20% | +20% |
| D5 | +10–20% | +10–20% |

Can also be applied to women on mixed insulin regimens (mixtard, novomix, Humalog mix)

* Many women will be delivered on Day 3. Insulin can still be safely ceased in women with GDM, as the absolute glycaemic derangement is generally mild.

## Conclusion

There is no doubt that GDM has adverse effects on pregnancy outcomes and implications for the long-term wellbeing of mother and infant. While screening for and managing GDM can be mandated on the basis of improved obstetric and neonatal outcomes, it is likely that the long-term cardiometabolic benefits to both mother and child is where the real value is to be found.


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# The dietitian's role in managing GDM

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Gestational diabetes mellitus (GDM) affects approximately 9.6 to 13.6 per cent of all pregnancies in Australia.[1] In most cases, GDM is often asymptomatic; therefore, all pregnant women not known to have pre-pregnancy diabetes or hyperglycaemia in pregnancy should have an oral glucose tolerance test (OGTT) at 24–28 weeks gestation.[2] Once GDM is diagnosed, a multidisciplinary team approach is important to reduce the risk of complications during pregnancy, at birth and reduce negative health outcomes for the infant as they mature. Ideally, a team consisting of an obstetrician, endocrinologist, GP, diabetes educator, midwife and dietitian is required to manage GDM. As part of the multidisciplinary team, dietitians play an important role, as lifestyle management is the cornerstone of management of GDM.

Dietitians use a toolbox of knowledge, skills and nutrition counselling techniques to assist women with making dietary and lifestyle modifications. Effective nutrition interventions can assist in normalising blood glucose levels to prevent or delay the need for medication, maximise nutrition to support the development of the fetus and minimise complications throughout the pregnancy and during delivery.

When first diagnosed with GDM, if referred, women receive education from a dietitian in a group or individual setting. Education is tailored to the individual needs, taking into account personal and cultural beliefs, food preferences, lifestyle, and willingness and ability to change behaviours.

Dietary requirements for those with GDM are the same for all pregnant women; however, emphasis is placed on the importance of regular meals and snacks, the role of carbohydrate foods, frequency, timing and quantity of carbohydrates consumed, and the glycaemic index of food. Dietitians also consider appropriate weight gain depending on the woman's pre-pregnancy BMI. During pregnancy, too much weight gain can contribute to high blood pressure and increase insulin resistance. Strict dieting is not usually recommended, as it is important for women to have a balanced diet to meet their nutritional requirements for pregnancy.

Dietitians consider a range of individual nutrition factors when reviewing women with gestational diabetes, including meal frequency or regularity, pre-pregnancy eating habits (for example, binging or fasting for long periods), religious or cultural beliefs with foods, allergies or intolerance, and quality and quantity of foods consumed at meal or snack times. It is also important to take into account appropriate portions of macronutrients and micronutrients based on the Australian Guide to Healthy Eating core food groups during pregnancy and the Nutrient Reference Values (NRVs), to help maximise nutrition for both mother and baby.

Challenges can arise when treating women with GDM, including access to resources and funding for timely follow-up; literacy levels of women; access to culturally appropriate resources and interpreter services; access to a multidisciplinary team; and patient compliance and adherence to nutrition recommendations.

It is important for the multidisciplinary team to be aware that a number of pregnant women with GDM try to restrict their carbohydrate intake to facilitate a reduction in postprandial blood glucose levels. This can increase risk of nutritional inadequacies and/or result in hypoglycemia for women on insulin.

Ideally, women with GDM should receive regular follow up from a dietitian throughout their pregnancy to review their nutritional progress, compliance with recommendations, blood glucose levels and implementation of physical activity to promote optimal blood glucose control. If diet and lifestyle interventions are not effective, dietitians can assist in identifying the need for the use of medication.

Women with GDM should have a follow-up OGTT, preferably at six to 12 weeks postpartum, to ensure there is no underlying type 2 diabetes mellitus.[2] Women diagnosed with hyperglycaemia during pregnancy should also be monitored as they have a 30 per cent risk of recurrence in a subsequent pregnancy and a risk of developing type 2 diabetes, ranging from 1.5 to ten per cent per year. Women contemplating another pregnancy should have an annual OGTT. Women tested for possible development of type 2 diabetes should have an OGTT or HbA1c every three years, or more frequently, depending on clinical circumstances. For women considered low-risk, a fasting plasma glucose test or HbA1c every one to two years should be sufficient.[2]

Breastfeeding has a number of benefits for both mother and baby, including weight reduction for mothers. Breastfeeding should be supported and encouraged postpartum.[3]

In summary, it is important that every woman diagnosed with gestational diabetes is referred to a dietitian for assessment and education during her pregnancy.

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# Weight management in pregnancy

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The prevalence of overweight and obesity is increasing at an alarming rate worldwide. In Australia, almost half of women of childbearing age are overweight or obese, with rates of 30–50 per cent reported in early pregnancy.[1]

## Excess gestational weight gain and obesity

The most commonly used measure to categorise overweight and obesity is body mass index (BMI). WHO classifies overweight as a BMI of 25 or greater, with further division into pre-obese (BMI 25–29.9kg/m$^2$), obese class I (30 to 34.9kg/m$^2$), class II (35 to 39.9kg/m$^2$) and class III (≥40kg/m$^2$).

A pre-pregnancy BMI greater than 25kg/m$^2$ affects fertility (subovulation and polycystic ovarian syndrome) and increases the risk of adverse maternal and fetal outcomes, including miscarriage, congenital abnormalities, gestational diabetes (GDM), hypertensive disorders, pre-term delivery, caesarean section and excess fetal growth (see Table 1).[2] Similar risks are seen in women with excess gestational weight gain (GWG), independent of their pre-pregnancy BMI.[4]

The Institute of Medicine revised (2009) recommendations for weight gain based on pre-pregnancy BMI group (see Table 2).[4] Despite these, almost half of pregnant women gain too much weight during pregnancy and a quarter of women do not gain enough.[5]

Although excess GWG can occur in all pre-pregnancy BMI groups, it is more prevalent in women who commence pregnancy with a BMI ≥ 25.[4] These women are also more likely to have higher weight retention postpartum and risk being overweight or obese in subsequent pregnancies.[4]

Offspring of mothers, who have a BMI ≥ to 25 (strongest predictor), excess GWG or GDM, have an increased future risk of obesity and type 2 diabetes. This raises questions about the effects of intrauterine exposure to overnutrition on fetal programming.[5]

**Table 1.** Association between pregnancy outcomes and BMI.[3]

| Variable | BMI (kg/m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| | <18.5 | 18.5–<25 | 25–<30 | 30–<35 | 35–<40 | ≥40 |
| Maternal outcome (%) | | | | | | |
| Hypertension in pregnancy | 1.1 | 1.7 | 3.3 | 5.1 | 7.0 | 9.6 |
| GDM | 1.0 | 1.2 | 2.1 | 3.4 | 5.5 | 6.9 |
| Type 1 and 2 diabetes mellitus | 0.2 | 0.5 | 0.3 | 1.7 | 2.8 | 4.1 |
| Spontaneous vaginal birth | 61 | 54.4 | 50.4 | 47.1 | 46.9 | 43.6 |
| Assisted birth | 13.3 | 12.9 | 10.0 | 8.4 | 5.9 | 4.9 |
| Caesarean section | 25.7 | 32.7 | 39.6 | 44.5 | 47.1 | 51.5 |
| Neonatal outcomes (%) | | | | | | |
| Perinatal death | 0.5 | 0.7 | 1.0 | 1.1 | 1.5 | 1.8 |
| Stillbirth | 0.2 | 0.4 | 0.5 | 0.7 | 0.8 | 0.7 |
| Neonatal death | 0.3 | 0.3 | 0.5 | 0.5 | 0.7 | 1.1 |
| Macrosomia | 5.4 | 10.6 | 15.9 | 18.7 | 20.1 | 20.8 |
| SGA | 12.4 | 10.9 | 12.2 | 13.4 | 15.7 | 18.7 |
| LGA | 10.5 | 11.0 | 12.4 | 13.3 | 14.0 | 15.9 |
| Pre-term birth < 37 weeks | 8.5 | 6.7 | 7.5 | 8.5 | 9.5 | 11.3 |
| Respiratory distress syndrome | 4.2 | 4.3 | 5.3 | 5.7 | 6.4 | 7.3 |
| Mechanical ventilation | 5.9 | 4.7 | 5.8 | 6.5 | 8.6 | 10.4 |
| Jaundice | 6.4 | 4.7 | 5.4 | 6.4 | 7.5 | 9.3 |
| Hypoglycaemia | 1.1 | 0.9 | 1.3 | 1.8 | 3.0 | 2.5 |

SGA=small for gestational age, LGA=large for gestational age, ≥ greater than or equal to, < less than. Source: adapted from McIntyre HD, Givvons KS, Flenady VJ, Callaway LK. Overweight and obesity in Australian mothers: epidemic or endemic?
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Table 2. Institute of Medicine GWG recommendations.[4]

| Pre-pregnancy BMI (kg/m²) | Rate of gain 2nd/3rd trimester (kg/week)* | Recommended range total gain (kg) |
|---|---|---|
| <18.5 | 0.45 | 12.5–18 |
| 18.5–24.9 | 0.45 | 11.5–16 |
| 25.0–29.9 | 0.28 | 7–11.5 |
| ≥30 | 0.22 | 5–9 |

* Calculations assume 0.5–2kg weight gain in the first trimester

## Weight management

Pregnancy is a time when women may be more receptive and motivated to change behaviours. It is a window of opportunity to introduce weight management strategies. It is also the most likely time for young women to interact with their healthcare providers. However, even in this engaged group, reducing BMI and GWG through lifestyle intervention with diet and exercise is challenging. These interventions reduce the risk of excess GWG, on average, by 20 per cent.[6] This potentially means lower rates of maternal hypertension, macrosomia, caesarean section delivery and newborn respiratory distress syndrome.[6]

An early antenatal visit allows timely referral to a multidisciplinary team, including a dietician. While guidelines on weight management in pregnancy lack clear guidance beyond generic lifestyle modification, a dietician can discuss GWG targets and counsel regarding:

- healthy eating recommendations (variety, portion size, sugar intake)[2]
- increased activity (20–30 minutes of moderate intensity exercise on most days of the week)[2]
- regularly tracking weight gain to identify trends[2]

There is currently no consensus on the level of caloric restriction in pregnancy to prevent excess GWG or avoid weight loss. No guidelines recommend weight loss during pregnancy, due to a greater risk of SGA infants.[7]

Particularly in women with higher classes of obesity, other multidisciplinary team members may include:

- **Obstetric physician**
  Antenatal assessment and management of obesity-related co-morbidities, such as hypertension, obstructive sleep apnoea, non-alcoholic steatohepatitis and renal dysfunction (including proteinuria), may modify pregnancy outcomes. If risk of pre-eclampsia is high, prophylaxis with low-dose aspirin and increased calcium may be warranted.[2]

- **Anaesthetist**
  Risks are increased in women with obesity for regional and general anaesthesia. Review in the third trimester will allow individualised risk assessment, additional testing, counselling and setting of expectations.[2]

- **Lactation consultant**
  Breastfeeding initiation and duration are lower in obese women and those with GDM. Furthermore, breastfeeding has been linked to lower risk of cardiovascular disease, type 2 diabetes and obesity, with less postpartum weight retention.[8] Specialist support may improve rates.

- **Physiotherapist/exercise physiologist**
  Individualised plans for meeting activity goals may assist with compliance.

- **Psychologist**
  Women with higher levels of obesity have a greater prevalence of mental health issues. Psychosocial stressors may also predict postpartum weight retention.[3]

Other considerations in management:

- Additional folic acid (5mg daily, from up to three months preconception until the end of the first trimester), as serum levels are lower than non-obese women.[2]
- Assessment of vitamin D, as low levels are more prevalent, and replacement to a normal range may be beneficial.[2]
- First trimester/first antenatal review screening for GDM, due to the higher prevalence and earlier onset of glucose intolerance. If normal, undertake routine screening at 24–28 weeks.[2]
- Greater frequency of reviews in the third trimester, due to increased risk of hypertensive disorders and abnormal fetal growth. Additional growth scans may be required to address difficulty in clinical assessment.[2]
- Planning timing, location and mode of delivery. Obese women, particularly in class III, have increased peripartum complications. Assessment of local resources and expertise to determine if safe peripartum care can be delivered, or if transfer of care to a higher level hospital should be considered.[2,3]
- Postpartum risk management to address: higher chance of PPH (antenatal optimisation of iron stores and greater vigilance after delivery); venous thromboembolism (assessment of risk factor profile, consider prophylaxis with low molecular weight heparin).[2]

Women with obesity are more likely to experience discrimination and prejudice than non-obese women.[2] Throughout the pregnancy, appropriate language and an open, non-judgemental manner can help to build a therapeutic relationship, support behavioural change and improve engagement with health professionals.[3]

## Bariatric surgery

Bariatric surgery is becoming commonplace in women of childbearing years. In women with higher classes of obesity, it is the most clinically effective treatment to achieve long-term weight loss and reduction in obesity-related complications.[9] Surgeries can be restrictive (laparoscopic adjustable gastric band or sleeve), malabsorptive (Roux-en-Y gastric bypass, biliopancreatic diversion) or a combination.[9]

The induced weight loss can increase fertility. Contraception should be discussed concurrently with surgery, to allow for planned conception. Weight loss may also interfere with absorption of oral hormonal contraception and alternate forms should be considered.[9]

Guidelines suggest delaying conception for 12–24 months post-surgery (particularly in malabsorptive procedures), to optimise maternal weight loss, allow stabilisation of the body's nutritional state and reduce the potential fetal risk of in utero malnutrition.[9] Despite this, limited studies comparing outcomes of women who conceive prior to, and after, the recommended minimum 12-month period do not show significant differences.[9]

Most pregnancies post-bariatric surgery will have successful outcomes. Small studies have demonstrated a reduced risk of GDM, hypertensive disorders, PPH and macrosomia. However, there is an increased risk of SGA infants and preterm delivery, compared with obese women. To date, no impact on neonatal mortality has been shown.[2]

Further considerations in the antenatal care of women post-bariatric surgery include:

- All women should have detailed nutritional biochemistry due to the greater prevalence of deficiencies.[2] These include iron, B12, folic acid, calcium and vitamin D. The degree of deficiency may be related to the type of surgery undertaken. Replacement should be initiated if deficits are detected.[9]
- Alternative methods of GDM screening may be needed, as the standard oral glucose tolerance testing may precipitate dumping syndrome.[9]
- In women with a laparoscopic gastric band, consider deflation of the band in pregnancy, particularly if persistent vomiting or poor weight gain occur.[9]

## Postpartum weight reduction

Given the limited impact of antenatal interventions, focusing on the preconception or interpregnancy period may yield better results; aiming for a preconception BMI in a non-obese range, rather than trying to limit GWG.[2]

After delivery, many women will not return to their pre-pregnancy weight and will gain more weight prior to their next pregnancy. Even modest interpregnancy weight gains are associated with increased adverse outcomes, including pre-eclampsia, GDM and stillbirth.[10] Interpregnancy weight loss reduces the risk of GDM (by almost 80 per cent),[11] an LGA infant, and improves rates of vaginal birth after caesarean section.[2]

A systematic review showed that interventions with diet and exercise improve postpartum weight loss and reduce incidence of type 2 diabetes. No significant impact on outcomes has been seen in studies using exercise alone.[2]

## Conclusion

Overweight and obese women are more likely to have adverse pregnancy outcomes. This risk is modifiable with optimisation of pre-conception weight and GWG. Although we are yet to understand the best approach to managing weight before and during pregnancy, we do know that addressing nutrition, improving health behaviours and managing co-morbidities in an individualised and multidisciplinary manner, can improve maternal and infant health well into the future.

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# Glucose: a bitter sweet tale

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Glucose is a paradox, best personified as a soccer hooligan. He arrives late for the important match with his mates after the ground is full and is not able to get through the turnstiles. Had he been more punctual, his exuberant energy would have been expended to drive his team over the line. Now this energy is released in other areas, creating havoc in the form of black eyes in pubs, overturned tables in cafes and broken windows. This analogy will become obvious as this article unfolds.

Diabetes affects more than 422 million people worldwide (WHO 2014). It is the leprosy of the 21st century. It causes microvascular disease, resulting in potential loss of limb, vision and renal function. On a different level, it accelerates macrovascular disease, a condition not exclusive to diabetics, but certainly augmented by hyperinsulinaemia due to insulin resistance, resulting in syndrome X. In gestational diabetes it has its own unique set of circumstances, with the fetus the focus of management. A large proportion of the health budget is spent on the prevention, diagnosis and management of this disease. Likewise, a significant portion of our clinical thinking time goes into managing patients with diabetes. We do understand the diagnosis, management and effects of this condition, but do we really understand why the seemingly harmless glucose molecule potentially causes so much damage?

Sugar connotes happiness, good times and contentment. How can such a nice substance cause such devastation? Glucose is the only brain fuel and is essential to the normal functioning of every living cell. However, we all know that we have to avoid excess sugar for our own good. As doctors we tell our diabetic patients to keep their blood sugar levels down, so they don't get the nasty complications of the disease, but do we really stop to consider what it is about glucose that makes it potentially so harmful? To refresh our memories, we need to go back to biochemistry in the first year of our medical studies.

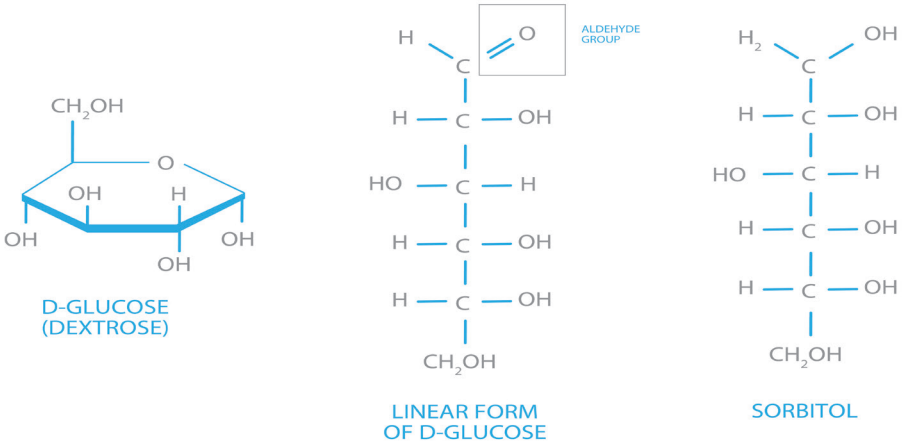
## The biochemistry

Glucose is intrinsic to cellular respiration. This complex series of enzymatic equations can be summarised thus: $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + energy (captured in the form of 38 adenosine triphosphate [ATP] molecules). This is the exact reverse of photosynthesis.

The glucose molecule is a complex molecule largely due to its stereochemistry, but essentially exists in two forms. There is the inert ring structure and the chemically active linear structure (Figure 1). It is important to notice how similar glucose is to sorbitol, another carbohydrate.

Cellular respiration is an exothermic reaction, of which the important end product is energy, harnessed in ATP molecules. One glucose molecule produces 38 ATPs and these are the 'alkaline energisers' for every cell in the human body. This is a complex process and occurs via glycolysis, the Krebs cycle and oxidative phosphorylation.

**Figure 1.** The two common isomers of glucose and sorbitol.



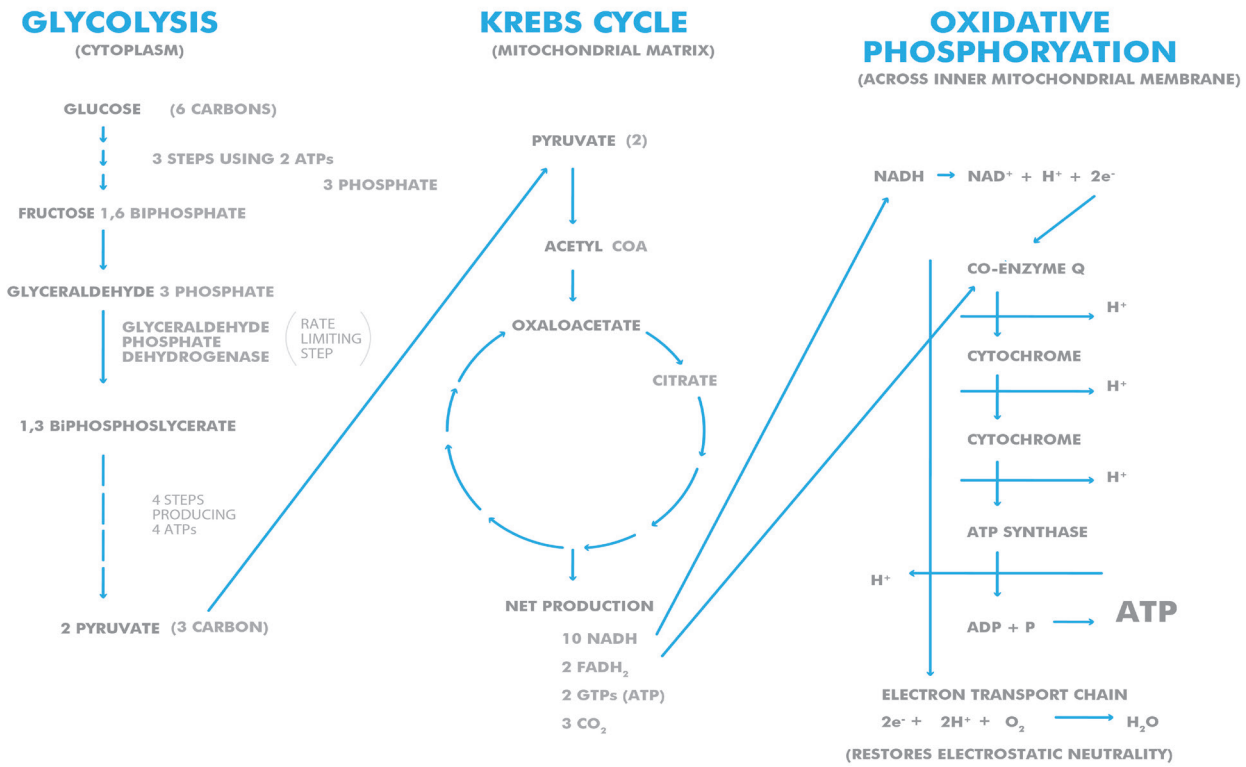



**Figure 2.** Very simplified version of cellular respiration.

In the cytoplasm of each cell, each glucose molecule (six carbons) is split into two pyruvate molecules (three carbons) via a series of enzymatic equations we call glycolysis. In this process, it produces a net two ATP molecules. Each pyruvate molecule acts as a substrate for the Krebs (citric acid) cycle. It enters the outer mitochondria and is converted to acetyl coenzyme A (acetyl CoA), which triggers the start of the citric acid cycle. In a cyclic series of complex energy-releasing reactions, citric acid is converted back to itself. The energy is captured in 2GTPs (similar to ATP), 10 NADHs and 2 FADHs. The latter two molecules are important cofactors in the electron transport chain, also known as oxidative phosphorylation, which occurs within the inner matrix of the mitochondria. They act as proton (hydrogen ion) donors and release electrons in this serial oxidative cascade. In this process, a hydrogen ion gradient is created across the inner mitochondrial membrane. To restore the osmotic balance, the hydrogen ion flux drives the ATPase enzyme, hence phosphorylating ADP to form the high energy ATP. Electrostatic neutrality is achieved by oxygen accepting electrons to form water. This is the only reason we breathe oxygen! Without it cellular respiration grinds to a halt. All in all, one glucose molecule produces a total of 38 ATPs, equivalent to 1272 kilojoules (304 kilocalories) of energy per mole of glucose metabolised.

So far so good, all the spectators have been accommodated and they can cheer on their teams. Their energy is directed for a positive good, but what happens when the turnstiles are shut?

As alluded to earlier, diabetics have an increased risk of macrovascular disease. As the HbA1c rises from 5.5 to 9.5, the risk of this complication is doubled. Peculiar to diabetes, however, a similar rise in HbA1c increases the risk of microvascular disease ten-fold. Why is this so? We know that when diabetics are hyperglycaemic, all cells in the body are bathed in glucose and most cells can excrete the glucose and restore homeostasis, but significantly, endothelial cells lack the capacity to do this.[1] The cells become damaged and this affects blood flow through the glomeruli in the kidney, retinal blood vessels and vasa nervorum. In turn, this results in chronic kidney disease, retinopathy and neuropathy.

## Why is it so?

The mechanisms by which hyperglycaemia results in cell damage have been gradually worked out since the 1970s, but there is still much to learn. There are four abnormal pathways so far identified, all involving side branches of glycolysis due to the flooding of the 'football stadium' of oxidative phosphorylation with glucose metabolites, which results in the overproduction of superoxide. This negatively feeds back, inhibiting the rate-limiting enzyme of glycolysis GADPH, which in our analogy would be the turnstile. The hooligans (excess glucose) now turn their abundant energy to other less useful and damaging directions.

The four abnormal pathways to cell damage:

1. **Increased polyol pathway activity**[2]
   There is an important enzyme in all cells called aldose reductase. This reduces toxic aldehydes (reactive oxygen species) to inactive alcohols (=O to -OH). Glucose is essentially an aldehyde with a terminal double bond O. At normoglycaemia, it only has a 1 per cent affinity for glucose, whereas in hyperglycaemia, this affinity rises to 33 per cent. By this pathway, glucose is converted to sorbitol and then to fructose. In doing so, it redeploys NADPH, an enzyme essential to activate glutathione, a very important anti-oxidant, which keeps the cell in a stable, reduced state. The end result of glucose being diverted into this pathway is increased cellular oxidative stress.

2. **The production of advanced glycation end products (AGEs)[3]**
These form endogenously throughout life from the embryonic stage, but can be taken exogenously in one's diet. Their formation is accelerated in hyperglycaemia. They are a heterogeneous group of molecules, formed by glucose binding covalently to and between proteins. As a harmless example, HbA1c is produced by this mechanism. These can alter the structure and function of affected tissues, for example, renal and retinal tissue.

   Receptors for AGEs (known as RAGEs) are found throughout most tissues, particularly mast cells, and these stimulate production of pro-inflammatory cytokines, pro-coagulants and vasoconstriction, resulting in tissue and blood vessel damage.

3. **Activation of protein kinase C (PKC)[4]**
PKCs are a family of enzymes involved in controlling the function of other proteins by phosphorylation. There are 12 isoforms and their production is stimulated by intracellular levels of diacylglycerol (DAG). These enzymes build up by inhibition of the enzyme GAPDH, the controlling enzyme in glycolysis, the soccer turnstile so to speak.

   Through the increased production of PKCs, more phosphorylation occurs, activating enzymes not normally activated in more quiescent times, for example: PDGF (platelet-derived growth factor), which cause cellular apoptosis; increased VEGF (vascular endothelial growth factor); reduction in production of nitric oxide which causes vasoconstriction; as well as multiple other adverse effects.

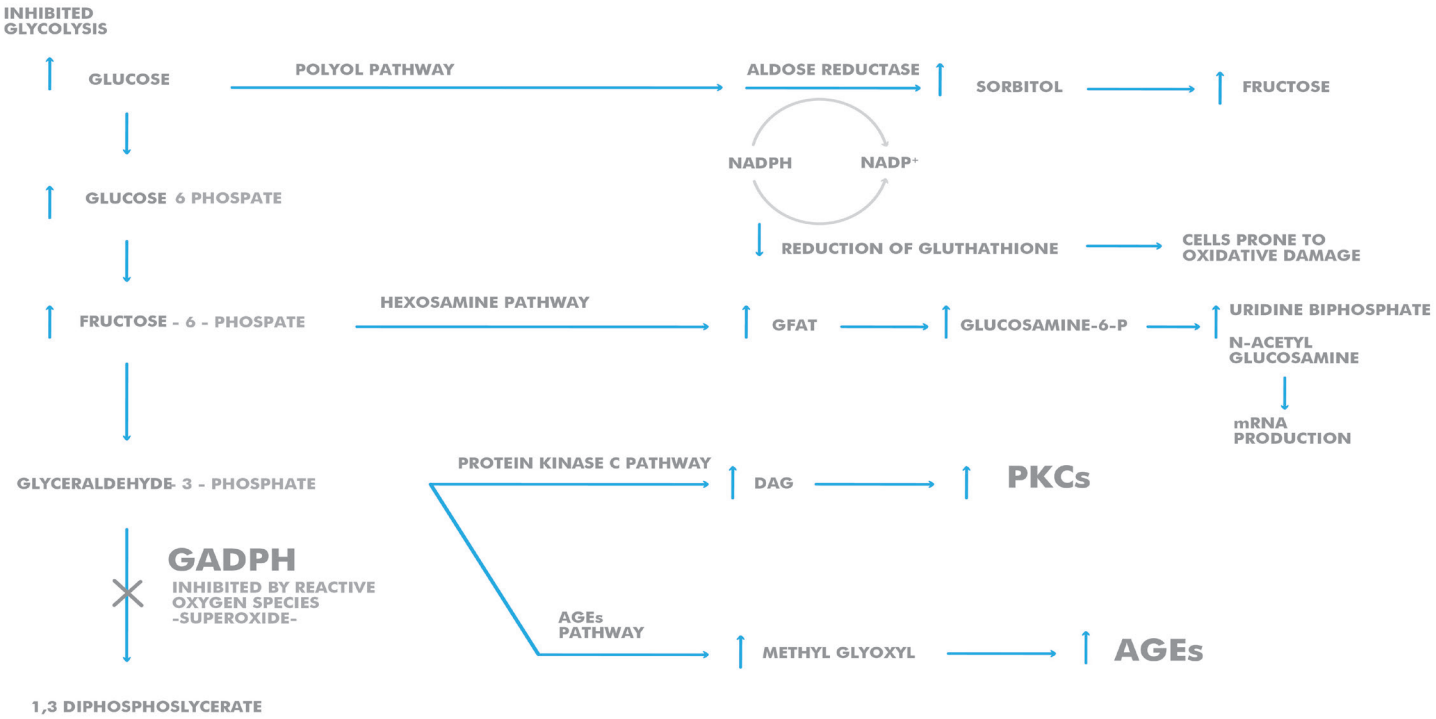
4. **Increased flux into the hexosamine pathway[5]**
This pathway is increased by a factor of 2.4 in hyperglycaemia and usually uses up only three to five per cent of total glucose. Fructose-6-phosphate, the second step in glycolysis, instead of converting to fructose 1,6-biphosphate is converted to glucosamine-6-phosphate, which binds to the base uridine to form uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). This gets incorporated into messenger RNA (mRNA), producing the cytokine proteins TGF (alpha and beta) and plasminogen activator 1. This is one of the pathways thought to damage pancreatic beta cells, hence increasing insulin resistance.

These four pathways are all activated by hyperglycaemia, which overloads the electron transport chain (the football stadium), resulting in an overproduction of superoxide and reactive oxygen species. These negatively feedback on the rate-limiting enzyme in glycolysis GAPDH (the turnstile), causing an increase in all products upstream and the fluxing of glucose (the redeployed soccer hooligans) into the four previously described pathways. The resulting oxidative stress causes tissue damage by all the mechanisms listed above. Without hyperglycaemia, none of this damage would occur. With freer turnstiles, the broken windows, overturned tables and black eyes would have been prevented!

## The epidemiology

This discussion has been all at a cellular level, but apart from our own clinical observation, how do we know that all of these complications from this nice but nasty glucose molecule occur at a population level? In the late 1970s, two important landmark studies, which due to prohibitive cost will never

**Figure 3.** The pathways to cellular destruction.



be repeated, were commenced. These were the Diabetes Control and Complications Trial (DCCT)[6] and the United Kingdom Prospective Diabetes Study (UKPDS). [7] The DCCT dealt with the early aggressive management of type 1 diabetes and the UKPDS addressed type 2 diabetes. Both proved that, with almost 20 years of observation, intensive glucose control resulted in fewer microvascular complications.

In the UKPDS[7] it was found that, for every point reduction in HbA1c (for example, from nine to eight), there was a 35 per cent reduction in complications. It was also established at the ten-year review that the reduction in complications was dependent upon early glycaemic control. Those with early poor control never achieved the same reductions as those with meticulous control from diagnosis, even if it slackened off after the trial finished. This is known as the legacy effect, due to glycaemic memory, and the mechanism is most likely epigenetic. Similarly, this is where the long-term effects of gestational diabetes arise.

## Epigenetics

So what is epigenetics? It's certainly a 21st century buzzword. For a detailed explanation see *O&G Magazine* Vol 18 No 2, page 22. In a nutshell, it means above genetics, therefore outside the normal paradigm of what we understand genetics to be. Epigenetics is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence. The human haploid genome contains three billion base pairs, but genes only account for 15 per cent of these. In each cell there is 1.8 metres of DNA. To be able to squeeze this length of DNA into every cell's nucleus, it has to be spooled around proteins called histones. The supercoiling involved is able to reduce the length of the DNA to 0.09nm. The way it is spooled affects gene expression for that particular cell and gives it this characteristic function. The spooling can be affected by exogenous factors such as hyperglycaemia. Methylation at certain base pairs can turn genes off and this is the most understood mechanism. How hyperglycaemia does this is not fully understood.

## The Barker hypothesis extended

In the same way that Professor David Barker hypothesised in the 1980s that poor fetal nourishment resulted in higher cardiovascular morbidity later in life, there is accumulating evidence that gestational diabetes leads to epigenetic changes, both in the mother and her infant. This can lead to a predisposition to obesity, type 2 diabetes (in mother and baby), as well as cardiovascular morbidity. So like a soccer hooligan, hyperglycaemia causes chaos at a number of levels. It induces hyperinsulinaemia, it causes tissue damage in its own right and induces potentially permanent epigenetic changes. So the moral of this tale is to keep those turnstiles open by maintaining normoglycaemia.

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# Assessment of the fetus of a diabetic mother

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The incidence of women with pre-existing diabetes mellitus (DM) falling pregnant, as well as the incidence of women with diabetes diagnosed during pregnancy, has increased over the last few years. Reasons for this include better glycaemic control improving fertility rates in pre-gestational DM, an increase in women with features of metabolic syndrome falling pregnant, and changes to the diagnostic criteria for gestational diabetes mellitus (GDM) – Australasian Diabetes in Pregnancy Society (ADIPS) criteria.[1] The high-risk nature of these pregnancies has meant an increase in ultrasound scans and cardiotocography (CTG) monitoring, without much evidence to support these. This review focuses on the various methods used to assess the fetus across the trimesters in pregnancies in women with DM.

## First trimester

The first trimester ultrasound is used to document viability and establish an accurate gestational age. The rate of miscarriage is increased in pregnancies complicated by DM, especially if the peri-conceptual glycaemia control has been poor. Establishment of a due date based on measurements of the developing embryo or fetus is the most accurate and evidence-based method of dating the pregnancy. It removes the inaccuracies that arise when the due date is calculated from the last menstrual period. This is more relevant for management in the third trimester, as most diabetic pregnancies have births scheduled. Rates of autosomal chromosomal aneuploidy are not increased with DM, but the rates of anatomical abnormalities and possible sex chromosome aneuploidy are increased, once again especially in women with poor control. The first trimester screen has the advantage of being an early anatomy scan. It can detect anomalies such as large neural tube defects and surrogate markers for congenital heart disease, for example, an increased nuchal translucency. Rates of these are increased in diabetic pregnancies. The combined first trimester screen is the most common method used to screen for chromosomal aneuploidy in Australia and New Zealand. The levels of pregnancy-associated plasma protein A (PAPPA-A) and free beta-human chorionic gonadotrophin ($\beta$-hCG) are reduced in pregnancies affected by DM, and therefore must be adjusted for this.[2]

Non-invasive prenatal testing for aneuploidy is not thought to be altered by DM in pregnancy, though this has not been specifically studied. In obese women, there is a higher chance of there being a 'no-call' result, due to reduced proportion of fetal cell-free DNA in the maternal circulation.

The Fetal Medicine Foundation[3] has developed risk assessments for pre-eclampsia, fetal macrosomia and intrauterine growth restriction (IUGR) using maternal, biochemical and sonographic parameters. There are several publications outlining the evidence for these assessment tools and they all have DM status as one of the maternal medical characteristics, acknowledging the increased incidence of these conditions in affected pregnancies.

## Second trimester

Assessment in the second trimester includes maternal serum screening and the anatomy scan around 20 weeks of gestation. Maternal serum screening is seldom performed in current obstetric practice, but can be if the woman is past the gestational age cut-off for the combined first trimester screen. Serum alfa-fetoprotein (AFP) and unconjugated oestriol are lower in diabetic pregnancies and adjustments need to be made for this.[2] AFP is no longer used as a screening tool for open neural tube defects, but if significantly elevated, a detailed scan looking for this and other fetal anomalies should be performed.

The mid-trimester anatomy scan is the most detailed ultrasound in pregnancy and is a screening tool to detect fetal abnormalities. Fetuses of diabetic mothers have an increased risk of a range of abnormalities (four to eight times the background population); mainly neural tube defects, congenital heart disease (CHD), and the very rare sacral agenesis (caudal regression syndrome), the incidence of which is increased many-fold in poorly controlled diabetes mellitus. CHD is the leading organ-specific

birth defect and is also the leading cause of infant mortality from congenital malformations.[4] CHD accounts for about 50 per cent of diabetes-related major congenital anomalies.[5] Attention should be paid to a detailed cardiac scan. Prenatal diagnosis of CHD remains a challenge, as the sensitivity of ultrasound has ranged from 15–39 per cent.[6] The International Society of Ultrasound in Obstetrics and Gynaecology's guidelines on examination of the fetal heart provide a systematic framework to detect CHD.[7] Some centres refer all pregnant diabetic women for fetal echocardiography, whereas others reserve it for those with an abnormal initial cardiac screen.

### Third trimester

The aims of fetal monitoring in the third trimester are to look for signs of the rare complication of impending fetal death in utero, to identify the macrosomic or IUGR fetus, and aim to schedule birth to minimise maternal and fetal complications. There are no large or randomised trials on which to make evidence-based recommendations as to which pregnancies should undergo fetal surveillance, when to start, what test to order, or how to perform it. Guidelines are therefore based on expert opinion and clinical experience. Monitoring is performed using serial ultrasound scans and CTG.

CTG technology was introduced in the 1980s and initial hopes that it would markedly reduce the perinatal mortality rates have not been proven. The latest *Cochrane* review in February 2016 on antenatal CTG for fetal assessment[8] highlighted that 'there is no clear evidence that antenatal CTG improves perinatal outcome, but further studies focusing on the use of computerised CTG in specific populations of women with increased risk of complications are warranted'. DM was one of the high-risk maternal conditions included in some studies in the review, but overall, the included studies were not of high quality. The consensus guidelines call for twice-weekly CTGs commencing from 32 weeks in complicated diabetic pregnancies, not limited to: fetal macrosomia or IUGR; pharmacological treatment; poor control; added risks such as hypertension or micro or macrovascular disease; and previous poor obstetric outcome. Intrapartum CTG monitoring is recommended in most circumstances, except for diet-controlled GDM with an unremarkable antenatal course.

Ultrasound has emerged as the other modality to assess and monitor the fetus in diabetic pregnancies. It is used to provide an estimate of the fetal weight and track fetal growth, and for fetal well-being when Doppler indices and amniotic fluid volume are assessed. Pregnancies in women with DM are commonly associated with accelerated growth, but are also at increased risk of IUGR. Guidelines exist from international societies on monitoring growth, ranging from a single third trimester scan, to serial growth scans beginning from 28 weeks gestation. A large for gestational age (LGA) fetus is variously defined as being over the 90th percentile for gestational age, or abdominal circumference over the 90th percentile, or both. The HAPO Study[9] showed increases in primary caesarean delivery, neonatal hypoglycaemia and other maternal and neonatal morbidity when a LGA fetus or neonate was identified, but the study looked at outcomes in pregnancies with hyperglycaemia less severe than DM. This data is often extrapolated to include diabetic pregnancies.

Increased fetal insulin production changes the anthropometric measurements of the fetus, specifically the chest-to-head and shoulder-to-head ratios, which accounts for the increase in the incidence of shoulder dystocia and associated birth injury, as compared to non-diabetic fetuses of a similar weight. There is no highly reliable method for identifying LGA fetuses antenatally as ultrasound tends to overestimate the fetal weight; the formula is very sensitive to measurement of the abdominal circumference. The increased prevalence of obesity in these women also reduces the ultrasound diagnostic quality, broadening the measurement error. Other parameters that have been studied include measuring the fetal liver, MRI, fractional limb volume, and subcutaneous fat measurements.[10] These are not used in routine clinical practice. On the flip side, impaired growth is common among women with diabetic vaculopathy and/or superimposed pre-eclampsia. If there is evidence of IUGR, then tests of fetal well-being should be initiated. Special consideration should be given to women with poor control, in which the fetus appears average or slightly small. This is the situation of the 'macrosomic growth restricted fetus', where the two situations combine to give a deceptively normal fetus. This pregnancy should be carefully monitored.

Assessment of the diabetic pregnancy also includes ultrasound for fetal well-being; namely amniotic fluid volume and Doppler assessment. The amniotic fluid volume is prone to be increased in diabetic pregnancies, with several potential reasons for this. A larger baby is thought to produce increased volumes of urine. The osmotic pull of increased glucose in a hyperglycaemic fetus means it produces increased urine volumes.

DM is associated with an increased risk of sudden fetal death. Data from cordocentesis have demonstrated an association between maternal hyperglycaemia and fetal acidaemia in the absence of fetal hypoxaemia. It is this fetal acidaemia, thought to be the consequence of an increased metabolic rate, that may be the cause of the unexplained stillbirths in diabetic pregnancies. The aim of Doppler ultrasound is to identify the fetus at risk of adverse perinatal outcomes. Studies so far in diabetic pregnancies have been disappointing due to the inability to predict sudden fetal death. Doppler indices may be more useful in those pregnancies with vascular consequences, hypertensive disease and IUGR, where there are established guidelines on managing abnormal results. The parameters measured are the umbilical artery systolic/diastolic (S/D) ratio and pulsatility index (PI), the middle cerebral artery PI, the ductus venosus, and the uterine artery PI. The cerebroplacental ratio (CPR), which is the ratio of the fetal middle cerebral artery PI to the umbilical artery PI, has gained prominence as a marker for fetal compromise.[11] A low CPR is associated with several adverse obstetric and perinatal outcomes, and can be considered a marker of suboptimal placental function. Gibbons et al recently showed that a low CPR in pregnancies complicated by GDM is associated with poorer neonatal outcomes, more so in the insulin-treated group.[12] These findings could be extrapolated to include pre-gestational DM.

As can be seen, assessment and monitoring of pregnancies with DM is complex, with several guidelines constructed around consensus expert opinion. Local protocols should be established to manage these pregnancies according to the available resources.

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# To pump or not to pump

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Women with pre-gestational diabetes represent a high-risk pregnancy group for obstetricians.[1] How can this be improved? Technology has changed the care of diabetes significantly in the last decade. Have you heard of insulin pumps, continuous glucose sensors and flash monitors? Obstetricians need to become aware of what is available to help women, especially those pregnant with type 1 diabetes. Insulin pumps are being used to manage type 1 diabetes in over ten per cent of young people,[2] and will become increasingly used to manage diabetes in pregnancy. However, insulin pumps are not for patients with gestational diabetes.

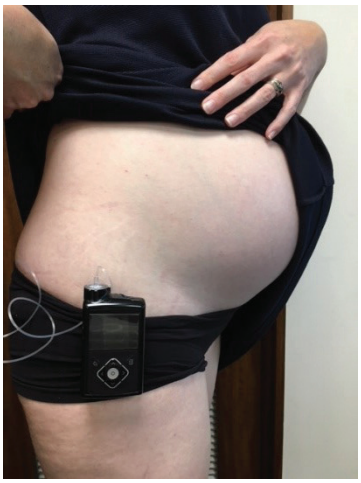

**Image 1.** An insulin pump clipped on a waistband.

What is an insulin pump? It is a device the size of a small mobile phone that usually has a 3ml vial of insulin attached to a cannula inserted in the anterior abdominal wall or buttocks. Most women wear the pump conveniently in their cleavage, or more discreetly, in a pocket or clipped on their waistline. The insulin used is quick-acting and continuously infused into subcutaneous tissue via a small cannula that is changed three times a week. Only one injection every two to three days instead of four to six injections a day – bonus! How does this work? The pump allows the insulin to be delivered at different rates through the day at basal doses for when the patient is not eating. The patient can then give bolus doses at the push of a button whenever they eat. Most patients love this device as it gives them freedom with what and when they can eat. They just need a dietician to teach them how to count carbohydrates. If the blood sugar is too high, a correction dose can be given to achieve a programmed target. If the blood sugar is too low or when the patient is sleeping or exercising, the basal rate can be reduced. All of this is achieved with the push of buttons and no extra needles.

You can imagine how much better the pump is for these women in pregnancy. It is very important to keep sugar levels as close to normal in pregnancy for optimal fetal outcomes, yet avoiding hypoglycaemia in the mother. This can be even harder in the first trimester when the woman is unpredictably vomiting, or in third trimester, when the morning sugar rises because of placental hormones. The pump's programming can be adjusted to manage all of this, with less risk for hypoglycaemia causing maternal harm or even death.

## Why isn't everyone using a pump?

Firstly, the literature doesn't show that women on the pump have better pregnancy outcomes.[3] There are a few reasons for this, including the trials using older pump technology and being small studies. Importantly, the good glycaemic control must also begin a few months pre-conception for optimal pregnancy outcomes, not just when the woman realises she is pregnant. Pre-conception counselling is very important for women with diabetes.[4] The other main confounder in the literature is the use of HbA1c as the marker of glycaemic control. HbA1c is lower in pregnancy by 0.5 per cent because of increased production of red blood cells and may not reflect better glycaemic control. In the small studies on insulin pumps in pregnancy, HbA1c has not been much different with those using multiple daily injections or the insulin pump.[3] However, HbA1c is not ideal for correlating glycaemic control in pregnancy and fetal outcomes. Think simply of gestational diabetes: HbA1c is always low to normal in these patients, but the effect of their blood glucose levels affect the baby. There is increasing evidence that measures of time of glucose in normal range would be the better marker of glycaemic control for effects on baby – we don't have a simple test for that yet. Future advances in continuous glucose sensing and closed-loop pumps will facilitate this.

Secondly, to have the pump, you hope the patient has top-level health cover. A pump is about $10,000 with health funds covering the entire cost (most funds even allow a patient a new pump every four years when the pump warranty from the company usually expires). The National Diabetes Services Scheme (NDSS) covers most of the cost of the ongoing consumables.

Thirdly, and another reason the pump is not a panacea for diabetes (like a Clexane script for pregnant women to reduce thromboembolism), the

patient needs to be educated by an experienced team of endocrinologist, diabetes educator and dietician who are familiar with managing diabetes in pregnancy. It is important to be ahead of the game keeping up with the increasing insulin resistance as pregnancy progresses. Insulin doses can double or triple at certain times of the day by the third trimester.

What about the pump in special situations in pregnancy or postpartum? It is fabulous. It is even possible to give women steroids, if needed, pre-delivery and adjust the pump rates appropriately without needing an intravenous insulin infusion. For labour, the insulin pump rates go down and again this means the woman is free of an intravenous pole with syringe driver attached (no need for complicated IV insulin infusions, though obviously an experienced endocrinologist still needs to supervise the pump rates). For postpartum, the insulin pump is back at often lower than pre-pregnancy rates and can be reduced further with breastfeeding, so there is less risk for hypoglycaemia and women can safely lose weight. What is there not to love? A cautionary note – patients need to be educated well about pump use and must be diligent in making proactive adjustments. The pump does not work by itself (as yet). Also, hospital staff are not trained to deal with insulin pumps, nor are they likely to be, so the patient and their endocrinologist need to be an effective team.

The following photos compare two babies from the same mother with type 1 diabetes – the first pregnancy without an insulin pump and the second pregnancy with an insulin pump. Her second baby did better, even with the mother gaining more weight in that pregnancy.

The woman's first baby (Image 2) was delivered by LSCS at 35+ weeks, with a birth weight of 3761g. The delivery was complicated by pre-eclampsia. The mother had a pre-pregnancy BMI of 35.6, gained 16kg in pregnancy and HbA1c 6.8–7.5%.

The woman's second baby (Image 3) was delivered by LSCS at 38 weeks, with a birth weight of 3480g. The mother had a pre-pregnancy BMI of 39.4, gained 20kg in pregnancy and HbA1c 5.5-5.6%.

For the motivated patient with a supportive, experienced health team, the insulin pump certainly provides a tool to improve their diabetes control to near-normal range in pregnancy, with less risk for hypoglycaemia and better outcomes for mother and baby. With the coming advances of continuous glucose sensors that either 'talk' to the pump or to smart phones, the future is open to achieve the Saint Vincent Declaration (1989), that women with diabetes should have similar healthy pregnancy outcomes as for women without diabetes.[5]

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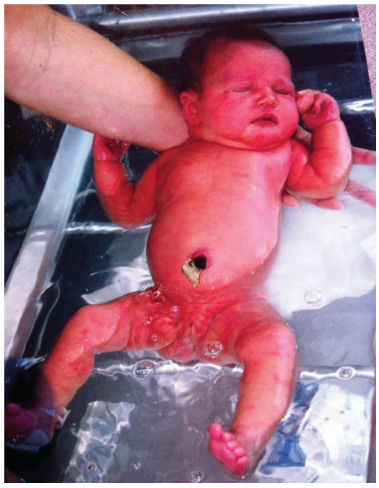

**Image 2.** First baby. The mother had multiple daily insulin injections during the pregnancy.

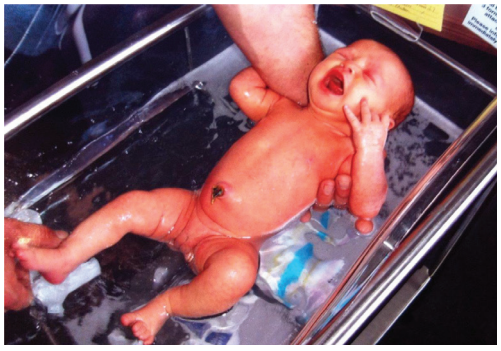

**Image 3.** Second baby. The mother used an insulin pump for this pregnancy.

# Expressing breastmilk during pregnancy

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Expressing milk antenatally has been mentioned in medical journals since the 1940s and 50s, but has only become common in maternity care in recent years. The practice has had a resurgence, probably due to a few factors including the World Health Organization developing the Baby Friendly Hospital Initiative in 1991 to promote, support and protect breastfeeding. As a result, health organisations have refocused on the benefits of breastfeeding for maternal and infant health, and now have breastfeeding targets to achieve during women's postpartum hospital stay.

Women with diabetes during pregnancy make up between seven and 14 per cent of the pregnant population. These women and their infants are at increased risk of complications during pregnancy. After the birth, the babies are at higher risk of hypoglycaemia than babies of women who do not have diabetes in pregnancy. These women are at increased risk of delayed lactogenesis II (breastmilk 'coming in' more than 72 hours postpartum). These complications and the delay in lactogenesis II may lead to mother-infant separation, early formula supplementation or shorter breastfeeding duration.[1] Despite the potential challenges, pregnant women with diabetes are actively encouraged to breastfeed because of the positive metabolic effects breastfeeding confers and the increased chance of delaying the onset of type 2 diabetes for women with gestational diabetes mellitus (GDM).

## Emerging practice of antenatal expressing despite little or no evidence

The purpose of expressing before the birth is to have an adequate volume of breastmilk available for supplementary feeding to treat neonatal hypoglycaemia, hopefully keep mother and baby together, promote earlier onset of lactogenesis II, and, possibly, increase women's breastfeeding confidence. Other reasons women might express antenatally are the 'just in case' scenario, or because of previous poor breastfeeding experiences. However, until recently, there has been very little evidence to support the practice other than case studies and two pilot studies.[2,3]

The topic of antenatal expressing became controversial, with some clinicians calling for the practice to cease until safety and efficacy were established. Others were of the belief that women have breastfed during pregnancy so antenatal expressing would not cause any harm. A 2014 *Cochrane* review[4] concluded that there was 'no high level systematic evidence to inform the safety and efficacy of the practice'.

## Diabetes and antenatal milk expressing (DAME): a randomised controlled trial

In order to establish evidence for this practice, the DAME trial was conducted in Melbourne from 2011 to 2015. The trial was a multicentre, two-group, unblinded randomised controlled trial involving six hospitals in Victoria, funded by the National Health and Medical Research Council. Six hundred and thirty-five eligible low-risk women with diabetes during pregnancy (93 per cent GDM) were randomised to hand express twice a day from 36 weeks or to have normal care (no expressing). Given this was the first trial of antenatal expressing in the world and women with diabetes have an increased degree of pregnancy risk, careful identification of pre-existing and pregnancy complications were considered and women needed to have a reassuring cardiotocograph prior to randomisation.

Women allocated to the expressing arm of the trial were taught how to hand express. They were given a diary to document the volume expressed and any other thoughts or feelings about expressing. The milk was frozen and stored at home in syringes. The frozen breastmilk was then brought to hospital and stored in the postnatal ward freezer ready for use if required. Follow up was by comprehensive data collection from medical records at birth and during telephone interview at two weeks and three months.

## Summary of results

The DAME trial was published in June 2017[5] and found no difference in the proportion of infants admitted to the NICU (primary outcome): 14.5 per cent (n=46) in the intervention (advised to express) arm compared with 140 per cent (n=44) in standard care (Adj. RR 1.06; 95% CI 0.66, 1.46). There was no difference in the mean gestational age at birth (mean difference 0.05; 95% CI–0.10, 0.21). There was moderate evidence of association between allocation to antenatal expressing during pregnancy and the proportion of infants receiving exclusive breastmilk in the first 24 hours of life (Adj. RR 1.15; 95% CI 1.02, 1.28), and some evidence of an association with receiving exclusive breastmilk during the initial hospital stay (Adj. RR 1.16; 95% CI 0.99, 1.33).

Women expressed many times before birth, with a median of 20 times (range 1, 59; IQR 9, 33). The median total volume expressed was 5.5mL (range 0, 905; IQR 0.25, 22), which was significantly less than many clinicians had expected.

**Image 1.** Marie and her baby. Marie expressed breast milk antenatally.

**Image 2**. Edel and her baby. Edel was a participant in the DAME trial.

## Interpreting the results

This trial was limited to a low-risk subset of women with diabetes during pregnancy. The results should not be extrapolated to high-risk groups, as the results may be different. Clinicians are asking, given the apparent safety for low-risk women with diabetes, should the practice of expressing antenatally be advised for all low-risk women, not just those with diabetes? Until there is further research in this field, we should be cautious about interrupting highly sensitive normal postpartum breastfeeding in the absence of medical indications (for example, neonatal hypoglycaemia). Additionally, given that most women expressed low volumes (median 5.5mL total), some women, especially primiparous women, may be concerned about their ability to produce adequate milk volumes after their baby is born.

Others argue that the act of antenatal expressing may in fact increase confidence with breastfeeding, as women will feel they have already mastered the valuable skill of hand expressing regardless of the volume of milk expressed. These are important questions for consideration and further research is required before routine advising of antenatal expressing.

## Where to from here?

Given the lack of evidence-based information, local and international dissemination of the findings has been undertaken to better inform clinicians and breastfeeding peer support groups. The DAME trial research group produced an article for the wider population in *The Conversation*, called 'Health Check: is it safe to express milk before giving birth?'[6] Members of the research group have also worked with the Australian Breastfeeding Association to update their online information for women.

In order to reflect best practice on antenatal expressing, members of the research group are working with the three tertiary maternity hospitals in Victoria to develop clinical practice guidelines and a fact sheet for women with diabetes during pregnancy. These guidelines will also provide consistent criteria and processes among maternity providers.

With hard work and great collaboration, we are moving towards better information for clinicians and women about antenatal expressing during pregnancy and have identified areas for further research.

**Image 3.** Syringes of antenatal breastmilk.

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# Induction of labour

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The complication of diabetes in pregnancy includes both pre-gestational diabetes (type 1 and type 2 diabetes mellitus) and gestational diabetes.

The adverse effect of type 1 diabetes on pregnancy is profound, but since the advent of synthetic insulin, outcomes have significantly improved from an era when the combination of type 1 diabetes and pregnancy was often a death sentence for mother and infant. While pregnancy outcomes are better for women with type 1 diabetes, the risk of complication is substantially higher than for non-diabetic women.[1]

Type 2 diabetes and its impact on pregnancy is becoming more apparent, with increasing rates of obesity in women of childbearing age. Women at risk often miss out on pre-pregnancy diagnosis, counselling and treatment.[2]

Increasing prevalence of gestational diabetes is linked to rates of obesity in the community and is also influenced by the changing demographics of the population, as ethnic background or country of birth effect the chance of diagnosis in pregnancy. Combined with changes to diagnostic thresholds, the number of women requiring additional education, monitoring and treatment for gestational diabetes has seen demands on clinicians grow.[3]

Women with type 1 and type 2 diabetes, and gestational diabetes to a lesser extent, are likely to develop a number of complications throughout pregnancy, but especially at term. For a woman, potential complications include caesarean delivery, operative vaginal birth and pre-eclampsia. Complications for the fetus might include macrosomia, shoulder dystocia, hypoglycaemia, jaundice and stillbirth.[4,5]

In the long-term, women with gestational diabetes remain at risk of developing type 2 (and type 1) diabetes over their lifetime. Their offspring are more likely to be obese and are susceptible to developing diabetes.[6]

## Induction of labour

The principle of induction of labour is that early birth reduces the likelihood of developing complications that an ongoing pregnancy would potentially inflict on a woman with diabetes and her baby.

Induction is usually considered to be indicated where there is evidence that inducing labour leads to better outcomes for mother and child and does not result in an increase in undesirable effects, such as a higher caesarean section rate or more babies being admitted to the special care unit.

Pre-gestational diabetes and gestational diabetes increase the risk of hypertensive disorders of pregnancy, including pre-eclampsia. The diagnosis of these superimposed conditions is an additional clear indication for induction of labour to reduce the occurrence of maternal morbidity, such as severe hypertension or the progression of pre-eclampsia.[7]

## Evidence base

While diabetes in pregnancy, especially gestational diabetes, is a relatively common clinical scenario, the lack of high-quality evidence to guide recommendations for induction of labour may be surprising.

Randomised controlled trials comparing induction of labour with expectant management for women with diabetes are few[8] and the majority of evidence supporting induction of labour recommendations is gathered from cohort studies.[9,10,11] Thankfully, the consistency of findings across a number of studies conducted in a range of countries and populations (most are from North America or Europe), gives confidence that we can provide adequate information to our patients.

## Considerations regarding timing of delivery

The recommendations on timing of delivery, and thus induction, are informed primarily by cohort studies examining the risk of a particular outcome, such as caesarean section or stillbirth, occurring in a population of women with diabetes at each week of gestation, compared to women without any pregnancy complication.

## Type 1 and type 2 diabetes

The risk of pregnancy complication for women with type 1 and type 2 diabetes is significantly greater than that of the general obstetric population and in women with gestational diabetes.[12]

Most importantly, the nadir for the rate of stillbirth for women with type 1 and type 2 diabetes was seen between 37 weeks and 38 weeks 6 days.[13]

Earlier delivery should be considered when end-organ complications are present, such as nephropathy, neuropathy and vasculopathy, or, when there is a poor obstetric history such as prior stillbirth.

Where significant fetal macrosomia is suspected in the presence of maternal diabetes, it is incumbent on clinicians to discuss the alternative of caesarean section, especially in light of the Montgomery v Lanarkshire case.[14] While no guidelines go so far as to recommend caesarean delivery for any particular birth weight, the option of caesarean to prevent traumatic delivery could be considered when birth weight is estimated at greater than 4000–4500g.[15]

## Gestational diabetes

In women with gestational diabetes, the lowest rate of stillbirth was seen in week 40, with a rise in the rate of stillbirth after 41 weeks greater than that observed in women without gestational diabetes.[16] Cohort studies show lower rates of macrosomia in women with gestational diabetes delivered in week 38, with no increase, or even a reduction, in the incidence of caesarean section. The studies showed

no reduction in the rate of shoulder dystocia.[9,10,11] There is evidence of benefit from induction of labour for large-for-date fetuses, when clinically suspected and supported with ultrasound findings. The Boulvain study has shown a reduction in the risk of shoulder dystocia and fetal and maternal morbidity. Women with gestational diabetes were not excluded from this trial, making up approximately 10 per cent of the numbers included in the analysis.[17]

## Methods of induction of labour

There is no evidence that a particular method of induction of labour for women with pre-gestational or gestational diabetes is preferred. Induction with prostaglandins and oxytocin were primarily used in the two randomised clinical trials. Mechanical methods with Foley balloon or double balloon are also used and may have benefits where concerns regarding fetal wellbeing mean that avoiding uterine hyperstimulation may be more desirable.

## Key points

For women with pre-gestational or gestational diabetes, induction of labour may reduce the chance of common outcomes like macrosomia, shoulder dystocia and uncommon but important outcomes such as stillbirth.

The effect of induction of labour as a result of diabetes on the likelihood of caesarean section is probably neutral or may reduce the rate.

Timing for type 1 and type 2 diabetes is usually recommended after 37 and before 40 weeks, with the risk of stillbirth lowest between 37 and 39 weeks. For women with gestational diabetes requiring treatment with medication, (most commonly insulin), induction between 38 and 40 weeks is often recommended. Induction of labour around 40 weeks and up to 41 weeks is considered reasonable for women with gestational diabetes controlled by diet.

Suspected fetal macrosomia should trigger consideration of earlier induction of labour at early term (37–38 weeks), or if the risk of difficult vaginal delivery is substantial, then the option of caesarean section should be discussed with the patient.

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# Management of infants of diabetic mothers

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Diabetes in pregnancy is associated with a range of neonatal complications, with infants of diabetic mothers at increased risk for mortality and morbidity, compared to those born to non-diabetic mothers. The management of the infant requires anticipation, early recognition and treatment of potential complications, while also providing routine neonatal care.

## Fetal effects

The development and severity of complications in the fetus of a diabetic mother is influenced by the degree, timing and duration of maternal hyperglycaemia. Good maternal glycaemic control during pregnancy reduces the risk of some, but not all, of the potential complications in infants. Diabetic embryopathy can occur if maternal hyperglycaemia is present at the time of conception and in the first trimester (generally with pre-existing type 1 or type 2 diabetes). This can result in birth defects and spontaneous abortions.[1] In the second and third trimesters, maternal hyperglycaemia results in fetal hyperglycaemia and subsequent fetal hyperinsulinaemia, leading to a range of complications in the neonate.[1]

## Neonatal effects

Complications can be present at birth or develop later in the neonatal period. They can be categorised into congenital abnormalities or birth/neonatal complications (Table 1).[2]

The physical examination of the infant should occur soon after birth, identifying any potential congenital anomalies, assessing respiratory and cardiac status, and assessing for the presence or absence of macrosomia, metabolic and haematological complications.

The infants have increased rates of neonatal intensive care unit admissions, compared to those born to non-diabetic mothers, however, unless there is clinical need for admission to the nursery (for example, blood glucose monitoring), infants should ideally remain on the post-natal ward for routine surveillance and monitoring.

## Macrosomia

Macrosomia, defined as a birth weight above the 90th percentile or greater than 4000g, is associated with disproportionate growth, with a subsequent predisposition to birth injuries, such as shoulder dystocia, clavicle fractures, brachial plexus injuries and perinatal asphyxia.[3,4] Macrosomic neonates are at increased risk for respiratory distress and metabolic complications.[3,4] The early identification of a macrosomic infant (ideally prenatally) is essential in allowing for a timely and safe delivery, with prevention, minimisation or early detection of complications.

## Respiratory distress

Respiratory distress is common and can be multifactorial in nature.[2,5] Maternal hyperglycaemia

**Table 1.** Potential neonatal complications in the infant of diabetic a mother.

| Congenital abnormalities | Neonatal complications |
|---|---|
| Congenital heart disease<br>• Transposition of the great arteries<br>• Double outlet right ventricle<br>• Ventricular septal defect<br>• Truncus arteriosus<br>• Tricuspid atresia<br>• Patent ductus arteriosus<br>Neural tube defects<br>• Anencephaly<br>• Spina bifida<br>Caudal regression syndrome<br>Small left colon syndrome<br>Cleft palate<br>Vertebral anomalies<br>Flexion contracture of the limbs<br>Intestinal anomalies | Prematurity (spontaneous or medically-induced)<br>Macrosomic/LGA infants<br>• including associated birth complications and injuries<br>Perinatal hypoxia<br>Respiratory distress<br>Metabolic complications<br>• Hypoglycaemia<br>• Hypocalcaemia<br>• Hypomagnesaemia<br>• Cardiomyopathy<br>Haematological complications<br>• Polycythaemia<br>• Low iron stores<br>Hyperbilirubinaemia |

appears to delay surfactant synthesis, resulting in an increased risk of respiratory distress syndrome, affecting both preterm and term neonates. Infants also have increased rates of transient tachypnoea of the newborn, cardiomyopathy and are more likely to be born prematurely,[2] thereby, increasing the risk of respiratory issues in the neonatal period. Targeted management of respiratory distress should focus on early identification of the underlying cause.

## Metabolic complications

### Hypoglycaemia

Fetal hyperglycaemia results in hyperinsulinaemia, through hypertrophy and hyperfunctioning of the beta cells in the fetal pancreas.[1] After birth, maternally-derived hyperglycaemia resolves. However, there is transient continuation of the hyperinsulinaemic state, as neonatal beta cells adjust to normal neonatal blood glucose levels. This hyperinsulinaemic state typically normalises within two to four days of birth.

While definitions of hypoglycaemia are somewhat arbitrary and still debated, in Australia, neonatal hypoglycaemia is commonly defined as a blood glucose of less than 2.6mmol/L.[6] Symptoms of hypoglycaemia are broad and may include poor feeding, jitteriness, irritability, apnoea, cyanosis, hypotonia, lethargy, seizures, pallor, sweating, tachycardia, vasomotor instability, bradycardia and hypotension.[7] Most infants with low blood glucose levels are initially asymptomatic and detection is based on routine surveillance. Infants of diabetic mothers with poor recent control, on high doses of insulin, or those with type 1 diabetes, are considered at high risk for hypoglycaemia and are often admitted directly to the nursery. All infants of diabetic mothers require early establishment of feeds and regular monitoring of blood glucose levels.

The management of hypoglycaemia depends on the timing and severity. Generally, for mild to moderate hypoglycaemia, management with oral or enteral feeds is appropriate and preferred. For severe hypoglycaemia (or in those infants with other complications such as prematurity or respiratory distress), intravenous management is required. Glucose gel (40 per cent) is now readily available and can be used for mild to moderate hypoglycaemia in infants whose glucose levels do not respond to an enteral feed, or in those with severe hypoglycaemia, where a delay in IV access is unavoidable. Blood glucose screening can generally cease after three consecutive readings of 2.6mmol/L or greater, if the infant is feeding well.[6]

## Hypocalcaemia and hypomagnesaemia

Hypocalcaemia and hypomagnesaemia are usually transient, asymptomatic and resolve without treatment.[2] However, they should be considered if the neonate is symptomatic (for example, seizures, jitteriness), or otherwise unwell. Treatment is through oral or intravenous supplementation.

## Cardiomyopathy

Fetal hyperinsulinaemia can lead to cardiac hypertrophy through increased synthesis and deposition of fat and glycogen in the myocardial cells.[8] Most neonates are asymptomatic, however, 5–10 per cent develop respiratory distress, signs of poor cardiac output or cardiac failure. Chest x-ray may show cardiomegaly and echocardiograph is diagnostic. Cardiomyopathy is transient, resolving with normalisation of plasma insulin levels,[9] therefore, management is supportive (intravenous fluids, propranolol).

## Haematological complications

### Polycythaemia and low iron stores

Polycythaemia, defined as a haematocrit of greater than 0.65 per cent, is thought to be a result of chronic fetal hypoxaemia and oxidative stress, leading to increased erythropoietin concentrations. Iron is believed to shunt into the red cell mass, resulting in low iron stores. The haematocrit should be measured within 12 hours of birth. Most polycythaemic infants are asymptomatic and can be managed supportively with careful monitoring of hydration status and glucose levels. Symptomatic infants, or those with severe polycythaemia, may require intravenous hydration or partial exchange transfusions.[10] Iron supplementation is not recommended, as iron reutilisation occurs after the breakdown of the red cell mass.

## Long-term effects

While most complications in infants of diabetic mothers are managed successfully in the neonatal period, there is evidence that prenatal exposure to hyperglycaemia can result in long-term metabolic and possibly neurodevelopmental complications. Ongoing follow up is required.

## Conclusion

Infants of diabetic mothers are known to be at increased risk for a variety of complications in the neonatal period, with increased mortality and morbidity, compared to infants born to non-diabetic mothers. Management should focus on good prenatal care and early identification and treatment of complications.


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# PCOS and its associated metabolic complications

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age; the exact incidence is dependent on diagnostic criteria used, but ranges from six to 20 per cent of the female population.[1] Since 2003, the diagnosis has been based on the Rotterdam Criteria encompassing the three facets of the syndrome: sonographic appearance of polycystic ovaries; clinical or biochemical evidence of hyperandrogenism; and oligomenorrhoea with presence of two of the three being diagnostic.[2]

Recent advances in ultrasound technology and a greater appreciation of androgenic features in certain ethnic groups and adolescents has generated discussion regarding the overdiagnosis of the condition and a move to making diagnostic criteria more exclusive. In 2013, the ultrasound criteria for the description of a polycystic ovary morphology were revised upwards to more than 25 follicles per ovary and an ovarian volume of greater than 10mL.[3] The most relevant phenotypical features of the PCOS diagnosis are being explored, with the aim to guide practitioners in identifying patients most at risk of the metabolic sequelae of PCOS. Patients with phenotypes A and B in the following table, therefore, the patients who have evidence of hyperandrogenism with ovulatory disorder as a feature of the disease, appear to be more at risk of metabolic complications than those with phenotype C and D.[4]

**Table 1.** Phenotypes of polycystic ovary syndrome.

| | Phenotypes of polycystic ovary syndrome |
|---|---|
| A | Biochemical or clinical hyperandrogenaemia and oligo/anovulation with PCO |
| B | Biochemical or clinical hyperandrogenaemia and oligo/anovulation without PCO |
| C | Biochemical or clinical hyperandrogenaemia and PCO with normal ovulation |
| D | Oligo/anovulation and PCO without biochemical or clinical hyperandrogenaemia |

The diagnosis of PCOS in adolescence is even more controversial, as many of the PCOS diagnostic criteria may be physiologically normal for puberty: oligomenorrhoea, cystic acne and PCO morphology, for example. Hirsutism, moderate inflammatory acne which is unresponsive to topical treatment, or persistent menstrual disturbance two years after menarche, raises concerns for PCOS in an adolescent patient, more so than adult criteria for diagnosis.[5] Of particular relevance for contraceptive discussions with adolescents is that, despite the fact their menstrual cycle may be very erratic, protracted and unpredictable, evidence suggests the majority are still ovulatory.[6]

## Investigation and management of the metabolic complications of PCOS

Why is it important to diagnose a woman with PCOS? We know patients with PCOS are more likely to develop metabolic complications, including: impaired glucose tolerance (IGT); gestational diabetes and type 2 diabetes mellitus (T2DM); visceral adiposity; dyslipidaemia; vascular endothelial dysfunction; and have a pro-thrombotic state.[7] Identifying these women, initiating investigation, and if necessary, lifestyle advice and treatment are integral parts of the management of PCOS.

## Obesity

Obesity is not a diagnostic feature of PCOS, but women with PCOS are twice as likely to be obese than women without PCOS. Many theories as to the association of PCOS and obesity have been explored. Women with PCOS, even lean women, have lower rates of lipolytic activity and larger adipocytes that respond at slower rates to lipolysis than matched non-PCOS controls.[8] Increased androgen levels have been shown to increase appetite and also reduce impulse control, resulting in larger energy consumption in women with PCOS. Gastrointestinal satiety peptides have been shown to be lower in women with PCOS than age and weight matched controls, further supporting the reduction in appetite control in women with PCOS.

The severity of all metabolic risk factors associated with PCOS are exaggerated in women with PCOS who are also overweight or obese. Obesity causes a chronic low-grade inflammation, increasing cardiovascular risk and insulin resistance. Adipose deposits are more likely to be visceral in women with PCOS based on anthropometric measurements of women with and without PCOS, which further increases cardiovascular risk. Weight loss and maintenance of weight within a healthy weight range is the hallmark of first-line treatment for PCOS. Lifestyle factors should be addressed with diet and exercise programs. No specific diet regimes have been shown to be significantly superior in women with PCOS, but high protein diets seem to be better tolerated with associated greater satiety.

If lifestyle factors have failed, bariatric surgery should be considered in women with a BMI greater than 40kg/m², or greater than 35kg/m² with additional evidence of metabolic disease. Bariatric surgery has been shown to be successful in reducing weight, PCOS symptoms and metabolic complications of the disorder. Metformin can also be employed and has been demonstrated to lead to reductions in BMI, in association with diet and exercise at a greater rate than lifestyle modifications alone. Other pharmacotherapies are showing promise although there is less safety data, particularly in women who wish to conceive. The glucagon-like peptide-1 (GLP-1) analogue, liraglutide, is a subcuticular injection that reduces appetite. Liraglutide has been successful in reducing bodyweight and fasting plasma glucose levels in obese PCOS patients, in combination with metformin, at greater rates than with metformin alone. Orlistat, a gastric and pancreatic lipase inhibitor that inhibits fat absorption, has better safety data than most weight loss medications on the market. Orlistat has good data demonstrating weight loss, an improved metabolic profile and increased ovulation rates in obese women with PCOS.

## Hyperinsulinaemia

Women with PCOS are more likely to be insulin resistant, independent of their BMI, with the incidence of gestational diabetes, impaired glucose tolerance and type 2 diabetes mellitus all being increased in women with PCOS when compared with age and BMI matched controls.[9] There is evidence of impaired glucose tolerance in 30 to 75 per cent of women with PCOS and a normal range BMI, while this increases to 95 per cent in PCOS patients who are overweight or obese.[9] Screening for insulin resistance in women with PCOS is a crucial part of management. Fasting insulin or fasting glucose levels lack sensitivity and result in underdiagnosis in this group of patients. The recommended test is a two-hour oral glucose tolerance test, repeated every two years.[9]

The primary treatment for insulin resistance is weight loss, with associated increase in physical activity. This also improves fertility, as well as pregnancy and mental health outcomes. Even if weight loss is not achieved, increased levels of physical activity will improve insulin resistance, as well as altering fat distribution and reducing overall cardiovascular risk. When this fails, medical treatment, often metformin as a first-line agent, can be commenced.

## Dyslipidaemia

Dyslipidaemia, like many metabolic complications of PCOS, is more pronounced in women with PCOS and increased BMI. However, even PCOS patients in the normal weight range are at increased risk of dyslipidaemia compared with age and weight matched controls. PCOS patients have lower levels of protective high density lipoprotein (HDL) cholesterol and higher levels of particularly triglycerides, but also very low density lipoprotein (VLDL) and total cholesterol.[10]

Specific testing for dyslipidaemia for all women with PCOS is not recommended. However, an appreciation of the increased risk of the condition in women with PCOS and thus incorporating the diagnosis into the decision for testing and subsequent treatment with statin therapy, should be made in conjunction with a review of other cardiovascular risk factors that are present.

## Cardiovascular disease

Although there is little evidence to support an increased rate of cardiovascular events in women with PCOS, surrogate markers of cardiovascular disease and significant risk factors for cardiovascular morbidity and mortality are increased in women with PCOS. Coronary artery calcification and carotid artery intima-media thickness have both been shown to be more prevalent in women with PCOS. Interestingly, a study looking at the presence of aortic plaque found no significant increased rate in women with PCOS, but the majority of these women were diagnosed based on PCO morphology and oligomenorrhoea only, with no hyperandrogenism features,[11] further suggesting the PCOS phenotypes A and B are at greater risk of metabolic disease. An appreciation of these findings should further guide practitioners to recommend weight loss, regular exercise and smoking cessation, as well as reducing other modifiable cardiovascular risk factors in women with PCOS.

## Thromboembolism

Women with PCOS are more likely to develop venous thromboembolism (VTE) irrespective of age and BMI.[12] Higher levels of fibrinogen, as well as increased rates of endothelial and platelet dysfunction, are thought to be the mechanisms placing PCOS patients at higher risk of VTE.[12] Populations studies have put the increased risk at 1.5 times the background risk for a patient's age and BMI. This is increased to twice the background risk for PCOS patients on the combined oral contraceptive pill (COCP), when compared with non-PCOS patients also on the COCP.[13] As the COCP is a commonly prescribed therapy for women with PCOS for treatment of hyperandrogenism, cycle regularity and endometrial protection, practitioners should be aware of the added risk above the population rate of VTE in PCOS women. Further review of other risk factors for VTE should be made when deciding to prescribe the COCP in these women.

PCOS is a metabolic disorder and is associated with an increased risk of multiple metabolic complications. Patients should be made aware of this with diagnosis and encouraged to achieve and maintain a healthy weight range while participating in regular exercise. Impaired glucose tolerance is the only metabolic complication that should be routinely screened for with an alternate yearly oral glucose tolerance test (OGTT). Other metabolic complications should be screened for and treated on a case by case basis, dependent on other cardiovascular risks.

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# Metformin in pregnancy

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Metformin is an oral hypoglycaemic medication with a long history. First isolated in 1922, it has been available in Australasia for more than 40 years. Metformin is central to local and international guidelines for the management of type 2 diabetes and has other widening clinical indications. Apart from lowering blood glucose levels, metformin helps combat hypertriglyceridemia, has some vasoactive properties and does not cause weight gain.[1]

Metformin is usually well tolerated, however, minor side effects such as nausea and diarrhoea are relatively common. The more serious side effect of lactic acidosis is very rare. For many years, metformin was tainted by experience with a related compound, phenformin, which could cause lactic acidosis due to variations in metabolism by the liver. Unlike phenformin, metformin is not metabolised by the liver and is excreted unchanged in the urine.

Treatment of diabetes in pregnancy has traditionally focused on the use of insulin. Australian Diabetes In Pregnancy Society (ADIPS) guidelines (2005) state that insulin is the therapy of choice for gestational diabetes (GDM), citing concerns about lack of evidence for the safety of metformin. However, more recent studies show that metformin, with or without insulin therapy, has several fetal and maternal advantages over insulin therapy alone. It is anticipated that metformin use in GDM and type 2 diabetes in pregnancy will increase, especially if longer term fetal safety, or even benefit, is shown. Other uses of metformin to be considered are in the treatment of insulin resistance syndromes, such as PCOS and prevention of type 2 diabetes following GDM.

## Metformin for women with gestational diabetes

The prevalence of GDM is increasing by four per cent annually and already occurs in five to ten per cent of pregnancies. GDM is associated with maternal and fetal complications, such as pre-eclampsia, macrosomia, shoulder dystocia and neonatal hypoglycaemia. GDM also increases the risk of obesity and type 2 diabetes in childhood in the offspring.[2] The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) showed that treatment of GDM with lifestyle modification and insulin, if necessary, is very effective, with the rate of serious perinatal outcomes reduced from four per cent to one per cent.[3] The longer term fetal benefit of GDM treatment with insulin is not so clear, with the follow-up study of offspring showing no difference in BMI between groups at four to five years of age.[4] While treatment of GDM has traditionally meant insulin therapy, there has been an increase in the use of oral hypoglycaemic agents as an alternative.[5] A recent meta-analysis by Butalia et al of 14 randomised controlled trials (RCT) compared metformin (with or without insulin) with insulin in pregnant women with GDM or type 2 diabetes, and reported maternal or fetal outcomes.[6] Eleven studies enrolled women with GDM (n=2062) and three studies enrolled women with type 2 diabetes (n=103). The included studies were from a broad geographical area, including North and South America, Australasia, Europe and the Middle East. The study found that 14 to 46 per cent of women with GDM in the metformin group required the addition of insulin to meet glycaemic targets in pregnancy, indicating that metformin therapy alone is often insufficient. Compared with insulin treatment alone, metformin treatment resulted in lowered risk of hypoglycaemia, large for gestational age babies and pregnancy-induced hypertension. Metformin did not increase preterm delivery, small for gestational age babies, perinatal mortality or caesarean section (see Table 1).

**Table 1.** Meta-analysis of metformin treatment (with insulin if necessary) versus insulin treatment alone.[6]

| Outcome | Relative risk(RR) | 95% Confidence interval(CI) |
|---|---|---|
| Neonatal hypoglycaemia | 0.63 | 0.45-0.87 |
| Large for gestational age babies | 0.8 | 0.64-0.99 |
| Pregnancy-induced hypertension | 0.56 | 0.37-0.85 |
| Preterm delivery | 1.18 | 0.67-2.07 |
| Small for gestational age babies | 1.2 | 0.67-2.14 |
| Perinatal mortality | 0.82 | 0.17-3.92 |
| Caesarean section | 0.97 | 0.8-1.19 |

The metformin treated group also had reduced maternal total weight gain (mean difference -2.07kg; 95% CI:-2.88 to -1.27). This result is important as rates of obesity are rising in our population. More than 40 per cent of women aged 25–34 in Australia are overweight or obese. The prevalence of severe obesity in Australia has tripled in the past 20 years. Obesity is independently associated with adverse maternal and fetal outcomes, so diabetes management in pregnancy that minimises weight gain is important.

This meta-analysis shows that in the short term metformin, with or without insulin treatment, outperforms insulin alone. The next question is how metformin compares with insulin treatment in the longer term.

## Long-term effects of metformin use in pregnancy

A major concern for many considering using metformin in pregnancy relates to some uncertainty regarding the effects of fetal exposure to metformin.

Unlike insulin, metformin does cross the placenta, with fetal levels being approximately half the maternal levels.[7]

When metformin is taken during the first trimester of pregnancy, there is no evidence of an increased risk for major fetal malformation. A meta-analysis of pregnancy outcome after metformin exposure in the first trimester in women with PCOS showed the fetal malformation rate was significantly lower than the disease matched control group (1.7% in metformin group, 7.2% in control group).[8]

The effect of metformin has been studied in in-vivo mouse models with both positive and negative results. Studies have found in-utero exposure to metformin reduces fetal inflammation and improves metabolic programming. Other studies have raised concerns that metformin may have harmful effects on testicular development; however, a five-year follow-up study after metformin treatment of GDM found no effect on testicular size in male offspring.[9]

Two studies in the meta-analysis by Butalia et al provide long-term follow-up data to assess the fetal effects of exposure to metformin in-utero.[6] One study reported growth and development at six, 12 and 18 months in children born to women with GDM, randomised to either metformin or insulin.[10] Children in the metformin group weighed more at 12 and 18 months, and were taller at 18 months compared to the insulin group, but their body composition, defined by mean ponderal index (PI), did not differ.

Rowan et al reported body composition of children two years of age born to women with GDM, randomised to either metformin or insulin.[11] Children of mothers in the metformin group had no difference in overall body composition as measured by dual-energy x-ray absorptiometry (DEXA) and bioimpedence. Anthropometry suggested these children had more fat stored in subcutaneous depots compared with those in the insulin group, a finding which potentially suggests benefit from metformin treatment.

Overall, the meta-analysis found that metformin in pregnancy had no short-term adverse effects on pregnancy and potential benefits in the neonatal period, but there was limited long-term follow-up information. We await the results of two further follow-up studies, including the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study on nine-year measures of visceral fat and insulin sensitivity, as well as ongoing trials, such as the Metformin in Women With Type 2 Diabetes in Pregnancy Kids trial (MiTy Kids).

## Prevention of type 2 diabetes

Women with GDM have a greater risk of developing diabetes in the future compared with those women who have normal glucose tolerance during pregnancy. In a follow-up trial conducted at Mercy Maternity Hospital, Melbourne, 447 women who had GDM have been retested at intervals of one to 12 years following diagnosis. 49 (11%) were found to be diabetic and 35 (7.8%) had impaired glucose tolerance.[12]

The Diabetes Prevention Program randomised women who had GDM to standard lifestyle and placebo, metformin therapy or to an intensive lifestyle intervention. The study found that both intensive lifestyle intervention and metformin are highly effective in delaying or preventing the devlopment of diabetes.[13] Intensive lifestyle intervention is recommended for all women who have had GDM. Metformin should be considered in women who have difficulty in adapting their lifestyle.

## In pregnancy for obese women without GDM

Obesity without GDM is associated with adverse maternal and infant outcomes. As metformin is shown to reduce weight gain and improve insulin sensitivity, its place in managing pregnant women without GDM is of interest. In a double blind placebo-controlled trial, pregnant women without diabetes who had a BMI of more than 35 were randomly assigned to receive metformin, at a dose of 3g per day, or placebo. There was greater reduced maternal weight gain in the metformin group than the placebo group (4.6kg [interquartile range, 1.3 to 7.2] versus 6.3kg [interquartile range, 2.9 to 9.2], p<0.001) but not neonatal birth weight (median neonatal birth weight z score 0.05 in the metformin group [interquartile range, -0.71 to 0.92] and 0.17 in placebo group [interquartile range, -0.62 to 0.89], P=0.66).[14] The study concluded that the antenatal administration of metformin among women with a bone mineral density (BMI) greater than 35, but without diabetes, resulted in reduction in maternal weight gain but not neonatal birth weight. This finding mirrors the effect of metformin on maternal weight gain in women with GDM or type 2 diabetes. However, without demonstration of fetal benefit, metformin is unlikely to be indicated for obese women without diabetes in pregnancy.

## In pregnancy for women with PCOS

Metformin has been shown to improve insulin resistance and ovulation in patients with PCOS. A randomised placebo-controlled, double blind multicentre study showed metformin treatment from the first trimester until delivery did not reduce pregnancy complications (pre-eclampsia, preterm delivery, GDM or fetal birth weight).[15]

A small (n=25) RCT of women with PCOS, randomised to metformin or placebo, reported eight-year follow-up data on their children.[16] Concerningly, in this very small study, systolic blood pressure and fasting glucose levels were higher in the children of mothers who used metformin. Currently, given the limited data regarding metformin use in pregnant women with PCOS, continuation of metformin in patients with PCOS in pregnancy is not recommended.

## In pregnancy for pre-existing type 2 diabetes

The prevalence of type 2 diabetes is increasing and it is strongly associated with obesity. The maternal and fetal risks of pregnancy complicated by type 2 diabetes are similar to risks associated with type 1 diabetes. Women with type 2 diabetes are often treated with metformin prior to pregnancy. To date, there have only been very small intervention trials comparing metformin with insulin treatment during pregnancy, in women with pre-existing type 2 diabetes. A recent *Cochrane* review concludes that there is insufficient RCT data to evaluate the use of oral anti-diabetic agents in pregnant women with pre-existing diabetes.[17] The results of ongoing trials in this area are awaited. The MiTy randomised placebo-controlled trial of metformin versus placebo, examining a composite end-point of early maternal and fetal outcomes, is currently recruiting women with type 2 diabetes at six weeks gestation.

## Conclusions

Metformin has been examined in the treatment of GDM in more than 2000 women. The short-term fetal and maternal outcomes favour metformin (with or without insulin) over insulin treatment alone. Metformin does not increase congenital abnormalities, is well tolerated and the risk of serious side effects is very low. Clinical trials in other conditions outside of pregnancy also add weight to the conclusion that metformin is safe and effective. The only unanswered questions are to do with the long-term fetal outcomes for which we await the results of ongoing trials.

As evidence accrues, our preference is not to use metformin universally for GDM. We consider metformin for women whom we think would benefit. Insulin treatment for GDM is very effective, however, the finding that metformin reduces maternal weight gain, compared with insulin, means that metformin should be considered for the growing number of women who are obese. Metformin can also be added to insulin therapy for women with diabetes who are inadequately controlled with insulin alone. Metformin is also an alternative treatment for women who refuse to start insulin.

Type 2 diabetes in pregnancy carries significantly higher risks than GDM, even with optimal treatment with insulin. Evidence regarding the use of metformin for type 2 diabetes in pregnancy is limited and therefore caution must be used. Opinions about whether to continue metformin are divided. Our approach is to continue metformin treatment on the basis that the limited data currently available do not favour insulin treatment over metformin, or vice versa. Emerging evidence supports the safety of metformin in pregnancy. For women with type 2 diabetes in pregnancy, we must continue to strive for treatments that achieve better outcomes than those achieved with insulin treatment alone.


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# Diabetes and its role in gynaecological malignancy

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Diabetes mellitus (DM) is one of the most common chronic diseases characterised by hyperglycaemia.[1] With a global prevalence in those aged over 18, rising from 4.7 per cent in 1980 to 8.5 per cent in 2014, it heralds a huge burden of disease.[2] The World Health Organization (WHO) predicts that by 2030, diabetes will be the seventh leading cause of death worldwide.[2]

Given the exponential growth of diabetes, many researchers are now investigating the association between diabetes and its related diseases, particularly cancer, with this association first being reported more than 100 years ago.[1] There is now a growing body of research that has associated diabetes with an increased risk of gynaecological cancers. In addition to this, there is evidence showing that gestational diabetes mellitus (GDM) also increases a woman's risk of developing a gynaecological malignancy.[4]

Endometrial cancer has a well-known association with type 2 diabetes, increasing a woman's risk of developing the disease two-fold.[3] Interestingly, despite endometrial cancer and type 2 diabetes sharing similar modifiable risk factors such as obesity,[1] a woman with type 2 diabetes is still at increased risk of developing endometrial cancer after controlling for body mass index (BMI).[3] Some studies have quoted an excess risk of developing endometrial cancer in women with type 2 diabetes of up to 30–400 per cent.[3] Additionally, most research has indicated that type 2 diabetes not only increases the risk of developing an endometrial cancer, but also increases a woman's risk of dying from it.[1]

When considering the association of diabetes with ovarian cancer, studies have been more limited, with some failing to show an elevated risk whereas others do.[3] However, a recent meta-analysis looking at 19 studies indicated that women with diabetes had an increased risk of ovarian cancer with a risk ratio (RR) of 1.17.[1] Moreover, other researchers have noted the outcomes of patients with ovarian cancer who have diabetes are poorer than those who do not, with median survival being four versus six years.[3] Furthermore, as a direct result of its co-morbidities, women with diabetes may undergo different treatment plans or less radical cytoreductive surgery, which may also affect outcomes.[3]

## Mechanisms of carcinogenesis in diabetes mellitus

### Glucose levels

In addition to glucose being an energy source that stimulates cellular proliferation in tumours, hyperglycaemia causes oxidated stress and glycation of proteins, which subsequently can lead to apoptosis and the activation of protein kinase C.[3] This oxidation process releases free radicals, also associated with cellular death.[3] In turn, these apoptotic changes can lead to the transformation of normal cells to dysplastic and malignant cells due to the imbalance between cellular repair and injury.[3]

### Ovarian steroid hormone and sex hormone-binding globulin regulation

Steroid hormones regulate the balance between cellular proliferation, differentiation and apoptosis in dysplastic and neoplastic cells.[3] Specifically, ovarian hormones are some of the most common hormones related to cancer generation and progression, in particular, endometrial, ovarian and breast cancers.[1] When considering sex hormone-binding globulin (SHBG), its level is one of the most important factors in cancer generation and development in postmenopausal women, as reduced levels lead to increased levels of bio-available ovarian steroid hormones.[1]

The hyperinsulinaemia and insulin resistance from type 2 diabetes not only induces ovarian steroid hormone production, but also causes a depression in the hepatic production of SHBG, leading to increased bio-availablility of ovarian steroid hormones.[1] In addition to this, and exacerbating this effect, is the increased insulin and insulin-like growth factor-1 (IGF-1) levels in type 2 diabetes, with these also increasing oestrogen receptor alpha (ERα) signalling, hence leading to a carcinogenic cellular environment.

### Chronic inflammation

Diabetes is associated with chronic inflammation, a known entity for cancer development and progression.[1,3] Several mediators of inflammatory pathways, including interleukin-6 (IL-6), tumour necrosis factor alpha (TNFα), and cyclooxygenase-2 (COX-2), are known to reduce tumour suppressor function and increase oncogene expression and cell cycling.[1]

In terms of the effect of diabetes on chronic inflammation, insulin resistance and

hyperinsulinaemia are known to promote a low-grade chronic inflammatory environment, which in turn aggravates insulin resistance.[1] Additionally, oestrogen, the levels of which are increased in women with diabetes, promotes increased gene expression of inflammatory mediators, further exacerbating this process.[1]

### Insulin and insulin-like growth factor signalling

Insulin growth factors (IGF) and insulin are involved in carbohydrate metabolism, cellular survival and proliferation.[1] They have important systemic regulatory roles in the body and show hormonal effects through insulin receptors (IR) and IGF receptors (IGFRs), which are widely expressed throughout the body.[1]

Many studies have shown an association between insulin and IGF-1 in the regulation of cancer, whereby increased levels such as those seen in type 2 diabetes are strongly associated with an increased risk of cancer and mortality.[1] In fact, some studies have demonstrated not only this point, but also that IGF-1 levels are proportional to cancer-related mortality.[1] Following on from this, it is now well-recognised that the presence of insulin resistance and hyperinsulinaemia are associated with an increased risk and mortality in women with cancer, particularly breast, endometrial and ovarian.[1]

### Gestational diabetes and gynaecological cancer

In addition to the association between type 2 diabetes and gynaecological malignancy, there is evidence that gestational diabetes increases a woman's chance of developing a gynaecological malignancy. The incidence of gestational diabetes is rising, now complicating around seven per cent of pregnancies worldwide, and it is associated with both neonatal and maternal morbidity.[4] One such maternal morbidity is its known association with the development of type 2 diabetes, with it heralding a seven-fold increase in the likelihood of developing the disease.[4]

Given that women with gestational diabetes are more likely to develop type 2 diabetes, they are also more at risk of gynaecological malignancies and a recent study has demonstrated this association.[4] Fuchs et al (2017) conducted a population-based study looking at the incidence of female malignancies in women with and without gestational diabetes. They looked at 9893 patients with a follow-up period of 12 years. Authors found that gestational diabetes was an independent risk factor for ovarian, endometrium and breast cancer. There was no association between the number of times gestational diabetes was diagnosed and the RR for malignancies.[4]

### Anti-diabetic agents and gynaecological cancer

There is now a growing body of evidence regarding the effects of anti-diabetic agents on the risk of cancer, with some being correlated with an elevated risk, while metformin seems to lower the risk.[3,5,6]

Metformin, a biguanide, inhibits insulin-dependent hepatic gluconeogenesis and promotes insulin uptake into surrounding cells via improving insulin resistance and reducing free fatty acids through the inhibition of lipolysis.[6] Metformin is first-line therapy for type 2 diabetes and is inexpensive, with a proven safety profile.[5,6] In addition to its well established anti-diabetic properties, there is growing evidence and interest regarding its anti-tumour properties.[1,3,5,6] The mechanism of this involves the activation of adenosine monophosphate-activated protein kinase (AMPK) and the inhibition of mammalian target of rapamycin (mTOR), which in combination reduce cell growth.[6]

In relation to gynaecologic oncology, as the carcinogenesis of endometrial cancer can involve obesity, type 2 diabetes and hyper-oestrogenic states, metformin has been investigated and proven to be therapeutic regarding the prevention and improvement of prognosis.[5,6] A recent review on metformin in gynaecological malignancies confirmed significant treatment efficacy.[5]

In addition to endometrial cancer, the review goes on to cite three studies that have shown a potential therapeutic effect on outcomes of women with ovarian cancer and its prevention, however, they are observational.[5] The review discusses cervical cancer, noting there to be no statistically significant effect of metformin on its prognosis.[5] The authors conclude by saying the reduction in cancer risk of women using metformin is apparent after more than five years of usage, however at this stage, evidence is not sufficient for its use in malignancies other than endometrial cancer, as more long-term randomised trials are needed.[5]

In terms of other anti-diabetic agents such as insulin, as noted, excessive insulin and IGF-1 signalling can cause the development and proliferation of cancer, and, as such, exogenous insulin is suspected to be a powerful carcinogenic factor in patients with diabetes mellitus.[1] In support of this, a meta-analysis recently showed insulin to increase a person's risk of cancer development with a RR of 1.39.[1] In relation to women's cancer, a number of studies have found that insulin glargine, a long-acting insulin analogue, increases the risk of breast cancer in women with type 2 diabetes who have been using it for more than five years.[1]

Globally, the rising levels of chronic diseases, in particular diabetes, pose significant challenges to the O&G practitioner. There is now a growing body of evidence showing that diabetes has significant implications for the development of gynaecological malignancies, increasing a woman's lifetime risk of developing cancer. We can expect to see a continued growth in the incidence of gynaecological malignancies, in particular endometrial cancer. Further research into the effect of diabetes on gynaecological malignancies and determining how the risk of diabetes can be moderated by anti-diabetic agents will be an exciting space to watch in the future.


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# Developmental origins of type 1 diabetes: the ENDIA Study

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The incidence of type 1 diabetes has doubled over the last 30 years in Australian children and has been increasing annually by around two to five per cent globally.[1-5] The majority of children who present with clinical type 1 diabetes are of school age. However, 80 per cent of children who develop type 1 diabetes by 18 years of age will have islet autoantibodies present at three years of age. Islet autoantibody development is the first detectable sign that an immune attack on pancreatic beta cell has commenced, although the precipitating event that initiates and drives this attack is unknown. The evolving concept that type 1 diabetes in many children has developmental origins has directed research questions in search of prevention back to pregnancy and early life. To this end, the world's first pregnancy to early childhood cohort study in at-risk children, the Australian Environmental Determinants of Islet Autoimmunity (ENDIA) Study, has been established in Australia.

Type 1 diabetes can be viewed as part of the non-communicable disease epidemic in our modern society. In some countries, the fastest rate of increase has been identified in children aged five years and under.[6] Two lines of evidence strongly support the role of the modern environment in the development of type 1 diabetes. First, the global increase in the incidence of type 1 diabetes, and, second, this is in parallel with a reduction in the proportion of individuals with the highest genetic risk. A striking example of the impact of the environment comes from two bordering regions (Finland and the Republic of Karelia). They share a similar genetic background, but the rates of type 1 diabetes are markedly different. Finland has the highest incidence in the world, at some 58 cases per 100,000. This is about six times higher than Karelia, where the rate is less than 10 cases per 100,000 per year.[7]


**Image 1.** ENDIA participants, Andy and his son, Finley (Canberra, ACT).

### Stages of type 1 diabetes

Some individuals who have increased genetic risk of type 1 diabetes progress at variable rates to immune activation and islet autoantibody presentation. The development of two or more islet antibodies (now termed stage 1 type 1 diabetes) ultimately progresses to asymptomatic intermittent raised blood glucose after food (stage 2 type 1 diabetes) and then to the symptoms of 'clinical' type 1 diabetes (stage 3 type 1 diabetes).

### Developmental origins of type 1 diabetes

If a child develops multiple islet autoantibodies by five years of age, there is virtually a 100 per cent risk of progressing to type 1 diabetes in the absence of any effective interventions.[8] In at-risk children who have a family member with type 1 diabetes, islet antibodies peak from nine to 30 months of age,[9] including in a previous Australian birth cohort.[10] Therefore, there is a strong imperative to look back to preconception and pregnancy to consider the drivers of type 1 diabetes in childhood.

### What are the modifiable exposures in early life that may be causing type 1 diabetes?

Parental age at conception, weight, nutrition, lifestyle, sleep and use of antibiotics during pregnancy and infancy have changed substantially over the last 30 years, during which time childhood type 1 diabetes has doubled in incidence in Australia. A mother's weight and nutrition during pregnancy alter the lifetime risk of overweight issues and type 2 diabetes in her child, but there is no prospective data for type 1 diabetes. Experimental models increasingly show that the father's weight, exercise and other environmental exposures before conception induce epigenetic changes in sperm that alter his child's metabolic health.[11]

Congenital rubella is a long-standing recognised, but fortunately now rare, environmental trigger. Other putative exposures are enterovirus infections during pregnancy and childhood, and the introduction of multiple foreign antigens in the infant diet. In at-risk children, concurrent breastfeeding at the time of cereal introduction may be protective.[12] Studies have found that breastfeeding and delay of the introduction of cow's milk do not alone influence a child's risk. Omega 3 fatty acids, which have anti-inflammatory properties, may have a small protective effect in early life.[13] Vitamin D metabolism, which also modulates immune and inflammatory systems, may also play a role, particularly in some genetic subtypes.

The modern environment provides for excess nutrition in mothers during pregnancy and for rapid growth and weight gain in children in early life, with an accompanying reduction in insulin sensitivity. About 50 per cent of mothers (and fathers) are overweight or obese at conception. Rapid weight gain in early childhood may accelerate both development of islet autoimmunity and progression to type 1 diabetes. Increased childhood weight gain in the first two years has shown an increase in the risk of islet autoimmunity in Australian children.[10]

### The 'omes

There is heightened interest in the interaction of the environment with biological systems (including the epigenome, microbiome and metabolome). These in turn can regulate immune tolerance.

A breakdown in immune tolerance and abnormal development of immune regulation in the infant, is one mechanism that is critical to the development of autoimmunity. Conception is an important time when the environment induces epigenetic changes in reproductive cells in both parents. Such epigenetic changes can influence disease development in the next and future generations. Environmental factors are likely to be interacting via 'the 'omes', including the virome, to increase the penetrance of type 1 diabetes risk genes.

The microbiome has been a particular focus of research in the development of type 1 diabetes. It is acquired before and at birth and is instrumental in shaping both innate and adaptive components of the immune system. This underscores the critical importance of prospective studies from early life to understand the genesis of childhood-onset diseases such as type 1 diabetes. A few studies in the Northern Hemisphere have reported changes in the gut microbiome in children at risk of type 1 diabetes, but results are not uniform. No microorganism has been causally related to development of, or protection against, type 1 diabetes. Identifying an infant gut microbiome signature of susceptibility to, or protection against, type 1 diabetes and its environmental drivers would be enormously significant for the prediction and prevention of type 1 diabetes. The identification of specific protective bacteria would enable the design and testing of bespoke probiotics and targeted nutrition education.

The infant microbiome is influenced by a number of factors, including the mother's microbiome, type of delivery (caesarean or vaginal), gestational age, infant feeding and interventions during and after birth, for example, administration of antibiotics. These bacteria rapidly change after birth, and for the first two years of life, as the child's environment and nutrition expands.

### Primary prevention trials

Primary prevention trials begin prior to development of islet autoimmunity, typically in young children at increased genetic risk of type 1 diabetes. Nutritional studies, as yet, have shown no benefit from delaying gluten exposure until 12 months of age. The Trial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR),[15] involving a large cohort of at-risk infants, showed no benefit of weaning to an extensively hydrolysed milk formula on the development of islet autoantibodies or type 1 diabetes. Immune tolerance studies are investigating the effects of oral insulin to modulate the immune system in children at increased genetic risk.

Future primary prevention targets being considered include the development of vaccines that induce immune tolerance in beta cells, a potential type 1 diabetes viral vaccine, and using microbiota and their products (pre- and/or probiotics) to induce immune-regulation in the infant.

### ENDIA Study

ENDIA has been set up to explore the developmental origins of type 1 diabetes and to identify the gene-environment interactions and the mechanisms in early life that precede the development of type 1 diabetes. ENDIA is the first type 1 diabetes cohort study in the world to recruit from early pregnancy. The overarching goal is to identify what modifiable exposures in the mother (during preconception and early life), father (during preconception) and child

(in early life) could guide us to primary prevention strategies.[14]

This national study aims to follow 1400 babies, with a first-degree relative living with type 1 diabetes, to identify the factors which protect or trigger the development of the condition.

The ENDIA Study is recruiting through 2018. Families living with type 1 diabetes, who are expecting a new baby, are sought to participate. This is a national observational study. There are no interventions and there is no impact on normal care. There is a regional program so families can participate from anywhere in Australia. For more information go to www.endia.org.au or contact endia@adelaide.edu.au.

ENDIA is currently recruiting participants.
The following individuals are eligible:

| ENDIA eligibility criteria |
|---|
| • Pregnant women with type 1 diabetes |
| • Men with type 1 diabetes whose partner is pregnant |
| • Pregnant women whose child has type 1 diabetes |
| • Babies less than 6 months of age whose parent or sibling has type 1 diabetes |
| **endia.org.au** |


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**Image 2.** ENDIA participants, Erin and her daughter, Laveena (Brisbane, QLD).

# Supporting better outcomes for migrant and refugee women

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Migration-related factors are recognised as social determinants of health.[1] Conditions surrounding migration and resettlement may exacerbate health inequities, exposing women and their families to increased health risks and poorer health outcomes. The Australian Bureau of Statistics estimates that there are more than three million overseas-born women in Australia and about 460,000 of them reported that they do not speak English well or at all.[2] It is vital that health providers are equipped with tools to provide person-centred and culturally responsive care that recognises the heterogeneity of individuals within cultures. Our colleges, societies and healthcare settings need to support these endeavours by providing culturally responsive care, with systems that support the engagement of interpreters and facilitate training for all health staff.

In response to this need, the Migrant and Refugee Women's Health Partnership (MRWHP) was established in late 2016. The Partnership brings together health practitioners and the community to improve the capacity of the Australian healthcare system to provide accessible and appropriate care to women of migrant and refugee backgrounds. The Partnership is driven by the imperative of fostering collaboration and consensus across clinical education, with its work overseen by a working group. The working group is chaired by RANZCOG President Prof Steve Robson and comprises representation from eleven medical colleges, professional bodies for nurses and midwives, other relevant health practitioner representation bodies, government and community.

The Partnership undertakes work in migrant and refugee women's health through: literature review; scoping of practice; policy and education by medical, nursing and midwifery colleges and societies; and workshops connecting health providers with women from the community.

## Health of migrant and refugee women

Women of migrant or refugee background are at increased risk of poor health in pregnancy (such as perinatal mortality, preterm birth and low birth weight).[3] Mental health (anxiety, depression and post-traumatic stress disorder)[4] and reproductive health are also areas of increased risk for these women.[5]

Factors contributing to health disparities are multi-faceted, but may include specific risks related to past environments (for example, infectious diseases and anaemia), or specific population-based risks (such as thalaessamia, diabetes, previous female genital mutilation).[6,7,8] Many factors, however, relate to broader issues, such as access to care,[3] interactions with the health system and health literacy.[9]

Challenges accessing care include socioeconomic factors, such as visa class, finance, transport and language barriers.[7,8] Many women have lower levels of health literacy, lack familiarity with preventative healthcare and have differing personal concepts of health and illness,[8] and therefore are more likely to access acute and emergency care.

Resettlement is an overwhelming process involving issues that lead to many migrant and refugee women failing to prioritise their own health. Difficulty adapting to a new culture and language barriers often result in social isolation and exclusion, all of which exacerbate psychosocial risk and vulnerability.[8] Women seeking asylum and those from refugee backgrounds, in particular, are at increased risk of poorer health and wellbeing due to both pre-migration experiences, including exposure to trauma, and post-resettlement experiences.

## Working with migrant and refugee women

Health practitioners should have the skills to work with women from refugee and migrant backgrounds, being aware of culture, community and past experiences and their influence on women's expectations for care, health beliefs and behaviours.[10] It is particularly important for health practitioners to be aware of the need to provide trauma-informed care, incorporating such factors as patient-centred communication and care, safe clinical environments and knowing when to refer for trauma screening.

Focus should be on supporting the capacity of health practitioners to communicate with migrant and refugee women. These women may have low English proficiency or health literacy and be unable to provide the practitioner with relevant information. They may lack the confidence necessary to be active participants in the process. Individual experiences can impact on women's knowledge of the healthcare system and their capacity to navigate it. This may include poor understanding of their rights as

consumers in the healthcare system. Women may also lack confidence in the healthcare system and need to be assured of the confidentiality between themselves, health practitioners and, if required, interpreters. They may feel more comfortable with female health practitioners and interpreters,[11] particularly when disclosing women's health issues.

When English is the woman's second language, an accredited interpreter is a vital part of ensuring optimal healthcare. To prevent language discordance and promote effective communication,[11] health practitioners must respect the woman's preference for the interpreter's gender, ethnicity and dialect.[12] When working with an interpreter, reaffirming confidentiality and the right to privacy are particularly important to provide women with the opportunity to disclose sensitive information. Issues may arise, however, if the woman and the interpreter are from the same small, tight-knit community and potentially know each other. In this instance, a telephone interpreter may be a preferable option.

Medical practitioners (general practitioners and medical specialists), as well as nursing and practice support staff, can access the free interpreting service delivered by Translating and Interpreting Service (TIS National) when providing Medicare rebateable services in private practice.[13] Clinicians working in state-funded health services can access their service's respective arrangements for interpreting. It is important to assess the need for engaging interpreters with appropriate credentials and to have systems available to make necessary arrangements through an appropriate language services provider. Not doing so may open the health professional to medico-legal redress.[12] This is consistent with the Medical Board of Australia Code of Conduct.[14]

## Strategic response

Culturally responsive practice needs to be embedded in health practitioner education, training and professional development to ensure improved individual client health and wellbeing outcomes.[15] MRWHP aims to promote systemic supports, competencies and appropriate resources to support better outcomes for women.

Initial steps undertaken by the partnership include a review of policies and practices developed by the peak medical, nursing and midwifery colleges and societies on the implementation of cultural responsiveness in clinical education. The review was informed by the findings of an extensive consultation undertaken with lead bodies who have responsibility for standard-setting, education and the continuing professional development for health practitioners.

Encouragingly, the report concluded that cultural responsiveness is increasingly considered a core pillar of education and training of health practitioners. A range of initiatives have been developed across curricula, training programs, publications, standards and practice guidelines, and research that could be shared.[16] Remaining gaps include insufficient information around how cultural responsiveness is included in core training and professional development, and the level of uptake. Additionally, there is insufficient information on the standards for communicating effectively with patients with low English proficiency and working with interpreters.

MRWHP is working to address these gaps by:

- Identifying strategies to develop the requisite skills, based on the seven domains or roles health providers have as identified by the CanMEDs framework.[17] These are: medical expert, communicator, collaborator, leader, health advocate, scholar and professional.
- Exploring ways to evaluate effectiveness and uptake of education across these domains.
- Promoting platforms and ways to share education, training and resources for all health providers.

Responding to the needs of women from migrant and refugee backgrounds requires leadership and collaboration across all the professional and consumer groups in the Migrant and Refugee Women's Health Partnership. Further information on the Partnership's work is available at www.culturaldiversityhealth.org.au or by contacting secretariat@culturaldiversityhealth.org.au.

Information about the free interpreting service is available from the Department of Social Services:www.dss.gov.au. Eligible medical practitioners can register to access the free interpreting service at: www.tisnational.gov.au/register.

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## Case report

# Perimortem caesarean section in response to anaphylactic shock

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The patient is a 26-year-old, G1P0, BMI 44, with a medical history including coeliac, depression and anxiety. She took no regular medications as she had ceased her Cymbalta prior to conception. She had an allergy to the measles, mumps and rubella (MMR) vaccine, resulting in reactive arthritis at age ten. Antenatal serology was unremarkable and she had normal glucose tolerance tests. She had an early ultrasound at nine weeks for per vaginal (PV) spotting and low-risk combined first trimester screening. On morphology scan, the heart was not adequately visualised and there was a 4mm choroid plexus cyst in the left ventricle. The placenta was posterior and clear. The patient had a growth scan at 30 weeks, revealing an estimated fetal weight on the 95th percentile and follow-up scan at 34 weeks, with growth on the 88th percentile. Her pregnancy was complicated by multiple antenatal triage assessments for high blood pressure from 30 weeks gestation. She was asymptomatic and her PET bloods were repeatedly normal. At 38+5 weeks, her blood pressure was 148/98. The patient was admitted, commenced on labetalol and an induction of labour was booked.

The patient had a Cervidil inserted at 39+1 weeks and had an artificial rupture of membranes the next day. Syntocinon was commenced, liquor was meconium strained and she was on continuous electrode fetal monitoring. The patient spiked a temperature of 38.6C and was given 2g of Cefazolin. She had an immediate allergic reaction, reporting itchiness all over and a dry, tight mouth. A rapid response call was activated.

The patient received IM adrenalin and began vomiting. Observations at the time were a BP of 120/70, HR 43 and sats at 84 per cent. Concurrently, there was fetal bradycardia. A scalp clip was placed and cervical dilatation was 4cm. A category one caesarean section was called for when the patient stabilised. However, she rapidly deteriorated, losing her airway and then cardiac output. She received IV adrenalin, CPR was commenced and she was intubated. At four minutes of CPR, a perimortem caesarean section was performed. A flat baby was delivered in meconium liquor and given to the paediatric team for resuscitation. Attempts to deliver the placenta were complicated by uterine inversion, which was immediately reverted and the placenta was manually removed. Bimanual compression of the uterus continued during CPR. A total of 14 minutes of CPR was performed and 4mg of adrenalin given. When cardiac output was re-established, she was given morphine, midazolam and vecuronium, and prepared for transfer to theatre.

The patient had very difficult vascular access and had a CVC and arterial line inserted. Haemostasis was achieved with a two-layer uterine closure, ergometrine, PG2Fα and a Bakri balloon. She had a VT arrest with an unsuccessful shock of 100J and a second shock of 200J to return her to sinus rhythm. Her arterial blood gas revealed a potassium of 7 and was treated with 10+10mmol of calcium carbonate, 15 units of actrapid and 50ml of 50 per cent glucose, as well as 25+25mmol of sodium bicarbonate. She was stabilised and transferred to ICU.

In ICU, the patient was intubated, on an adrenalin/noradrenalin infusion and had another PEA/hypotensive arrest, requiring a further five minutes of CPR, adrenalin and calcium gluconate. Issues included a new right bundle branch block on ECG and ECHO showing moderate global impairment of systolic function and low urine output. The patient was hyperkalemic and acidotic, febrile, coagulopathic, and high-risk for aspiration pneumonia and pulmonary embolism.

The patient was extubated and received IV antibiotics, 4xPRBC, 2xFFP and vitamin K. She received three days of dialysis and deep vein thrombosis (DVT) prophylaxis and was discharged from ICU on day ten. Her ward stay was complicated by continued high temperatures and multiple septic work-ups. The only source of infection was a wound on her right forearm from a cannula site, which grew E.coli. This was treated with antibiotics and dressings. She was discharged home on day 17 with cardiology and renal follow up.

The infant, at birth, was pale, floppy and had a heart rate of 40. He received immediate intermittent positive-pressure ventilation (IPPV) and cardiac compressions, which were ceased at 50 seconds of life. He was intubated and had meconium liquor suction from below the cords. His APGARs were 3, 3, 4 and 7 at 1, 5, 10 and 20 minutes of age. He weighed 3.7kg and his arterial gas showed a pH of 6.87, lactate 11.9 and base excess of -20, paired with venous pH

6.89, lactate 12.1 and base excess of -20. NETS were called to arrange transport to NICU. Repeat gas at seven hours of age was pH 7.31, lactate 2.14 and base excess -7. The baby had an uncomplicated admission and was cooled from one hour of age to day three. He had a normal EEG and a head ultrasound showed no intraventricular haemorrhage. The baby was transferred back on day four and discharged home to the care of his father at day five and bottle fed.

## Discussion

Cardiopulmonary arrest during pregnancy presents a unique situation that involves potentially two patients, the mother and the fetus, and is associated with high maternal and neonatal mortality rates. The prevalence of cardiac arrest in pregnancy varies from one in 20,000 to one in 50,000 and may be related to conditions that are either unique to pregnancy, or that are found in the non-gravid state.[1,2] The most common causes of arrest are: pulmonary thromboembolism (PE); haemorrhage; sepsis; peripartum cardiomyopathy; stroke; pre-eclampsia; eclampsia; complications related to anaesthesia; amniotic fluid embolism (AFE); acute myocardial infarction (AMI); pre-existing cardiac disease; and trauma.[1,2,3] The prevalence of anaphylaxis in pregnancy is estimated at three in 100,000, with antibiotics being the most common trigger.[3]

Cardiopulmonary arrest requires a rapid multidisciplinary approach, including obstetrics, anaesthetics and paediatrics. BLS and ALS algorithms apply, with some changes necessary to accommodate the anatomical and physiological changes of pregnancy.[2]

- **Airway:**
  A difficult intubation needs to be anticipated in a pregnant patient. This case was more challenging, as she was term, obese and anaphylactic. She was also at greater risk of aspiration given she was labouring and not fasted.
- **Breathing:**
  Ventilation is more difficult secondary to splinting of the diaphragm, as well as the increased oxygen requirements.
- **Circulation:**
  Aortocaval compression needs to accounted for from 20 weeks gestation with a 15 degree tilt. This can reduce the efficacy of chest compressions.
- **Drugs:**
  Increased plasma volume results in dilutional anaemia and reduced oxygen-carrying capacity.

Evidence-based practice for the management of an arrest in pregnancy is limited, with most data being drawn from case and cohort studies.[2-5] Consensus statements suggest a perimortem caesarean section should begin at four minutes of age, with the fetus delivered by five minutes, and that it is a resuscitative process performed primarily in the interest of the mother.[2-5] The aim is to avoid irreversible anoxic brain damage by increasing the effectiveness of the CPR. The emptying of the uterus allows for easier ventilation, more effective cardiac compressions, an increase in circulating blood volume and relief of the aortocaval compression, resulting in a 60–80 per cent increase in cardiac output. Although not a fetocentric measure, a perimortem caesarean section resulting in the delivery of the fetus by five minutes also increases the likelihood of intact fetal survival.[3,4]

Classically described, a perimortem caesarean section should be a midline incision with a classical uterine incision, however, the operator should use whichever approach they are most comfortable with. Perimortem caesarean section is considered beneficial and in no incidences proved detrimental.[5]

In this case, understanding the principles of maternal collapse and advanced life support in obstetrics allowed for confidence in decision-making to take the urgent action required. Prompt action and great team work were fundamental in the positive outcomes for both mother and baby. A perimortem caesarean section is a rarely encountered and challenging clinical situation, requiring training in the principles of advanced life support and thorough understanding of the role of operative intervention.


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## Case report

# Secondary postpartum haemorrhage from a uterine arteriovenous malformation

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Postpartum haemorrhage (PPH) complicates 18 per cent of births and is the most common maternal morbidity in developed countries. Secondary PPH is defined as excessive vaginal bleeding from 24 hours after delivery, up to six weeks postpartum. It is rare, brief and self-limiting, with the most common cause being retained products of conception.

Uterine arteriovenous malformation (AVM) is a rare cause of PPH, with fewer than 100 cases in current literature. It is potentially life-threatening, as patients can present with profuse bleeding. Uterine AVM is thought to be present in 0.22 per cent of postpartum women, but as not all are symptomatic, many go undiagnosed. While ultrasound is the first-line of investigation, the current gold standard for diagnosis is by angiography.

Management of uterine AVM varies depending on haemodynamic status, degree of bleeding, age of the patient and desire for future fertility. Conservative management by uterine artery embolisation is the preferred treatment, in order to avoid a hysterectomy in women of child-bearing age. Bilateral uterine artery embolisation has a reported 90 per cent success rate in managing uterine AVM.

### Case report

The patient is a 22-year-old, G1P1, who was referred to our tertiary facility with a secondary PPH of 500ml at four weeks postpartum.

It was the patient's first pregnancy by spontaneous conception, with no history of previous surgeries. She had a low-risk pregnancy until 39 weeks gestation, when she developed pre-eclampsia. She was induced at 39 weeks and had a normal vaginal delivery one day later. She had a postpartum haemorrhage of 2700ml, which was managed medically. Surgery was not required. Her bleeding settled and she was discharged home.

### Postnatal course

The patient represented to hospital four weeks postpartum after losing approximately 500ml of blood at home. Ultrasound showed no retained products, but suggested the possibility of a uterine AVM. She was transferred to our facility for consideration of further management. On arrival, she had stopped bleeding and was observed for 48 hours. The decision was made for conservative treatment, given that she was haemodynamically stable and no longer having blood loss. She was discharged home and advised to return should she have another haemorrhagic event.

The patient represented to her previous hospital two days later with another bleed of 500–600ml. She was taken to theatre and had a Foley catheter inserted into the uterus, filled with 40ml normal saline to tamponade the bleeding. Ultrasound, again, showed no retained products of conception, but still suggested a potential uterine AVM. The patient was transferred back to our facility for a uterine artery embolisation. She was haemodynamically stable with haemoglobin of 87g/L on arrival. All other blood test results were unremarkable.

Her ultrasound images were reviewed by our interventional radiology team and a recommendation was made for angiography and bilateral uterine artery embolisation.

The procedure was successful and the patient was observed in our facility for another 48 hours post-embolisation, before being discharged home. We reviewed her six weeks post-procedure with a repeat ultrasound. She was well and had no further bleeding. She had one normal menstrual cycle which was not heavy. She has now been discharged from our clinic. For her next pregnancy, we have recommended an early ultrasound and referral to a tertiary centre to monitor for any abnormal placentation.

**Image 1.** Gray scale ultrasound showing the serpiginous structures within the myometrium, which raised the concern for a uterine AVM.

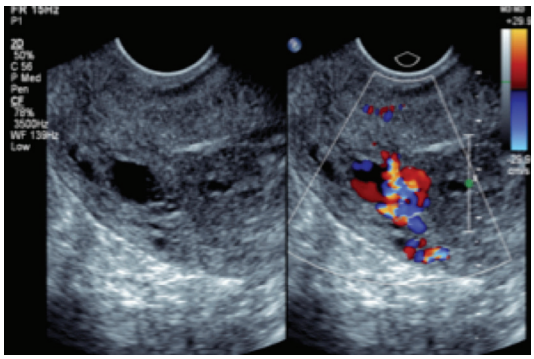


**Image 2.** Angiography: Pre R) uterine artery embolisation. Note the serpiginous tangle of vessels.

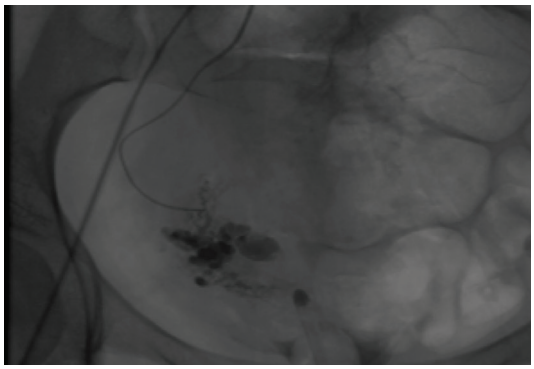


**Image 3.** Angiography: Post R) uterine artery embolisation.

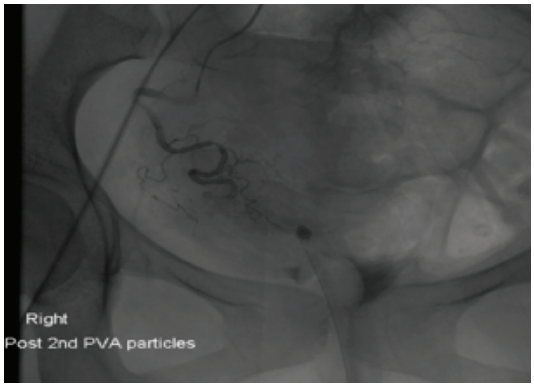



**Image 4.** Pre L) uterine artery embolisation.

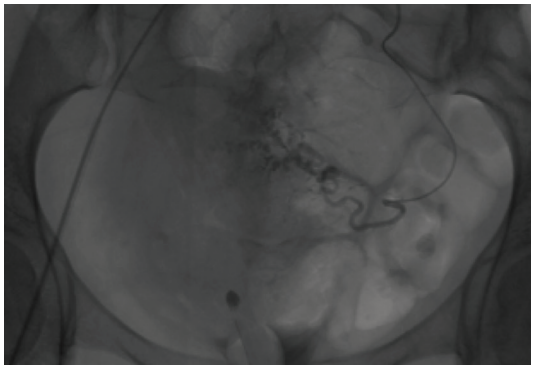


**Image 5.** Post L) uterine artery embolisation.

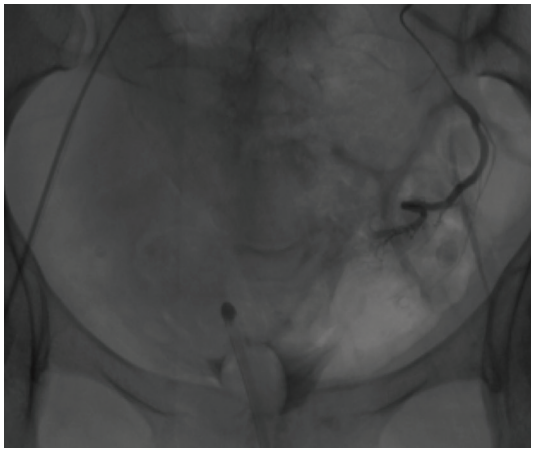
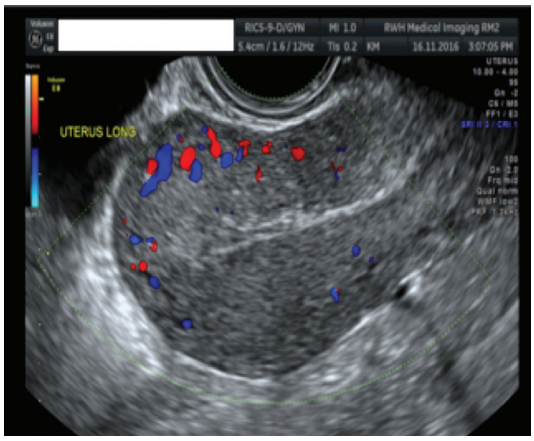


**Image 6.** 6/52 post-bilateral uterine artery embolisation.




## Discussion

A uterine AVM consists of proliferation of vascular channels, with fistula formation and an admixture of small capillary-like channels. The size of these vessels vary considerably. There are congenital or acquired uterine AVMs and the latter are more common.

Acquired uterine AVMs are associated with conditions, such as multiple pregnancies, miscarriage, previous surgery (for example, dilatation and curettage), termination of pregnancy and caesarean section. None of these are applicable to our case. However, pregnancy appears to play an important role in the pathogenesis of uterine AVM. It is suggested that these malformations may arise when venous sinuses become incorporated in scars within the myometrium, after necrosis of the chorionic villi.

From a clinical perspective, these vascular anomalies most commonly present with abnormal uterine bleeding. Depending on the presentation, some women may be haemodynamically unstable. Torrential bleeding may occur post-uterine curettage, as there is often only a thin layer of endometrium overlying the malformation, which may be disrupted. This would explain the intermittent bleeding pattern. Diagnosis of uterine AVM has been proven difficult and treatment has often been hysterectomy. However, that is not ideal for a woman who would like to preserve her fertility.

There are different modalities available for imaging, but the current gold standard for diagnosis is angiography. While it is considered more invasive than gray-scale ultrasonography, angiography helps to identify the leading 'feeder' vessels, where embolisation may be indicated as a conservative treatment option.

Pelvic MRI was another non-invasive investigation considered in this case. However, given the clinical context and after discussion with our interventional radiology team, we made the decision to proceed straight to angiography and bilateral uterine artery embolisation concurrently.

Bilateral uterine artery embolisation has a reported 90 per cent success rate in managing uterine AVM and proved to be an effective treatment option in our case study.

While uterine AVMs are rare, it is an important differential to consider in patients with otherwise unexplained secondary PPH.

**Acknowledgements**
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# The leg-up


**Your regular legal update to keep you informed on current medicolegal issues in the practice of obstetrics and gynaecology**

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## Is it ever justified for doctors to sue their patients?

A central tenet of medical ethics is 'to first do no harm' to patients (non-maleficence). A recent legal case upheld the view that, in some circumstances, patients waiver their rights to this obligation by their doctor.

Dr Al Muderis is an orthopaedic surgeon who has been decorated in Australia for his charity work, involvement in the Australian Defence Forces, and cutting-edge medical innovations in osseointegration technology. In March 2010, he performed a hip arthroscopy on a private patient, Mr Mazzella, which resulted in a claim of adverse outcomes, including numbness in the penis and loss of sexual function. The claims, based on a supposition of pudendal nerve injury, were never proven. The patient's injuries were judged to be related to lifestyle issues and pre-existing conditions for which he had received a pre-operative warning by Dr Al Muderis.

The vindictiveness of the patient was such that the following attempts were made for retribution:

1. **Civil case of medical negligence**
   Proceedings were commenced in the New South Wales Court for medical negligence against Dr Al Muderis. Mr Mazzella's case involved a long drawn-out affair, with non-compliance of orders for expert witnesses and vacating of multiple hearing dates, all at significant emotional and financial cost to the doctor. The action was dismissed and the patient was ordered to pay costs.

2. **Disciplinary complaint**
   The patient subsequently lodged an unsuccessful complaint with the Health Care Complaints Commission, claiming that the doctor's skill and judgment was below standard.

3. **Frequent direct approaches to Dr Al Muderis**
   The patient contacted the doctor on multiple occasions, with specific threats that he would not leave Dr Al Muderis alone until he received 'the explanation he sought' for his injuries.

4. **Online harassment**
   The patient and his brother created websites, YouTube media, Facebook pages, and publications in Pinterest and Dailymotion under different names, dedicated to harassing, menacing and offending the doctor. Examples found included, '... as a surgeon butchers his patients' and '... is a low and disgusting monster who mutilates his patients' genitalia'. There were even published threats to cut off the doctor's penis and kill him. In the initial phase of the online activity, the matter brought a conviction against the patient for the offences of intimidation and using a carriage service to harass, including an authorised violence order (AVO). This did not halt the patient's online defamatory, menacing and intimidating behaviour.

Six years of harassment culminated in a successful defamation action against the patient, with an award of damages to the doctor for A$480,000. The consolation was for personal distress and hurt, reparation of the business reputation and the doctor's personal reputation.

It seems that the increasing use of doctor rating websites is welcomed by patients, who rely on them to inform their views about doctors' reputations. However, online presence of rating sites creates vulnerability for medical practitioners. The potential harms from false or malicious accounts to reputation, in the emotional sphere of childbirth, are likely to be heightened. There are examples in the USA and South Africa where doctors have sued their patients following negative reviews posted online. For the most part, it would be unethical for a healthcare practitioner to pursue legal action against a patient, since it is in conflict with the obligation of non-maleficence. However, defamation action by Dr Al Muderis, to protect himself and his family, is entirely justified as a last resort to halt the threats and intimidation by the vindictive patient.

Freckleton cautions us to consider the pragmatic advice of many lawyers before suing a patient for reputational damage. Such a legal response may initiate the 'Streisand effect', that is, 'it will generate more publicity and interest in the offensive publication than it would otherwise receive' by ignoring it.

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WOMEN'S HEALTH

# Journal Club

Had time to read the latest journals? Catch up on some recent research by reading these mini-reviews by Dr Brett Daniels.

## Vitamin D supplementation in pregnancy

Current RANZCOG guidelines suggest antenatal supplementation of vitamin D in pregnant women; either as part of antenatal multivitamins, or in higher doses if they are found to be vitamin D deficient.[1] The guideline cites maternal vitamin D deficiency being associated with an increased incidence of neonatal hypocalcaemic seizures and impaired skeletal development.[1] Interestingly, the World Health Organization guidelines for antenatal care advise against routine vitamin D supplementation in pregnancy.[2] The present research published in *BMJ* again reviews the evidence for the effect of antenatal vitamin D supplementation on maternal, neonatal and infant outcomes.[3] After initial searches identified 3810 possible articles, the researchers included 43 articles with over 8000 participants in their meta-analysis. The results of the analysis showed that prenatal vitamin D supplementation significantly increased maternal and cord vitamin D levels at delivery and reduced maternal hypocalcaemia, compared to control groups. The authors found that results on other maternal outcomes were widely variable, with the confidence intervals (CI) for measures such as pre-eclampsia, gestational diabetes, hypertension, stillbirth, preterm labour or birth, and casearean section all including the null (risk ratio=1.0). For neonatal and infant outcomes, prenatal vitamin D increased mean birth weight by 58 grams (95% CI 19-99 grams), reduced the risk of SGA births (risk ratio 0.60, 95% CI 0.40 to 0.90) and reduced the risk of infant wheeze by three years of age (risk ratio 0.81, 95% CI 0.67 to 0.98).

The authors generally were not positive about the current state of research into prenatal vitamin D supplementation, concluding that '...most trials on prenatal vitamin D published by September 2017 were small and of low quality. The evidence to date seems insufficient to guide clinical or policy recommendations'. The authors noted that there are currently 35 registered trials of prenatal vitamin D either currently completed and unpublished, ongoing or planned, with over 12,000 participants. The results of these trials will potentially inform guideline development in this common clinical scenario.

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## Barbed sutures in laparoscopic hysterectomy

For most surgeons, the use of barbed sutures to close the vaginal vault at laparoscopic hysterectomy (LH) increases the ease and speed of surgery, compared to interrupted sutures. These three retrospective studies analysed over 1200 cases of laparoscopic hysterectomy, comparing clinical results and complications between vault closure using barbed sutures and conventional non-barbed sutures. None of the trials were randomised. The largest study of 490 participants compared V-Loc™ barbed suture to absorbable Polysorb™, showing a significant reduction in operative time, blood loss and hospital stay for the barbed suture group.[1] There was no significant difference in the rates of vault dehiscence. A second study of 334 cases replicated the significant result in reduced operative time with barbed sutures, showing no increased risk of vault dehiscence.[2] A third study of 474 cases similarly found a significantly reduced operative time and hospital stay, but no significant difference in vault dehiscence, blood loss or infection.[3] In combination, these studies provide confirmation that the use of barbed sutures for vault closure at LH is both convenient and safe.

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# Smartphones: protecting your patient's privacy

**Dr Nicole Woodrow**
**MBBS, MRCOG, FRANZCOG, DDU, COGU, MBioeth**
**Royal Women's Hospital, Melbourne**
**Women's Ultrasound Melbourne (WUMe)**

*Registrar to Consultant (showing an image on a smartphone): 'Have a look at this case!'*

*Consultant (horrified): 'You have a picture of a patient's vagina and vulva on your personal device.'*

*Registrar: 'She was anaethetised.'*

*Consultant (panicked): 'What consent did you obtain?'*

*Registrar: 'Don't worry! All cool. She is a young adolescent. She, her mum and I have a really good relationship.'*

*Consultant (terrified, thinking): 'If you were scrubbed, then who took that photo? And why did no one in the theatre stop it?*

Have you ever captured a patient image on your smartphone? Digital technology is ubiquitous in hospitals and medical care, with readily available devices for capturing, sending and reproducing patient images. It is likely that this is a common event in your hospital to aid with diagnosis and teaching. It is particularly useful in rural and remote areas where doctors can instantly send images for help with patient management from tertiary experts. Allowing the capture of images for immediate communication with specialists can ensure rural patients receive time-critical, lifesaving interventions. However, digital dissemination of patient information has significant implications for privacy, security, ethics and the law.

The Privacy Act 1988 is the starting point for legislation concerning use of digital images in healthcare. However, when the Act was drafted, patient consent for medical images involved allowing photographs to be physically stored in hospitals with tight rules for authorisation, reproduction and access. Smartphones speed up this process with immediate transmission of patient images. There is no intermediary regulatory figure to check for patient consent and take accountability for dissemination of the files.

In response to the potential harms from digital devices, amendments to Australian privacy laws were effected in March 2014. They uphold that medical professionals with unsecured patient images on their smart devices could face fines up to A$340,000 and institutions up to A$1,700,000.00 for breaches of privacy.

Mandatory data breach notification obligations will come into force in early 2018. The Notifiable Data Breaches scheme establishes requirements for entities to respond legally to a 'data breach', where it is likely to result 'in serious harm' to any individuals whose personal information is exposed. From 12 February 2018, this obligation involves all agencies and organisations (including healthcare), with existing personal information security obligations under the Australian Privacy Act 1988. The notification is to the individual whose privacy has been breached and the Australian Information Commissioner. Part of the review process for the entity with the data breach (for example, hospital) is to consider reporting the incident to, amongst others, the police and relevant professional bodies. It seems likely this will involve (as a minimum) lodging a complaint to a Disciplinary Board. Be mindful!

# RANZCOG Training Support Unit

**Paula Fernandez**
**Senior Coordinator, Trainee Liaison**
**Training Support Unit, RANZCOG**

Paula is the Trainee Liaison within the newly established Training Support Unit (TSU). Her role is to offer all RANZCOG trainees a professional and impartial support service. This service extends to Specialist International Medical Graduates (SIMGs), and FRANZCOG, Subspecialty, Certificate of Women's Health (CWH) and Diploma trainees in the programs across Australia and New Zealand.

The College recognises that trainees may experience periods of professional and personal difficulty. Coping with the demands of a busy profession, maintaining skills and knowledge, as well as balancing family and personal commitments can be challenging. In order to better support you, the TSU has been created.

Unfortunately, forms of bullying or harassment are real problems in the medical profession that can compromise trainee development and patient safety. Any complaints you have about these types of experiences will be managed by the TSU in a fair and transparent manner. Be assured that RANZCOG recognises the difficulties in lodging a complaint and these concerns will be managed sensitively.

RANZCOG is committed to supporting the wellbeing of doctors and enhancing a culture of respect and professionalism. The College has developed a number of resources, some of which will be managed by the TSU, including the 'Respectful Workplaces' workshop; a mentoring program; and an eLearning module on providing effective feedback as a supervisor.

Paula will work with trainees to identify a range of potential intervention strategies; and provide valuable resources and appropriate referrals to internal and external support services. With the establishment of the TSU, the College also partnered with Converge, an external Employee Assistance Program (EAP) service. Converge International is a support service open to all trainees 365 days of the year and can be utilised for any personal or work-related matter. This is a great initiative and trainees are encouraged to use the service if they need to speak with a professional psychologist, social worker or crisis counsellor. Support will be tailored to meet your needs. The service is completely private and confidential.

For further information on the TSU, please go to the RANZCOG Training Support Unit online: www.ranzcog.edu.au/Training/Training-Support-Unit. More information will be added. If there is a topic you would like to see included, do not hesitate to contact Paula. These webpages are dedicated to informing and supporting all RANZCOG trainees.

Contact Paula Fernandez
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# Stranger in paradise, medicine on Malolo

**Prof Mike O'Connor AM**
**MD DCH DDU FRCOG FRANZCOG MHL**
**MForensMed FACLM**
**Western Sydney University**

The Pacific Medical Students Association (PMSA) is a relatively new organisation based in Fiji, representing medical students from a variety of South Pacific nations. Its aims are to foster collaboration between medical schools and provide medical education beyond that offered within the respective curriculum of each school.

In December 2017, PMSA organised an inaugural medical camp on the island of Malolo, in a tribal area distant from the tourist destinations. The program offered the following topics:

- climate change and natural disasters
- environmental health
- jungle medicine, animal attacks and basic survival
- emergency medicine
- mental health

Approximately 120 medical students (mostly year three and above) from Fiji, Tonga, Samoa, New Zealand, Papua New Guinea and Australia, attended and camped in tents in the grassy schoolyard adjacent to the village.

The students constructed a small covered dais for speakers, while they sat 25 yards away under cover from the blazing sun. I gave a talk on maternal sepsis, followed by a five-hour workshop on basic obstetric ultrasound using the Vinno 6 portable system. The brochure for that machine suggests that it is suitable for outdoor use, however, the bright sunlight prevented anyone from viewing the screen, so we had to retire to a hot, stuffy but darkened classroom for group training.

Some of the other outstanding lectures included:

- New radiotherapy services for Fiji (Prof Mike Barton, UNSW)
- Child and adolescent psychiatry, trauma, attachment and behavioural difficulties (Dr Klaus Martin Beckmann, Qld)
- An assessment of Pacific Island climate projections (Dr Paul Spence, Oceanographer, UNSW)
- Impact of climate change on food security (Prof Roslyn Gleadow, Monash)
- Climate change (A/Prof Simon Hales, Dunedin)

It was interesting to see the students' real concern about a changing world climate and its implications for the South Pacific. Paul Spence noted that some experts predict sea levels would rise by seven metres over the next 30 years. If so, I will move my funeral from Sydney to the Blue Mountains!


**Image 1**. Prof Mike O'Connor giving a talk at an inaugural medical camp organised by PMSA in Fiji.

The return journey to Musket Cove was by open boat launch in rough conditions. I was clinging to the Vinno 6 machine (generously loaned by the company) and an obstetric phantom (courtesy of Glen McNally and the Australian Institute of Healthcare Education), lest they wound up 'in the drink'. Nineteen years previously, the late Dr Chris Kohlenberg, FRANZCOG, taught Fijian doctors the art of practical ultrasound for the Asia and Oceania Federation of Obstetrics and Gynaecology. After one such course, Chris died in a plane crash en route from Suva to Nadi in July 1999.

I urge other Fellows to consider supporting the PMSA, as they are eager to further the cause of a broad-based medical education. The medical camp is expected to be an annual event.

ANZJOG

# From the editor's desk

Prof Caroline de Costa
FRANZCOG
Editor-in-Chief
ANZJOG

Welcome to *ANZJOG* for 2018! The beginning of this year has seen some changes in the Editorial Board. Professor Neil Johnson has retired, having begun his stint as Associate Editor in 2008. His ten years of service have been greatly appreciated by several Editors, including myself, and the many readers of *ANZJOG*. In Neil's stead, Dr Hayden Homer has accepted an invitation to become an Associate Editor, with particular expertise in reproductive endocrinology and infertility. I look forward to working with Hayden. Dr Salwan Al-Salihi has also resigned and Dr Oliver Daly has joined the Board. As well as bringing urogynaecological expertise, Oliver is now the CROWN (CoRe Outcomes in Women's and Newborn health) representative for *ANZJOG*. This represents the commitment of the journal, and RANZCOG, to the CROWN initiative. CROWN represents a group of 80 peer-reviewed journals, covering both women's and newborn health, that came together in 2014 to support the development and introduction of Core Outcome Sets (COS) into research and publication in our joint disciplines.

COS are currently being developed in many disciplines, to provide a defined measure of treatment success that is uniform across clinical trials and which can be easily assessed in systematic reviews and meta-analyses. In the February issue of *ANZJOG*, Oliver explains exactly what COS are, how they are developed, and their importance in providing uniform outcome measures in the research we undertake to improve the health of women and babies.[1] This work on COS dates back to 2011, when the International Committee of Medical Journal Editors (ICMJE) established the Core Outcome Measures in Effectiveness Trials (COMET) initiative for all medical disciplines. This, in turn, has given birth to the CROWN initiative.

From the February issue onwards, the cover of *ANZJOG* will carry the CROWN logo. *ANZJOG* is a proud supporter of the CROWN initiative and looks forward to the benefits COS will offer researchers, with trial design and translation of research findings to clinical practice, in order to improve outcomes for women's and newborn health.

From the beginning of 2018, *ANZJOG* will have two Assistant Editors. These are new posts that will be filled for two-year appointments by younger Fellows or senior RANZCOG trainees who have demonstrated interest in and commitment to academic obstetrics and gynaecology. The appointees will, we hope, gain an understanding of the academic publishing and editing processes. Dr Charlotte Royston and Dr Amanda Poprzeczny have accepted invitations to become Associate Editors for 2018–2019 and I look forward to working with them.

Looking back, the December 2017 issue begins with an Invited Editorial from Prof Neville Hacker, which complements an important report in the Gynaecology Original Articles by Nicklin et al, on the Queensland experience of neo-adjuvant chemotherapy and interval debulking surgery for managing advanced ovarian and related cancers. I am sure these two contributions are of great interest to *ANZJOG* readers.[2,3] In the Current Controversies section, more gynaecological debate, with A/Prof Jason Abbott supporting surgery and A/Prof Anusch Yazdani, IVF, for the management of infertility associated with endometriosis. There are robust arguments on both sides![4,5]

The December issue also contains a large number of obstetric articles from Australia, New Zealand and Papua New Guinea, evidence of the large number of obstetric submissions *ANZJOG* now receives. Prenatal testing in New Zealand,[6,7] and pregnancy outcomes among adolescents and in women conceiving with ART,[8,9] are among the topics covered.

The February issue, following Oliver Daly's editorial, presents the Arthur Wilson Oration, given by Prof Cindy Farquhar, at the Auckland ASM last year. Cindy spoke about the role of evidence-based medicine in obstetrics and gynaecology and her own important contribution to the development of this. I found it fascinating at the time and equally enjoyed reading it here.[10] This is followed by a systematic review of the use of intravenous iron therapies from the department at Flinders that should interest all obstetric clinicians,[11] and a helpful study from Westmead assessing new devices now available for the measurement of fetal blood lactate.[12] The issue also contains the Current Controversies Right of Reply responses from Abbott and Yazdani, who continue to strongly occupy their respective sides of the ring.[13,14]

In conclusion, I am happy to be able to tell you that our delightful *ANZJOG* Publications Coordinator, Sarah Ortenzio (currently being replaced during her maternity leave by the equally delightful Julia Berglund), had a baby girl, Elka, on 16 January. All is well. The Editorial Board send our congratulations and warmest wishes to Sarah and hope she has a wonderful first year with Elka.


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## Statement from the Editorial Board: The objectives of ANZJOG

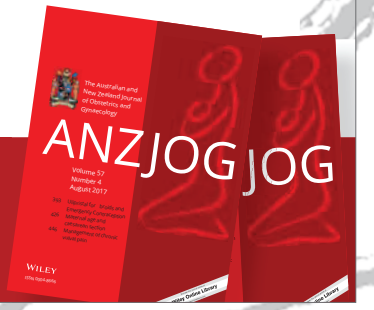
- We intend that ANZJOG will be a high quality academic journal with the main objective of publishing original research from both established and emerging researchers working in obstetrics, gynaecology and related areas. ANZJOG will also publish comment from practitioners in these fields.
- We anticipate that most ANZJOG readers will be obstetricians and gynaecologists who practice in Australia and New Zealand and nearby countries of Asia and Oceania. Other interested readers may be general practitioners, midwives, women's health nurses and Indigenous health workers, as well as non-clinical scientists, epidemiologists and policy makers. Thus while submission is open to all we expect that most papers published will originate in these regions.
- We believe that ANZJOG should be accessible to clinicians across the spectrum of obstetrics and gynaecology. On occasion ANZJOG will publish papers with a primarily subspecialist slant, however such papers would normally have broad appeal amongst the readership of ANZJOG, including obstetricians and gynaecologists with general interests.

## In addition...

- In addition to Original Articles ANZJOG will publish high-quality expert reviews of topics of current interest in obstetrics, gynaecology and women's health; editorials commenting on current practice and research; and other articles including opinion pieces that are well referenced and which contribute meaningfully to the intellectual debate within the specialty. In general, opinion pieces expressing a particular view will be balanced by the publication of a second piece reflecting a differing viewpoint.
- Letters to the Editor on topics in previously published articles will be encouraged.
- There will be six issues annually, each of around 100 pages.
- All original research and other articles will be available online on EarlyView as soon as the proof reading and correction process has been finalised.
- A turnaround time of six weeks or less from reception of submissions to first decision* should be the norm for the majority of submissions.
- At all times the Editorial Board should be composed of members representing the full range of practice within the specialty of obstetrics and gynaecology.

*Acceptance, revision or rejection

**For more information, please visit:**
www.ranzcog.edu.au/members/Publications/ANZJOG



# Letters to the Editor

**Dr Criton Kasby**
**FRANZCOG DDU**

I write in regard to an article on the treatment of uterine inversion (*O&G Magazine*, Winter 2017). I have personally experienced this problem on three occasions during my training in the UK and can testify to the effectiveness of the hydrostatic approach, which was successful on the two occasions I used it.

The first experience I had with this problem unfortunately had a fatal outcome. As a Senior House Officer in 1974, I was the obstetric arm of a flying squad to a peripheral unit 45 minutes drive from Salisbury. Following an instrumental birth, a young primigravid woman collapsed for no obvious reason without excessive blood loss. Examination in less than ideal circumstances showed a firm contracted uterus and minimal ongoing vaginal blood loss. Despite vigorous attempts to revive her, she died following transfer to the main unit with a presumptive diagnosis of amniotic fluid embolism. The autopsy demonstrated a partial inversion with the uterine fundus just protruding through the dilated cervical os. This was a salutary lesson for a junior trainee.

Two subsequent and obvious cases were treated expeditiously using the hydrostatic technique. This was performed simply by returning the inverted uterus into the vagina, cupping both hands to occlude the vaginal introitus and inserting a wide-bore tube in the space between the overlapping thumbs and forefingers. Warm liquid from a canister under hydrostatic pressure was enough to distend the vagina and cervical ring to allow the inverted uterus to be relocated successfully.

**Dr Graeme Dennerstein**
**FRANZCOG**

In their otherwise excellent article (*O&G Magazine*, Spring 2017) on dysmenorrhoea in adolescents, Moeed and Mellor have made a significant omission, namely the back-up option of depot medroxyprogesterone acetate (DMPA). I do not dispute that the oral contraceptive pill is the first-line treatment, but when it fails to provide sufficient symptom relief, recourse to DMPA will help to prevent a large number of potentially unnecessary laparoscopies.

I am aware of the reluctance of some of our colleagues to promote DMPA, especially for adolescents, because of the occasional side effects (mostly reversible with estrogen) and the fear of loss of bone mineral density, which has been shown to be of little or no long-term clinical significance and is reversible. These considerations pale to insignificance compared with the risks and costs of unnecessary surgery.

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# RANZCOG members awarded honours on Australia Day

RANZCOG would like to congratulate our Fellows and Honorary Fellow for being awarded honours on Australia Day 2018.

Member (AM) in the General Division of the Order of Australia:
- Professor Ian Hammond
- Professor Mark Umstad

Prof Hammond was awarded for significant service to medicine in the field of gynaecological oncology as a clinician, to cancer support and palliative care, and to professional groups. Prof Umstad was awarded for significant service to medicine in the field of obstetrics, particularly complex pregnancies, as a clinician, consultant and academic.

Officer (AO) in the General Division of the Order of Australia:
- Professor Suzanne Garland

Honorary Fellow Prof Suzanne Garland has been awarded for distinguished service to medicine in the field of clinical microbiology, particularly to infectious diseases in reproductive and neonatal health as a physician, administrator, researcher and author, and to professional medical organisations.

RANZCOG is proud to count such distinguished individuals as part of its community.

### Notice of Deceased Fellows

The College was saddened to learn of the death of the following RANZCOG Fellows:

Dr Patrick Giles, NZ, 5 November 2017
Dr Donald Harry Bashford, NZ, 18 January 2018

# College Statements update
## November 2017

### Revised College Statements

The following revised statements were approved by RANZCOG Council and Board in November 2017:

- **Home births (C-Obs 2)**

  Revisions include:
  - A patient summary
  - Removal of RANZCOG position that planned homebirth should not be offered as a model of care as it is associated with an unacceptably high rate of adverse outcomes
  - Section 3 'Perinatal and maternal outcomes' has been removed and replaced with Appendix A: Homebirth research looking specifically at perinatal and maternal outcomes, the limitation of high-quality evidence and how it informs practice in Australia and New Zealand
  - The recommendations are based on 'in the event that a woman chooses a planned homebirth' a number of practices/arrangements/criteria are put in place:
    - Highlighting relevant guidelines and policies
    - Skill levels of practitioners
    - Access to services
    - Back up and emergency transfer arrangements
    - Multidisciplinary collaboration
- **Pre-pregnancy counselling (C-Obs 3a)**

  Revisions include:
  - Updated references and strengthening of evidence
- **Diagnosis of gestational diabetes mellitus (C-Obs 7)**

  Revisions include:
  - Updated references and aligned with ADIPS Consensus Guidelines
- **Warm water immersion during labour and birth (C-Obs 24)**

  Revisions include:
  - A patient summary
  - Updated references and aligned with national guidelines
  - New summary of recommendations
  - Supporting clinicians where waterbirth is outside their scope of practice
- **Provision of routine intrapartum care in the absence of pregnancy complications (C-Obs 31)**

  Revisions include:
  - A patient summary
  - New recommendations regarding the prevention of perineal tears
  - New recommendations regarding delayed cord clamping
  - New paragraph regarding the value of debriefing following labour and birth
- **Term prelabour rupture of membranes (Term PROM) (C-Obs 36)**

  Revisions include:
  - Updated references and strengthening of evidence
- **Management of monochorionic twins (C-Obs 42)**

  Revisions include:
  - Updated references and strengthening of evidence
- **Use of the Veress needle (C-Gyn 7)**

  Revisions include:
  - Updated references and strengthening of guidance regarding insufflation
- **Polypropylene vaginal mesh implants for vaginal prolapse (C-Gyn 20)**

  Revisions include:
  - Guidance on the regulatory action by the Therapeutic Goods Administration (TGA) that came into effect on 4 January 2018
- **Position statement on midurethral slings (C-Gyn 32)**

  Revisions include:
  - Guidance on the regulatory action by the TGA that came into effect on 4 January 2018
- **Tissue extraction at minimally invasive procedures (C-Gyn 33)**

  Revisions include:
  - Updated references and strengthening of evidence
- **Surrogacy in Australia and New Zealand (C-Gen 16)**

  Revisions include:
  - Addition of regulatory and legislative requirements
- **RANZCOG training registrar supervision guideline (C-Trg 5)**

  Replaces previous guideline 'Supervision of trainees in the birthing unit (C-Trg 5)'
  Revisions include:
  - Additions incorporated:
    - Consultant attendance
    - Clinical handover
    - Workplace difficulties

A full list of College Statements can be viewed at: www.ranzcog.edu.au/Statements-Guidelines.

### RANZCOG Patient Information

There are 30 RANZCOG Patient Information Pamphlets, including the new Pregnancy and Childbirth pack of 18 pamphlets, now available. All of these products can be viewed and ordered at: https://printstore.ranzcog.edu.au/. College members can order using their existing RANZCOG member number and registered email address.

The following titles were approved for publication and are now available:
- Cervical screening in Australia
- Pre-eclampsia and high blood pressure during pregnancy
- Why your weight matters

Prof Yee Leung
Chair, RANZCOG Women's Health Committee

# Obituaries

## Dr Patrick Francis Hunter Giles

**(1927–2017)**

Patrick Francis Hunter Giles was born in New Zealand, the oldest of four children. He was Dux of St Patrick's College, Wellington, and went on to study science at Victoria University of Wellington. He then moved to Dunedin to study medicine at the University of Otago. As a junior doctor, Patrick enjoyed being sent to remote areas, one of which was Masterton Hospital (now Wairarapa Hospital) in the North Island of New Zealand. It was there he met and married Mary, then a student nurse.

Patrick began training in obstetrics and gynaecology in Dunedin. He then worked at the Royal Women's Hospital in Melbourne from 1960–1961, before travelling to the UK for the specialist exams, where he worked in Hull, then Oxford. He returned to the Royal Women's Hospital in Melbourne from 1964 to 1966, before moving to Perth.

In Perth, Patrick was Reader, then Associate Professor at the University of Western Australia, in the Department of Obstetrics and Gynaecology at King Edward Memorial Hospital, until his retirement in 1992. With regard to obstetrics, he was interested in the medical treatment of infertility.

Patrick was devoted to his students and seemed to take a particular interest in teaching them, winning a Tutor of the Year award in 1992.

His son Philip was accidentally killed in 1969, aged 9, at a pedestrian crossing. He separated from his wife in 1983. Despite these life events, he regarded himself as having lived a fortunate life.

Patrick died peacefully aged 90. He is survived by his two daughters, Marian and Sophie, his son Adrian and his grandson Hunter.

Marian Giles

## Dr Donald Harry Bashford

**(1941–2018)**

Donald Harry Bashford, known as Harry, was born in Brightwater, near Nelson, New Zealand. He attended Nelson College, then studied medicine at the University of Otago. Harry spent two years in Christchurch as a house surgeon after graduating in 1966, then headed to the West Coast of NZ to work as a GP.

While working in Whataroa, Harry delivered dozens of babies and decided to specialise in obstetrics and gynaecology. He went to Christchurch Women's Hospital for specialist training, then to Australia and the UK to take up other positions. He returned to Christchurch Women's Hospital in 1975 as a tutor specialist.

Several different roles followed, as did a move into private practice. In 1988, Harry became clinical director of the department of obstetrics and gynaecology at Christchurch Women's Hospital, a role he held for 15 years.

Harry delivered an estimated 7000 babies during his lengthy career, including the first New Zealand baby conceived through IVF, in 1981.

Harry was a dedicated family man. He married Susie in 1967 and had three children, Andrew, Anna and Charlotte. Harry was a caring and empathetic person, whose profession was an integral part of his life.

Harry died aged 76. He is survived by his wife, three children and nine grandchildren.

Adapted from stuff.co.nz article by Oliver Lewis, 3 February 2018.