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Pharmacology

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Pharmacology

Women's health

The College

A Pocket Guide to Medicines Your Patients Take

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From the President

Prof Michael Permezel
President

I write to you having recently attended an outstanding Indigenous Women's Health Meeting in Adelaide. Much more needs to be done at all levels, but many Fellows, Diplomates and Trainees are making great contributions to Indigenous women's health, both in Australia and New Zealand. Indigenous women's health is embedded in the FRANZCOG Curriculum and it is pleasing to note the plans to further increase online resources and increased incorporation into College assessments.

The highlight of the meeting was the launch of the College's Reconciliation Action Plan (RAP). The development of a RAP was initiated by the Indigenous Women's Health Committee in 2012. Aboriginal Fellow Dr Marilyn Clarke chaired a Working Party that, in consultation with Reconciliation Australia, developed a plan that sets measurable and achievable goals, timelines and responsibilities to provide the necessary framework for that change to occur. Marilyn, Dr Jacquie Boyle (Chair of the Indigenous Women's Health Committee) and the Working Party are to be congratulated on this important development towards ultimately 'Closing the Gap' in Aboriginal and Torres Strait Islander women's health. The RAP is available on the College website at: www.ranzcog.edu.au/womens-health/reconciliation-action-plan.html .

Education and training

Examinations

As this has to be written some weeks before publication, my registrars are currently preparing for their May Structured Oral Examinations (SOE). The College is rightly proud that it has been a leader in examination processes such as the rigour employed in the reviewing and workshopping of cases and in our standard-setting procedures. Further positive developments continue and the College will always strive for fair and transparent assessment processes that ensure new Fellows achieve the standard necessary for best-practice outcomes in women's health.

Examining for the College is one of the most rewarding ways for a Fellow or Diplomate to make a contribution; having a productive exchange with senior colleagues in developing examination questions – while accruing significant CPD points. In encouraging colleagues to become examiners, the response is often: I am a clinician, examining is for academics. Nothing could be further from the truth. The essence of College examinations is assessment by contemporary peers. It is precisely those who describe themselves as a clinician not an academic who are most needed as examiners.

What is the meaning of MRANZCOG?

Awarding MRANZCOG dates back to a time where many of the specialist Colleges had Membership awarded during training, as a staging point on the way to Fellowship. RANZCOG remains one of the very few Colleges to retain a post-nominal (MRANZCOG) that does not meaningfully translate to readiness for specialist practice.

During the two years of Advanced (elective) Training, the prospective specialist acquires and enhances the attributes necessary for specialist practice. Within an increasingly defined scope of practice, the Trainee moves from resident (novice) to senior registrar level during the first four years of Core Training and from senior registrar level to consultant specialist (expert) during Advanced Training.

A further confusion is the differing definitions of member and Member. The former includes all Fellows, Diplomates, Trainees, Associate Members, Educational Affiliates and Certificate holders, while the latter refers only to those who have completed Core Training. It could be time for the College to reconsider the awarding of the post-nominal MRANZCOG during training. Like other Colleges, the FRANZCOG would become the primary post-nominal of specialist training in O and G.

Scope of practice

It was to be expected that changes to the FRANZCOG scope of practice under the revised training program would provoke some interest. It is understandably disappointing to many that a future Fellow being awarded FRANZCOG may not necessarily have the same broad scope of practice of a current Fellow. Some change to the scope of practice of all new Fellows is the inevitable consequence of several factors including the reduction in both training hours and training opportunities in comparison to past Trainees.
It would be an undesirable consequence of the revised training program if credentialing committees, hospital administrators or patients developed a view that the new Fellow with an area of special interest became the preferred provider in that scope of practice, ahead of an established Fellow who has a wealth of training, experience, expertise and CPD across a broad scope of practice that includes the relevant field. The College has limited capacity to influence patient choice; however, it potentially could guide a credentialing committee.

Credentialing

Credentialing is defined by the Australian Commission on Safety and Quality in Health Care as referring to 'the formal process used to verify the qualifications, experience, professional standing and other relevant professional attributes of medical practitioners for the purpose of forming a view about their competence, performance and professional suitability to provide safe, high-quality health care services within specific organisational environments'.

The College is not a credentialing body. Who does what in a hospital or health authority is rightly determined by a local credentialing committee, which considers the circumstances of the applicant in the context of local conditions. However, the College does have a role in assisting the hospital or health service with credentialing.

Firstly, the College has a broad statement that outlines key principles and process matters for credentialing committees, including appropriate persons for membership. The College statement does not give specific directions in the matters that a credentialing committee might consider in making their decision with respect to credentialing for a specific scope of practice: training, currency, continuing professional development and participation in audit of outcomes. Given that other bodies are now making credentialing recommendations, it is perhaps time that the College more specifically gives direction criteria for credentialing.

FRANZCOG in the current training program

The College training programs provide a structure for assessment of satisfactory training by a credentialing committee. Attainment of FRANZCOG is the most important benchmark of training used in determining credentialing in our discipline. It is therefore critical that the College is able to clearly describe the training for every FRANZCOG. For all those that commenced training prior to December 2013, the possession of FRANZCOG means 'satisfactory training across a generalist scope of practice'. There may also be special interest scopes of practice that can be evidenced by additional training such as subspecialty qualifications or other documentation of satisfactory training in an area of special interest.

FRANZCOG in the Revised Training Program

In contrast to the previous uniformity of the qualification, Trainees who commence training after December 2013 will not all have the 'generalist scope of practice'. With increasing diversity in training (for example, subspecialisation during Advanced Training), the definition of a 'common scope of practice' has become necessary – practice in which all those who hold the FRANZCOG have had satisfactory training. As outlined in my previous report, the broader 'generalist scope of practice' will no longer apply to every FRANZCOG.

Credentialing during training

The College has begun to look at credentialing for the Trainee during training. While recognising that varying degrees of supervision are required for all Trainees, hospitals and health services expect some procedures to be performed by Trainees without direct supervision. It is challenging to say that at year level 'n', all FRANZCOG Trainees should be able to perform procedure 'x' without direct supervision. Even basic labour ward skills create controversy. Some Trainees are reaching year level 3 or 4 of training without the capacity to perform both a simple vacuum and forceps delivery. While each procedure has its passionate advocates, few would argue that a junior Trainee should not be trained in the use of both instruments. The current suggestion before the Education Strategy Committee is that Trainees should be signed off in both techniques of instrumental birth by the end of year level 2. Further discussion will take place through the College committees, but it seems reasonable for a health service to expect that a year level 3 Trainee could accomplish an urgent low instrumental delivery with either forceps or vacuum.

Training beyond FRANZCOG

Imperative in credentialing is a recognition that training does not end with obtaining the FRANZCOG. A review of past clinical performance of the procedure or a proctored for 'x' procedures should provide evidence of satisfactory training and competence not implicit in FRANZCOG or other qualifications. A credentialing committee is not performing its duty properly if it only considers qualifications in its assessments.

Currency and CPD

Currency (evidence of continuing to practice in that scope) and CPD are more challenging concepts when it comes to credentialing because they can be misused by vested interests to disenfranchise the generalist – confining specific procedures to a smaller number of clinicians with more limited scopes of practice. If a credentialing committee were to mandate high procedure numbers or a large proportion of CPD in a specific area of practice, a very competent generalist may not be able to reach the specified threshold. As stated in previous reports, there is obviously a place for subspecialisation, but preservation of the generalist is particularly important in countries where the tyranny of distance can mean loss of service provision.

Participation in audit of clinical outcomes

Participation in an audit of clinical outcomes sounds to be the most onerous but should be part of every clinician's practice. Increasingly, hospitals are including private patients in their clinical audit processes such as perinatal mortality and morbidity or gynaecology morbidity meetings. The Audit of Surgical Mortality is available to all Fellows and a majority are registered.

Colposcopy and ultrasound are two areas where practice may be largely outside the remit of a hospital or health service clinical audit. It is no coincidence that the much discussed C-QuIP is in colposcopy – an area of practice outside the jurisdiction of a hospital credentialing committee. Requests are now coming to the College to improve clinical audit with respect to diagnosis of fetal anomalies on the mid-trimester ultrasound – an area of practice also mostly outside the jurisdiction of a hospital credentialing committee. Of course, most of the latter are not performed by Fellows, but the College may still have a role in the oversight of audit in an area so important to our discipline.

Revalidation

Revalidation can be defined as 'a regular demonstration by medical practitioners that they remain fit to practice across their chosen scope of practice'. Some view it as a 'souped-up' CPD, but the UK model is considerably more than the College's current CPD program.
The Medical Board of Australia (MBA) began a 'revalidation conversation with stakeholders' in March 2013. The conversation continues, but increasingly the MBA seems to be looking to the Colleges to develop

their own versions of revalidation. Watch this space: it is something that is likely to have a substantial impact on us all.

Women's Health
The presence of two sets of gestational diabetes mellitus (GDM) diagnostic criteria (ADIPS ad hoc criteria 1998 and WHO criteria 2013) continues to cause significant confusion among obstetricians, midwives, pathologists, physicians and patients. As flagged in this report six months ago, Council has now endorsed both recommendations of the Multidisciplinary GDM Working Party. A single step OGTT at 26–28 weeks is recommended to be implemented by 1 July 2014, and the target for adoption of WHO 2013 diagnostic criteria is 1 January 2015.

It seems likely that physicians will remain passionately divided over the issue, with some demanding yet another RCT when perhaps precious research resources might be directed to those areas where there is a greater paucity of evidence. Nevertheless, the current situation of dual criteria operating in adjacent hospitals is ludicrous and it has become an issue where the College can no longer sit on the fence.

I had previously thought that this would nearly be my last President's report for *O&G Magazine*. I now find there are to be quite a few more.

From the College

A/Prof Stephen Robson
FRANZCOG
Vice-President

Our College can justifiably be proud of the many ways in which we support the health of women and their families. Not least among these are the large number of philanthropic endeavours supported by the College, Fellows and other members.

Through our support of the RANZCOG Research Foundation, we provide opportunities for leading researchers to explore new frontiers in women's health. The scholarships and fellowships offered by the foundation give researchers the support they need to further develop their research or the opportunities to undertake additional study overseas, bringing back new concepts and approaches for the benefit of women in Australia and New Zealand.

The RANZCOG Asia Pacific Women's Health Fund provides another channel for the College to support initiatives aimed at long-term improvements in women's health in Asia and the Pacific. Many Fellows volunteer their time to provide much-needed support and services throughout the Asia Pacific region. We also work closely with partners throughout the region and, supported by your donations as well as funding from organisations such as AusAID (now the Department of Foreign Affairs and Trade), the College strives to facilitate skill sharing and collaboration on areas of need in the region.

A good example of this is the RANZCOG Pacific Midwifery Leadership Fellowship Program. The goal of this program is to improve the safety of birth in the Pacific islands by improving the knowledge and capacity of Pacific midwives. Through a series of short-term attachments at Nepean or Liverpool Hospitals in Sydney or Middlemore Hospital in Auckland, these midwives can develop their leadership skills and share innovative ideas and practice.

The College also supports the activities of the Brian Spurrett Foundation, created in memory of the late A/Prof Brian Spurrett, which also supports activities in reproductive health in the Pacific.

Across 'the ditch', our New Zealand colleagues work with the Mercia Barnes Trust (see article on p64) to assist and promote research covering a variety of subjects in the area of women's and reproductive health. This trust plays a complementary role to the RANZCOG Research Foundation.

And all this is before we consider the work of the Beresford Buttery Trust or the Friends of the College Collection, who raise funds to develop, maintain and conserve the College's art and artefacts.

While all this activity is laudable, there is a growing sense that the College's philanthropy is quite disparate and our structure overly complex. There are many different committees and boards governing these various activities, leading to a lack of co-ordination and unity in our messaging.

The College Board, along with our new CEO, have been looking at ways to provide a sharper focus to our philanthropy.

One approach might be a 'RANZCOG Foundation' that, if properly structured, would create more scale and focus for our activities. Such a new body, working within the College, would provide an 'umbrella' for all College philanthropic activities. It would allow us to improve our marketing message and better engage with Fellows, Trainees and Diplomates as future donors. Bringing all this together would provide a more sound structure and, over time, it is hoped that we would engender a 'culture of giving' within the College.

> '...the College is viewed as a flagship body for women's health and is therefore a very attractive potential destination for funds...'

While this is all in the very early, exploratory phase, we have had some discussions with the Board of the RANZCOG Research Foundation to look at how this 'umbrella' model might work in practice.

Undeniably, the College is viewed as a flagship body for women's health and is therefore a very attractive potential destination for funds for a wide gamut of philanthropic activities, provided we can get this structure right.

As an example of this, an organisation which I chair, Send Hope Not Flowers (SHNF), has recently donated $30 000 to the College to support the work of Dr Barry Kirby in Papua New Guinea (PNG). These funds will be used to provide a range of practical support and activities in PNG to enable health workers to provide quality care to women and babies. The project will include provision of a range of essential equipment and consumables, educational support to facilitate capacity building of the maternal and child health workforce and practical assistance to healthcare workers to support them in their roles.

The College and SHNF supported the address of Dr Kirby at the National Press Club in early May. Dr Kirby spoke movingly of his work in the Milne Bay province to an audience of almost 200, including many of Australia's leading journalists. After his address, the College and SHNF joined Dr Kirby on a panel to take questions from journalist members of the press club. The entire event was televised. Having access to this sort of 'publicity' is an excellent way to get our collective message out regarding the challenges facing maternal healthcare workers in PNG and across the broader region.

SHNF is now looking at a more formal, long-term relationship with the College to provide an ongoing stream of funds to support practical, on-the-ground activities for maternal care throughout the Asia Pacific. It is this sort of support that other philanthropic trusts may look to provide if we can create a more united, focused foundation within our College.

Editorial

Dr John Schibeci
DRANZCOG

She had never forgotten that, if you drink too much from a bottle marked 'poison', it is almost certain to disagree with you, sooner or later.
– Alice's Adventures in Wonderland, Lewis Carroll

As a GP, I often note that one concept patients have difficulty understanding is the role of the physician. They seem to know well what a surgeon does, but not so the specialist physician. I explain a surgeon treats you by operating and physicians treat you by giving you drugs. This is, of course, a gross oversimplification of current practice, as surgeons often use medications to treat their patients and physicians increasingly perform procedures. Having said this, I feel there is no area of medicine where the use of drugs and surgery is more balanced than in obstetrics and gynaecology. This specialty is steeped in the history of surgery, but there is no doubt that drugs are as much a tool of the trade to the obstetrician and gynaecologist as are the Hegar dilator or the Neville Barnes forceps.

> '...drugs are an important part of our practice and we need a basic understanding of what we are giving our patients...'

The history of drugs and pharmacology is as old as mankind. The alchemist, pharmacognosist and apothecary were the progenitors of modern pharmacology. It was really not until the concept of receptor theory was developed by Paul Ehrlich and John Newport Langley at the turn of last century that pharmacology came of age. We all think of drugs as keys in a lock resulting in the ignition of cellular chemical reactions. This is a fine way to think about it as the chemistry of this is mind-bogglingly complex. The locks are most commonly proteins embedded in the cell membrane, but can be nucleic acids or, much less commonly, lipids and even sugars.

Pharmacology, depending on the individual, can be either fascinating or terminally boring. To this latter group we don't apologise for this issue. Regardless of your preferences, drugs are an important part of our practice and we need a basic understanding of what we are giving our patients, lest we should ignore the therapeutic margins and poison our patients, as Alice alludes to in the quote above.

In this issue, we have tried to cover most therapeutic groups relevant to this specialty. In addition to this, we are quite chuffed with our first *O&G Pocket Guide:* a mini guide on the other drug groups our patients take, but we don't usually prescribe ourselves. We hope it serves as a reference for our consult rooms, allowing us to stay more in touch with our patients.

We would like to remind you also of the *O&G* app. Not only are some of the articles of each issue of this magazine on it, but also there are mini assessments on some of them as well and CPD points can be earned just by reading and learning. Finally, we would like to commend this issue to you and thank all the contributors for the effort and valuable time they have put into their articles.

Combined oral contraceptives

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The pharmacology of combined oral contraceptive pills old and new.

Access to contraceptive choice is important for women, and their partners, to control the number and spacing of their children. Contraceptives can be classified by their duration of action. Despite the increasing recognition that the long-acting reversible contraception (LARC) methods, namely implants, intrauterine methods and depot injections, offer highly effective and cost-effective pregnancy prevention across the reproductive lifespan, the combined oral contraceptive pill (COC) remains the most commonly used method by Australian women. Reasons for the relatively high use of the COC and low use of LARC, compared to similar developed countries appear to include lack of awareness and misconceptions by women and their healthcare providers, habitual prescribing by GPs and an ability to stop and start the COC without medical intervention.[1] Additional non-contraceptive benefits of the COC, including acne control and an ability to manipulate bleeding patterns, can be attractive attributes for some women.[2]

This article focuses on the pharmacology of the various combined oral contraceptive (COC) pills available on the Australian market, with specific reference to their side-effect and risk profile.

The first COCs, marketed in 1961, contained relatively high doses of oestrogen and progestogen hormones and were associated with a relatively high risk of venous thromboembolic (VTE) and arterial disease and a high likelihood of unwanted side-effects such as nausea and breast tenderness. The risks have been reduced by the development of COCs with lower doses of oestrogen and an awareness of safe prescribing. Safe prescribing, taking a woman's risk factors in to account, remains paramount. Guidelines for the safe provision of contraception include the World Health Organisation (WHO) Medical Eligibility Criteria (MEC)[3] and UK-based MEC guidelines from the Faculty of Sexual and Reproductive Health (FSRH).[4,5]

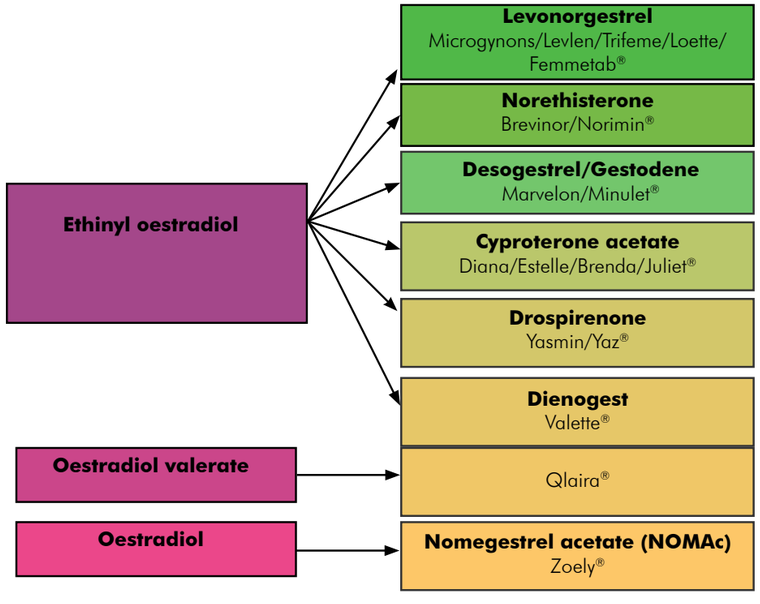

Figure 1. COCP types in Australia (not all generics are included).

Developments in COC formulations

The earliest contraceptive pill was a progestogen-only formulation at a dose that effectively inhibited ovulation although, in common with today's progestogen-only contraceptives, it was associated with unpredictable 'breakthrough' bleeding resulting from an unstable endometrium. Historically, the accidental contamination of some pill batches with oestrogen resulted in improved 'cycle control' as well as enhanced contraceptive effectiveness – and as a result the 'combined pill' was born.[2] The original COC contained norethynodrel, a derivative of 19-nor testosterone, and 150μg of mestranol, a prodrug of ethinyl oestradiol (EE).[2]

Newer progestogens were subsequently developed in an attempt to minimise androgenic and other troublesome side-effects while the dose of EE was reduced to potentially lower the VTE risk and oestrogenic side-effects such as nausea and breast tenderness. All currently available COCs have an effect on metabolic parameters, including oestrogen-related increases in sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) angiotensinogen and apolipoprotein A1 and a change in various coagulation and fibrinolysis factors, which are modulated by the combination and dose of oestrogen and progestogen in a given pill type.[6] It is important to note, however, that the effects of hormonal combinations on metabolic markers for vascular disease do not always directly translate into disease outcomes and controversy continues about the modulating effect of progestogen type on VTE risk. The dose effect of EE on VTE risk is clearer however with today's low dose COCs, containing 35μg of EE or less, posing a low VTE risk when appropriately prescribed. Since 2010, COCs containing either 17 β oestradial or its prodrug oestradiol valerate in place of EE have been available. These oestrogens are structurally identical to the 17 β oestradiol (E2) produced by the ovary. In the laboratory setting, COCs with 17 β oestradiol/oestradiol valerate perform favourably compared with EE pills in relation to their effect on coagulation factors and insulin resistance. However, we will need to wait some years until the completion of post-marketing surveillance studies on these newer pill formulations to see if these effects translate into improved health outcomes.[2]

In relation to the COC progestogen component, earlier laboratory and registry studies suggested that pills with levonorgestrel (LNG) are associated with a lower VTE risk than those containing newer progestogens. However, later large, well-designed cohort studies have not confirmed a difference in risk between progestogen types[7] and a recent controlled, prospective, observational, active surveillance study of more than 85 000 women that compared a COC containing 30μg EE and drospirenone in an extended 24-day regimen to other commonly used COCs in a routine clinical setting, supports a lack of difference in the risk of serious adverse cardiovascular events between available COC types.[8] While all large database studies can be criticised for bias[7], it is reasonable to conclude that a woman's own underlying risk factors for VTE or arterial vascular disease have a much more significant impact on her risk than any differences between product constituents.[6]

The oestrogen component of the COC

Figure 1 shows the constituents of most of the different COCs available in Australia. The majority contain the potent synthetic steroid EE which, as a result of its 17α ethinyl group, has a pronounced effect on hepatic metabolism. Today's low-dose COCs contain 35μg or less of EE. It is unknown whether the lowest dose pill formulations available in Australia (with 20μg EE) offer a safety benefit over those with 35 or 30μg EE and any potential safety advantage must be offset by an increased chance of unpredictable breakthrough bleeding.[5]

Administering EE via a non-oral route, as a vaginal ring or patch (not currently available in Australia), does not appear to mitigate its hepatic impact[6] with one study suggesting an increased risk of VTE for non-oral delivery methods.[9] Earlier attempts to substitute EE with oestradiol, in an effort to potentially reduce cardiovascular risk, had been thwarted owing to unfavourable bleeding patterns, but this has been successfully overcome by novel combinations with either desogestrel (Qlaira) or nomogestrol acetate (Zoely) thanks to their strong anti-proliferative endometrial effect.[10] The 17β-oestrodiol/nomogestrel acetate pill is monophasic (in other words all pills contain the same hormonal dose) with a four-day hormone-free break while the oestradiol valerate/desogestrel combination is quadriphasic with an increasing oestrogen and decreasing progestogen dose through the pill pack. While all COCs reduce menstrual blood loss and can be useful for the management of heavy menstrual bleeding (HMB), both the 17β-oestrodiol and oestradiol valerate pills are associated with a high chance of an absent withdrawal bleed in the pill-free break. Qlaira has an additional indication for the management of HMB in women requiring contraception.

In addition to their effect on blood loss, 17β-oestrodiol and its pro-drug oestrodiol valerate, are associated with less pronounced effects on haemostatic and lipid variables.[6] Whereas EE increases VLDL levels, 17β-oestradiol increases the HDL level without increasing the VLDL level.[6] While the effects on laboratory-based vascular disease markers are favourable for these newer COCs, evidence for their effect on VTE and arterial vascular disease is pending.

The progestogen component of the COC

While progesterone itself cannot be used in the COC owing to its rapid liver metabolism, the synthetic progestogens in COCs are structurally related either to progesterone (pregnanes and 19-norpregnanes) or to testosterone (T) (estranes and gonanes), see Table 1. Several newer progestogens have been developed to bind more selectively to the progesterone receptor while minimising androgenic, oestrogenic and/or glucocorticoid receptor interactions and their related potential side-effects.[6] The earliest progestogens, LNG and norethisterone (NET) are derived from testosterone. while the later progestogens have been derived from progesterone or its related mineralocorticoid, spironolactone (see Figure 2).

Progestogens and vascular risk

Progestogen-only contraceptives including the progestogen-only pills, the contraceptive implant and LNG-releasing IUD, do not appear to increase the risk of VTE. Despite a growing body of evidence pointing to a minimal role of progestogen type in the COC on VTE risk compared to oestrogen, this topic remains controversial.[7] Recurrent media scares about the pill and VTE risk create confusion and anxiety for women, so it is essential for doctors to provide clear balanced evidence-based information when prescribing contraception. The risk of VTE for women using any of the low-dose COCs (pills containing 35μg or less of EE) appears to be approximately two-to-six fold[2] compared to non-users which is substantially lower than the risk associated with pregnancy or the postnatal period.

Despite the lack of strong evidence for a clinically relevant

Table 1. Pharmacologic classification of progestogens used in contraceptives (available contraceptives and contraceptive agents in development).[6]

Related to progesterone	Related to testosterone
Pure progestational (19nor-pregnanes) • Nestorone • Nomegestrol Ac • Trimegestone	Partly estrogenic and androgenic (estranes) • Norethisterone
Antiandrogenic • Cyproterone Ac • Nomegestrol Ac • Chlormadinone Ac	Partly androgenic (gonanes) • Levonorgestrel • Gestodene • Desogestrel▶ etonogestrel • Norgestimate▶ norelgestromin
Partly glucocorticoid • Medroxyprogesterone Ac	Anti-androgenic (non-ethyl estrane) • Dienogest
Related to spironolactone antialdosterone and antiandrogenic • Drospirenone	

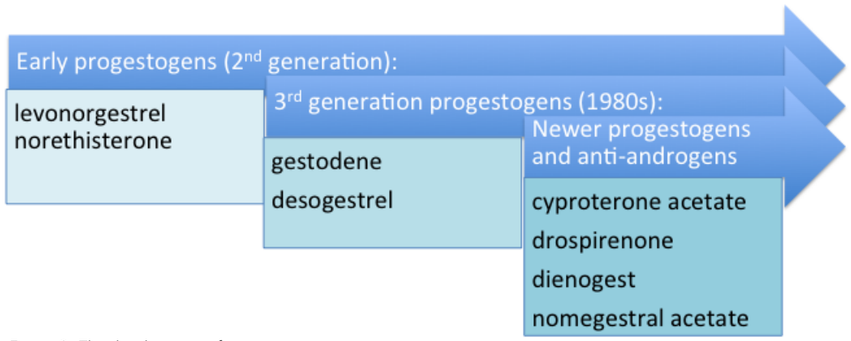

Figure 2. The development of progestogens.

difference between progestogens, it is postulated that the more androgenic progestogens, such as LNG and NET, are able to counteract the potent EE-induced stimulation of liver proteins and coagulation factors, while non- or anti-androgenic progestogens such as drospirenone have a limited mitigating effect on EE's action.[6] The COCs which contain the anti-androgen cyproterone acetate have also been associated with an increased risk of VTE compared to LNG COCs[11], although this information is based on relatively small case-control studies.

The most androgenic progestogens may be associated with impaired glucose tolerance and increased insulin resistance, both risk factors for cardiovascular disease and Type II diabetes mellitus.[6] Again, evidence for clinically relevant differences between progestogen types is lacking and the use of COCs in women with polycystic ovarian syndrome (PCOS) has not, for example, been found to be associated with clinically significant adverse metabolic consequences.[12]

In contrast to VTE risk, the delivery of oestrogen and progestogen vaginally via the EE/etonogestrel vaginal ring does not appear to affect insulin sensitivity.[6] Progestogen-only pills, the contraceptive implant and LNG-releasing IUD have a minimal effect on lipids.[6]

In practice, we can conclude that women with pre-existing risk factors for venous or arterial disease, which make the COC an unsafe option, still have progestogen-only or non-hormonal highly effective methods to choose from (see Table 2). Conversely, women with no contraindications to the use of oestrogen can potentially use any of the available COCs with choice being determined by side-effects, additional non-contraceptive benefits, cost and personal preference.

Side-effects and non-contraceptive benefits

Drosperinone, dienogest and nomegestrol acetate are newer progestogens designed to bind more specifically to the progesterone receptor and to minimise side effects related to androgenic, oestrogenic or glucocorticoid receptor interactions experienced with the earlier progestogens.[6] Drosperinone, a derivative of spironolactone, counteracts the effect of EE-induced increases in angiotensin and aldosterone production, which lead to water and salt retention.[13] It also has anti-androgenic properties. Dienogest is a non-ethyl estrane progestogen that has no androgenic action, but rather an anti-androgenic effect.[14] Nomegestrol acetate (NOMAc) is a derivative of 19-norprogesterone, with a strong anti-proliferative effect on the endometrium, producing good cycle control combined with some anti-androgenic properties.[15] In a randomised, open label, comparative trial evaluating effects on haemostasis, lipids and carbohydrate metabolism, NOMAc 2.5mg/17β oestradiol (E2) 1.5mg showed less impact overall on lipid metabolism as well as other parameters than a COC containing LNG 150μg/EE 30μg per daily pill.[16]

Cyproterone acetate, an anti-androgen with weak progestogenic activity, in combination with EE provides highly effective treatment for hyperandrogenism as well as providing effective contraception. COCs with anti-androgenic progestogens (drospirenone or dienogest) or less androgenic progestogens (gestodene, desogestrel or NOMAc) also have a theoretical advantage for women who request treatment for androgenic symptoms. However, it is important to be aware that the oestrogenic component of all COCs is likely to improve acne via increased SHBG levels and a reduction of free testosterone, even at a low dose and even when combined with an androgenic progestogen. A Cochrane review concluded that few important differences were found between COC types in their effectiveness for treating acne.[5]

In practice, the evidence for the benefit of one COC type over another is often limited in relation to the management of troublesome side effects or for additional non-contraceptive benefits on acne and menstrual bleeding and it may be a matter of trial and error in finding the most appropriate formulation to suit an individual woman.

Conclusion

While increasing awareness and uptake of LARC methods are likely to impact on the proportion of women using the COC in the future, many women will continue to choose an oral method of fertility control. There have been significant changes to COC formulations over the past 50 years, including the development of progestogens with anti-androgenic activity and positive benefits on HMB, and the replacement of EE with oestradiol. However, future developments in hormonal contraception are more likely to be related to alternative delivery systems, especially those which can be either self-administered or minimise the woman's need to interact with the health system.

In the meantime, it remains imperative that COCs are prescribed safely according to the WHO/FSRH Medical Eligibility Criteria. Since differences between COC types as a result of their progestogen and oestrogenic constituents appear to have little impact on relative safety, COC choice for eligible women will therefore be based on individual preference in relation to potential side-effect profile, additional non-contraceptive benefits as well as cost. While the earlier LNG and NET COCs are subsidised by the PBS in Australia, subsidy of the newer formulations would require a body of evidence demonstrating clinical and/or economic superiority over the older established pill types. We await with interest the outcomes of post-marketing surveillance studies of the newer COC formulations.

Table 2 MEC categories with risk factors for VTE (not including the first six weeks postpartum).[5]*

Condition		CHCs	POPs ENG implants, DMPA, LNG-IUD	Cu-IUD	LNG-EC
Past history of VTE		4	2	1	1
Current VTE, on anticoagulant		4	2	1	2
Family history of VTE	First degree relative aged <45	3	1	1	1
	First degree relative aged ≥45 years	2	1	1	1
Known thrombogenic mutation		4	2	1	1
BMI 30-34kg/m^2		2	1	1	1
BMI ≥35kg/m^2		3	1	1	1
Surgery with prolonged immobilisation		4	2	1	1
Surgery without prolonged immobilisation		2	1	1	1
Immobilisation unrelated to surgery		3	1	1	1
Thrombophlebitis		2	1	1	1

**MEC 1: a condition for which there is no restriction for the use of the contraceptive method*
MEC 2: a condition where the advantages of using the method generally outweigh the theoretical or proven risks
MEC 3: a condition where the theoretical or proven risks usually outweigh the advantages of using the method
MEC 4: a condition which represents an unacceptable health risk if the contraceptive method is used

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The enduring duo

The role of mifepristone and misoprostol for medical termination of pregnancy.

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Neither of the medications now used for medical termination of pregnancy were first developed for that role. In the case of misoprostol, its effect on the pregnant uterus was initially regarded as an unwanted side effect of an anti-ulcer medication, while mifepristone was initially designed to strongly bind to progesterone receptors for experimental reasons, without regard to any clinical use. Today, a combination of these medications provides a reliable method of pregnancy termination used widely throughout the world.

Mifepristone

The first steps in the development of mifepristone grew out of research done at the French pharmaceutical laboratories of Roussel Uclaf, conducted by chemists Georges Teutsch and Alain Belanger in the late 1970s. At the research facility in Paris, Teutsch and Belanger were investigating steroid receptors and how to modify binding. To assist their work, they developed synthetic steroids that would bind to steroid receptors. One of the compounds the group synthesised was named RU-486 and a member of their team found that RU-486 occupied the progesterone receptor with a strong affinity, not allowing natural progesterone to bind and have its physiological effect. RU-486 was synthesised by taking a 19-norsteroid moiety and substituting a p-dimethylamino phenyl group at the 11b position. Its binding affinity for the progesterone receptor is up to five times that of progesterone.[1]

This 'anti-progesterone' function of RU-486 was duly noted, but the full significance of the results did not become apparent to the team at the time. It was not until an endocrinologist also working for Roussel Uclaf, Etienne-Emile Baulieu, recognised that RU-486 could play a role in fertility regulation that further work was undertaken. Baulieu used RU-486 in various laboratory animals and found that it prevented the physiological change from proliferative to secretory endometrium during the animals' oestrus cycle, and led to spontaneous pregnancy loss if given after pregnancy was established. Perhaps most importantly, RU-486 did not appear to have toxic side effects, even in relatively high doses. Encouraged by these animal data, Roussel Uclaf funded further testing of RU-486 in human subjects, with very similar results to the animal studies. Subsequent large studies across Europe and Asia confirmed that low oral doses of RU-486 provoked early pregnancy loss with few complications and minimal side effects.

It should not be surprising that RU-486, or mifepristone as it is now usually known, has such a profound effect once it blocks the progesterone receptor. Progesterone maintains pregnancy through a number of physiological actions. It prevents the typical cervical changes that lead to labour – interstitial hydration, apoptosis of smooth muscle cells, denaturation of the collagen framework and opening of elastin fibres. It also reduces synthesis and release of prostaglandins from the decidual cells, and stabilises myocytes and inhibits the formation of a muscle bundle syncytium with gap junction formation that is necessary for co-ordinate contraction during labour.

When the progesterone receptor is blocked endogenous progesterone cannot bind and this leads to vascular injury, necrosis of the decidual tissue and these effects ultimately result in bleeding.[2,3] Mifepristone administration will thus counteract all of the progesterone actions, leading to cervical softening, increased sensitivity to prostaglandins and increased spontaneous contractility.[4] Indeed, mifepristone administration increases myometrial sensitivity with increases in frequency and amplitude of contractions of up to five times and its effects peak at between 36 and 48 hours after administration.[5]

Misoprostol

Misoprostol was originally synthesised in 1973, by Paul Collins, a chemist working with American pharmaceutical giant Searle. It had long been recognised that prostaglandin-E series compounds inhibited gastric acid secretion, hence Collins' research. However, its potential went unrecognised until it was first licenced by Searle in 1985, at the same time the company was embroiled in controversy and was in the process of withdrawing its Copper-7 intrauterine device from sale in the wake of the Dalkon Shield disaster. At the time, gastric ulcers associated with non-steroidal anti-inflammatory drug (NSAID) use were a major problem and the original H2-antagonists, cimetidine and ranitidine, were making huge profits for other companies. Searle was keen to enter this lucrative market and misoprostol, as a synthetic PGE1 analogue, had been licenced specifically for the prevention and treatment of peptic ulcer disease in patients on long-term therapy with NSAIDs, such as naproxen and aspirin, for conditions such as rheumatoid arthritis. Misoprostol was the first compound to receive formal FDA approval for that indication, giving Searle a major commercial advantage.

Collins and his group knew well that prostaglandins affected uterine smooth muscle and conducted experiments using misoprostol only to find they were unable to counter the potentially disastrous side effect. Misoprostol induces cervical ripening and labour by direct action on the cervix and by the stimulation of myometrial activity. Thus, misoprostol was released with strong warnings about its potential effect in women of childbearing age, and especially in pregnancy. The significance of this effect was not lost on other researchers and misoprostol was subsequently used 'off-licence' as an abortifacient.[6] Today, misoprostol, either alone or in combination with other drugs, may be used to deliberately induce uterine contractions at any stage of pregnancy.

Misoprostol has a number of very useful properties: it is inexpensive; it is very stable at room temperature; it can be stored in austere conditions for long periods of time; and tablets are readily absorbed and effective if taken orally or used vaginally or rectally. Following oral administration, the plasma concentration of misoprostol peaks at about 30 minutes, but declines rapidly thereafter with a terminal half-life of between 20 and 40 minutes. In contrast, after vaginal administration, the levels increase gradually and peak after about 75 minutes, but remain detectable for a significantly longer time. In medical termination of pregnancy, both the oral and vaginal routes are effective, but patient acceptability has led to oral administration being most commonly used, particularly in early pregnancy. Importantly, misoprostol has minimal effects on airways and has few side effects.

For termination of pregnancy

Despite mifepristone increasing uterine contractility and causing cervical softening, less than one per cent of women proceed to abortion after administration of mifepristone alone.[7] For this reason, medical termination of pregnancy is usually undertaken using a combination of mifepristone and a prostaglandin analogue, in most cases misoprostol. In effect, mifepristone primes the myometrium to potentiate the effect of the misoprostol, resulting in abortion. A combination of mifepristone and misoprostol is approved for medical termination of early intrauterine pregnancy in both Australia and New Zealand (see Table 1).

The timing of the misoprostol dosage does not appear critically different between 24 and 48 hours following the mifepristone, with both intervals resulting in a similar induction to abortion time and comparable efficacy.[8] Mifepristone reaches peak plasma concentrations within one-to-two hours of administration and slowly decreases with a mean half-life of 24 hours[9], which could account for the lack of difference in efficacy despite timing differences. The effectiveness of this combination of mifepristone and misoprostol for medical termination of pregnancy is at least 93 per cent if performed before 49 days gestation. Less than five per cent of women who receive mifepristone followed by misoprostol require surgical intervention: in between two and four per cent of women it is required for retained products; and in about one per cent it is necessary for ongoing pregnancy. Women undergoing medical termination must to be followed up to three weeks after medication, to ensure complete expulsion of the pregnancy and cessation of bleeding.

Currently, GyMiso is licensed in Australia for use up to 49 days gestation, however, in many other countries – including, upon the recommendations of the Royal College of Obstetricians and Gynaecologists, the UK – the combination is recommended for use for medical termination until 63 days gestation. The priming effect of mifepristone on the myometrium may also be used in mid trimester termination of pregnancy with misoprostol. Mifepristone 200mg is administered 36–48 hours prior to the start of a misoprostol regime designed to induce a mid-trimester abortion. In this case, mifepristone has been shown to reduce the total dose of misoprostol required.

Table 1. Mifepristone and misoprostol regimens for termination of intrauterine pregnancy up to 49 days gestation.

Country	Mifepristone dose	Misoprostol dose
Australia	200mg oral single dose	800μg single oral dose OR two 400μg oral doses two hours apart, 36–48 hours post mifepristone
New Zealand	200mg oral single dose	800μg vaginally 36–48 hours post mifepristone

Worldwide, 47 000 maternal deaths occur owing to unsafe abortion each year[10] and medical management provides an alternative to the previously favoured surgical termination, that is not always readily available. Fortunately in Australia there is access to safe options and, though such decisions can never be easy, the remarkable synergistic combination of mifepristone and misoprostol provides a therapeutic option with a number of advantages at a very difficult time. These advantages include: increased options for the patient a misoprostol induction of a labour in later pregnancy, including intrauterine fetal death; an effective alternative to surgical termination in early gestations; an option that can be undertaken as an outpatient with the support of loved ones; and simply the ability of the patient to be involved in choice, permitting patient preference and increased satisfaction in this difficult time.[11]

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Pharmacology of ART

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The pharmaceutical landscape of assisted reproductive technologies is constantly evolving, led by the explosion in our understanding of human reproduction and the promise of lucrative returns in this growth industry.

One in six Australian and New Zealand couples seeks fertility treatment. Most will proceed to some form of assisted reproduction, ranging from the induction of ovulation to in vitro fertilisation (IVF). Assisted reproductive technology (ART) is the summative term applied to laboratory or clinical technology to gametes and/or embryos for the purposes of reproduction. These treatments typically involve the administration of pharmaceuticals to stimulate follicular development, prevent premature ovulation and trigger timely ovulation.

Ovulation induction

A number of preparations are used to induce ovulation, including selective oestrogen receptor modulators (SERMs), metformin, gonadotrophins, aromatase inhibitors and pulsatile gonadotrophin releasing hormone (GnRH). The latter are used uncommonly. Ovulation induction may be performed in conjunction with intrauterine insemination.

Clomiphene is widely used for ovulation induction and is the most commonly used selective SERM. Its primary action is to block oestrogen receptors in the hypothalamus. This causes a loss of negative feedback and an increase in pituitary secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH).

Metformin is an oral biguanide that can be used for ovulation induction. Systematic meta-analyses of randomised trials have confirmed that in non-obese women with polycystic ovarian syndrome, metformin has similar pregnancy rates to clomiphene.[1] Although the routine addition of metformin to clomiphene does not improve chances of conception, co-treatment is often used for women resistant to clomiphene alone.[2]

The principal gonadotrophin, FSH, is a glycoprotein that presently can only be administered by subcutaneous injection. FSH is administered daily and monitored by ultrasound and/or hormone levels. Dosing is determined by clinical parameters, such as age and ovarian reserve. FSH doses are much lower than used during IVF. The risk of multiple pregnancy is as high as 20 per cent. This may be decreased when sonographic monitoring is used in conjunction with a rigid cancellation policy.[3] Ovulation may be triggered with human chorionic gonadotrophin (hCG), as an analogue to the natural surge in LH. hCG is a suitable trigger as biochemically it is very similar to LH. hCG, LH, FSH and TSH are glycoprotein heterodimers consisting of an alpha and a beta subunit. The α-subunits are identical, however, the β-subunits differ, giving these glycoproteins their individual characteristics. Insemination or intercourse is usually timed 24–48 hours from the trigger injection.

Aromatase inhibitors are currently not approved for ovulation induction in Australia or New Zealand. Aromatase inhibitors block ovarian oestrogen production. This causes a loss of oestrogen negative feedback and increase in gonadotrophin secretion. Aromatase inhibitors appear to have similar efficacy to clomiphene, but with a substantially reduced risk of multiple pregnancy because the normal feedback mechanisms remain functional.

The current evidence does not support the routine use of naltrexone, a central opioid receptor antagonist, or dopamine agonists, such as bromocriptine. Pulsatile GnRH is rarely used given its expense and difficultly of administration.

In vitro fertilisation

Controlled ovarian hyperstimulation

Women undergoing IVF treatment have an improved chance of conception through collection of multiple mature oocytes. This is achieved through controlled ovarian hyperstimulation. In Australia and New Zealand, controlled ovarian hyperstimulation is most commonly performed with recombinant FSH preparations. The two recombinant products on the market, follitropin-alpha (Gonal-F) and follitropin-beta (Puregon), are manufactured using a modified Chinese hamster cell line.

Corifollitropin alfa (Elonva) is a long-acting recombinant FSH that replaces seven days of rFSH injections. It is a hybrid of FSH and the β-carboxyl terminal of hCG, which increases its half-life by reducing its rate of metabolism. Patients require six fewer injections compared to standard FSH cycles. Elonva is not suitable for women at risk of excessive response: those with polycystic ovaries or previous hyperstimulation syndrome. Evidence has demonstrated non-inferiority of this product when compared with standard FSH protocols.

Older urinary FSH preparations, such as Pergonal, Humegon and Bravelle, are no longer available on the Australasian market. While inexpensive, there were concerns regarding purity, batch variability and supply reliability. Recently, urinary gonadotrophins have had a revival with Menopur, a human menopausal gonadotrophin. The manufacturer has overcome the challenges to present a highly purified preparation that contains FSH, LH and hCG. Currently, there is little evidence that the routine use of the combination of FSH and LH increases the chances of pregnancy over the use of FSH alone.[4]

Prevention of premature LH surge

Before the development of GnRH agonists, IVF clinicians were hampered by ovulation prior to egg retrieval. This occurred in up to 40 per cent of IVF cycles. GnRH agonists, initially developed to induce ovulation, revolutionised IVF by preventing this premature LH surge. Developers found, however, a few days after administration, the GnRH receptor was downregulated and ovulation suppressed. The mechanism of receptor downregulation is incompletely understood.

Alternatively, the premature LH surge may be prevented by GnRH antagonists, which competitively bind and block gonadotrophin receptors. Worldwide, GnRH agonists remain more widely used in IVF, despite GnRH antagonist cycles being more patient friendly. GnRH antagonist cycles are shorter and patients do not suffer oestrogen deprivation side effects. Furthermore, there is a more than 50 per cent reduction in the risk of ovarian hyperstimulation syndrome (OHSS).[5]

The utility of early GnRH antagonists was limited by histamine reactions. This is now an infrequent problem with the current third-generation GnRH antagonists Orgalutran and Cetrotide.

There have been three Cochrane meta-analyses comparing agonist to antagonist cycles in IVF. The first, in 2001, demonstrated a significantly lower clinical pregnancy rate in GnRH antagonist protocols. The 2006 meta-analysis found no significant difference in clinical pregnancy rate and also no difference in live birth rate. The most recent Cochrane, in 2011, shows no difference in live birth rate, but a slightly reduced clinical pregnancy rate in antagonist cycles (OR 0.84, 0.75–0.94).[5]

It is likely that GnRH antagonists were initially more commonly used in poorer prognosis patients, such as those with previous poor response or suboptimal outcome. Further studies will likely further dilute the evidence favouring GnRH agonists.

Ovulation trigger

During an IVF cycle, oocyte maturation must be triggered to complete the final meiotic division. Transvaginal oocyte retrieval is performed 36–38 hours following the trigger injection, a few hours before expected ovulation with ensuant follicular rupture and extrusion of the mature oocyte into the peritoneal cavity.

Oocyte maturation is induced using 250–500μg of recombinant (Ovidrel) or 5000–10 000IU of urinary (Pregyl) hCG. Triggering ovulation with hCG is substantially cheaper than LH and is associated with higher implantation rates.[6] To date, 5000 IU of urinary hCG appears to be as effective as 10 000 IU, but is associated with a lower rate of OHSS. Similarly, 5000IU uhCG is equally as effective as 250μg of recombinant hCG.[7]

In antagonist cycles, GnRH agonists can be used for ovulation triggering by inducing an endogenous LH surge. The major benefit of an agonist trigger is that OHSS is almost completely prevented. Unfortunately, clinical pregnancy and live birth rates are significantly reduced with agonist trigger.[8] GnRH agonists cause an attenuated LH surge, sufficient for resumption of ovarian maturation, but insufficient for luteal support. If an agonist trigger is used, viable embryos are generally frozen and replaced later. An agonist trigger is commonly used in patients undergoing oocyte or embryo cryopreservation for fertility preservation, in oocyte donation or to avoid cycle cancellation in women with excessive ovarian response who may be at risk of ovarian hyperstimulation syndrome.

Luteal support

Abundant follicles created by hyperstimulation cause a marked increase in oestrogen production, leading to an advanced endometrium. This is followed by dysfunctional corpora lutea as a result of damage by the process of surgical oocyte retrieval. Thus pregnancy rates are higher if the luteal phase is supported by exogenous progesterone.

Exogenous progesterone may be administered orally, intramusculalry or vaginally. The latter is most common in Australasia. Oral progesterone is generally ineffective, as huge doses of oral and transdermal progesterone are required to give a similar bioavailability as vaginal pessaries or gel, resulting in unacceptable side-effect profiles. Intramuscular progesterone is similarly effective, but administration is painful and associated with risk of injection site abscess. Luteal phase support is continued for two weeks following oocyte retrieval. There is no evidence to support continuing use past the time of positive serum hCG.

Complications

If an hCG trigger is used, approximately 2–5 per cent of IVF cycles are complicated by OHSS. Less than one per cent of women undergoing IVF are hospitalised for monitoring and treatment of OHSS. The hCG trigger may be withheld if OHSS is suspected and the cycle may be cancelled. If an hCG trigger is administered, but an embryo transfer is felt to be unsafe because of the OHSS risk, a 'freeze all' embryo approach may be undertaken.

The dopamine agonist carbergoline can be given at the time of oocyte retrieval to help prevent OHSS. Carbergoline acts to prevent the increased vascular permeability seen in OHSS. It only appears to be effective in reducing the incidence of mild or moderate early-onset OHSS. Intravenous albumin administered at oocyte retrieval has also been postulated as a means to reduce OHSS. Results, however, have been conflicting. Use of the intravenous fluid hydroxyethyl starch at oocyte retrieval may aid in prevention of severe OHSS.[9]

Future directions

Kisspeptins are the product of the KISS1 gene. Kisspeptins are involved in control of GnRH secretion and appear to be a vital mediator in the communication between the ovary and hypothalamus. Kisspeptin hormone has been used for ovarian stimulation in clinical trials. In time, these agents may become more readily available. Adjuvant IVF treatments such as DHEA, testosterone, melatonin, heparin, prednisolone, co-enzyme Q10 and growth hormone remain largely empiric. Testosterone, DHEA and growth hormone may have a role in the 'poor responder', however, more evidence is required before they can be introduced into routine practice.

Conclusion

Pharmaceuticals form a vital part of ART. To safely use these drugs we must understand how they work and their deficiencies. To develop new drugs for fertility treatment, costly clinical trials are required to demonstrate efficacy and safety. The ART landscape has moved from urinary gonadotrophins and GnRH agonists to recombinant technology and GnRH antagonist ovulation suppression. Long-acting FSH may become increasingly popular in coming years.

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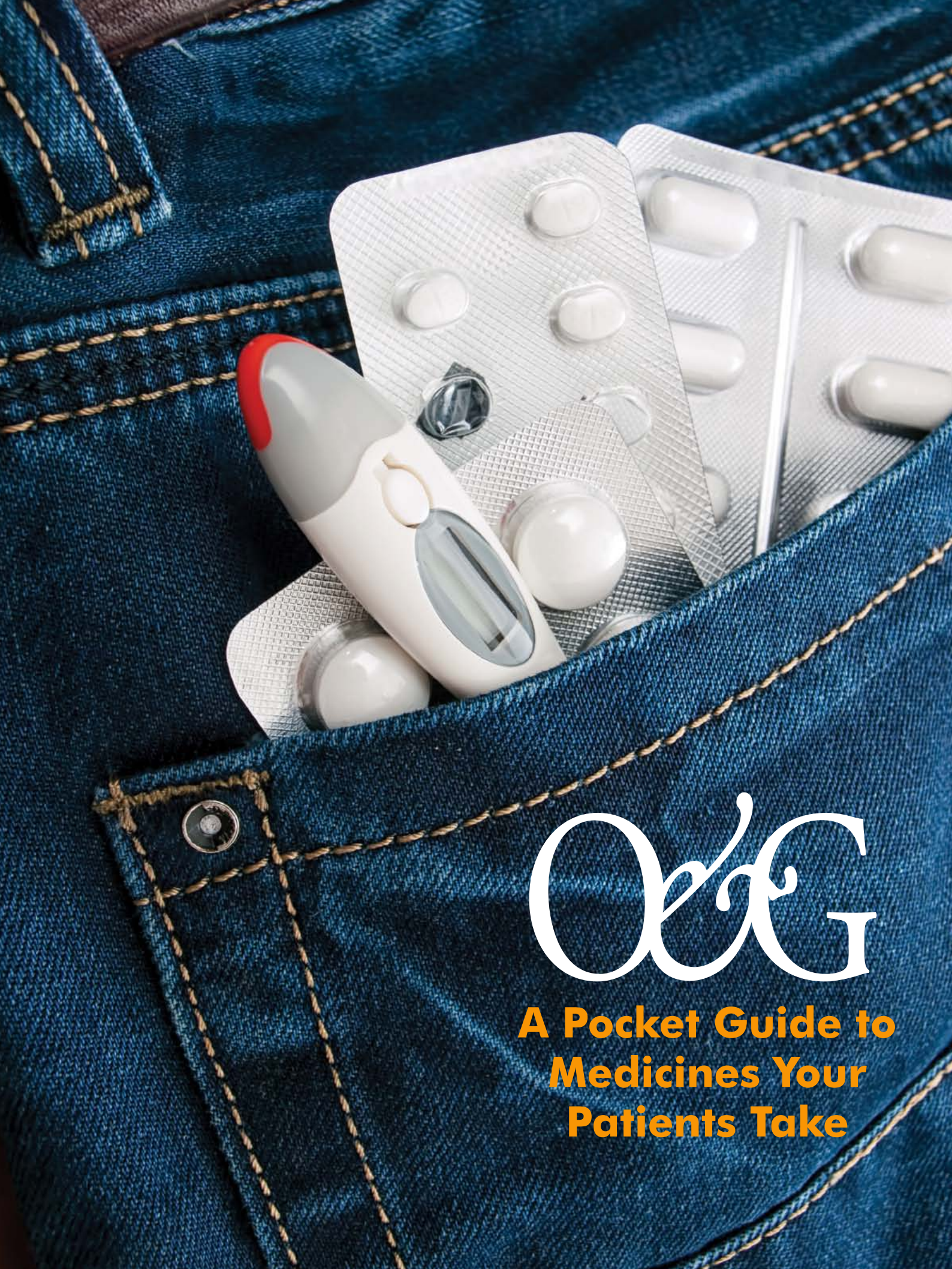

O&G

A Pocket Guide to Medicines Your Patients Take

Respiratory medications

Dr Lucille Wilkinson
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A summary of the safety in pregnancy profile of commonly prescribed respiratory medications.

Medication	Route/frequency	Safety in pregnancy/ category	Side effects	Cautions
B2 agonists				
Salbutamol	Inhaled/nebulised up to hourly	Yes (A)	Tachycardia, tremor	Major cardiac disease in high dose
	IV – stat dose or infusion	Yes	Pulmonary oedema, low K+	Major cardiac disease
Salmeterol	Inhaled once/twice daily	Yes (B3)	Tachycardia, tremor	Not for acute treatment
Corticosteroids				
Fluticasone propionate	Inhaled twice daily	Yes (B3)	Oral thrush, hoarseness	Use spacer for all inhaled agents
Beclomethasone				
Budesonide				
Prednisone	Oral daily	Yes (A)	Diabetes, infection	PPROM, adrenal suppression
Other therapies				
Chromoglycates	Inhaled qid	Yes (A)	Minimal	Not for acute treatment
Ipratropium bromide	Inhaled/nebulised qid	Yes (B1)	Blurred vision, urinary retention	
Magnesium	IV infusion	Yes (A)	Headache, flushing	For acute severe asthma
Methylxanthines				
Theophylline	Oral BD	Yes (A)	GI, insomnia, tachycardia	Not for acute treatment, levels
Aminophylline	IV infusion/ monitor levels	Yes (A)	Arrhythmia, seizures	Only for acute severe asthma
Leukotriene receptor antagonists				
Montelukast	Oral daily	Yes (B1)	GI, allergy, mood disorder	Not for acute treatment
Antihistamines				
Loratadine	Oral daily	Yes (B1)	Headache, drowsiness	
Cetirizine	Oral daily	Yes (B2)	Drowsiness	

Anticoagulants

Dr Alexa Bendall
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A basic guide to anticoagulants, including our old favourites and some newer, and welcomed, alternatives.

Warfarin
Wafarin works by inhibition of vitamin K-dependent synthesis of factors II, VII, IX and X. The benefits of warfarin for anticoagulation are that it is highly efficacious and reversible with administration of vitamin K. Disadvantages include its: narrow therapeutic window; variable dose-response relationship that requires monitoring; numerous drug and dietary interactions; limited safety, compliance and thus efficacy; slow onset of action; risks of haemorrhage (0.9–2.7 per cent annual risk of severe bleeding) and risks of warfarin necrosis and osteoporosis. Surgery is usually safe with an international normalised ratio of less than or equal to 1.5. It is generally withheld five days before elective surgery. Bridging anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) may be used in the interim, depending on the indication for anticoagulation. Prothrombinex or FFP are used as reversal in emergency settings while vitamin K reversal can be used in less-urgent scenarios.

Warfarin crosses the placenta. It is teratogenic (dose related – doses <5mg/day are the safest; risk less than ten per cent). It causes bone and cartilage abnormalities, simulating chondromalacia punctata, and central nervous system abnormalities. It can cause fetal anticoagulation, potentially leading to complications. Caesarean delivery should be considered in women taking warfarin who go into preterm labour, owing to bleeding risks in the neonate. It is used in pregnancy only in women at very high-risk, for example, those with prosthetic heart valves, and even then only once past the period of organeogensis. It should ideally be ceased during weeks 6–12 to minimise the risk of teratogenesis.

Heparin and its analogues
Heparin works by activating anti-thrombin 3. Benefits of this group of drugs are the rapid onset of action and the fact that they do not cross the placenta. Disadvantages include the risk of heparin-induced thrombocytopenia (HIT) in which heparin induces production of an anti-platelet antibody that activates the affected platelets, leading to potentially fatal arterial and venous thrombosis. HIT is less likely to occur with LMWH than UFH and is uncommon in pregnancy. Monitor for HIT with intermittent platelet counts.

LMWH should be ceased at least 12 hours before elective surgery, whereas UFH can be ceased six hours prior. Neuraxial anaesthesia can be inserted 12 hours or more after the last prophylactic dose of LMWH or 24 hours after a therapeutic dose. When using UFH, neuraxial anaesthesia can be used once APTT has normalised. These anticoagulants can be resumed four hours after removal of the epidural catheter.

LMWH
LMWH is the preferred anticoagulant in pregnancy as: it is safe and effective; it is easier to administer than UFH; it produces a more predictable anticoagulant response; and it does not require monitoring. Disadvantages are: it is not reversible and its metabolism is renal and should therefore be avoided if creatinine clearance is <30ml/ml.

UFH
UFH is cheaper than LMWH and reversal is possible with protamine. Its metabolism is renal and hepatic and it is, therefore, safer in renal failure than LMWH. Disadvantages are: it requires monitoring with activated partial thromboplastin time tests; closer control of anticoagulant effect requires intravenous administration; there tends to be reduced compliance, owing to the issues listed previously; and use for more than a few weeks can lead to a reduction in bone mineral density.

Factor Xa inhibitors: rivaroxaban, apixaban, edoxaban
These are newer agents that work by direct, highly selective, inhibition of Factor Xa. They should be ceased at least 48 hours before surgery. They do not require therapeutic monitoring. There are some oral agents, such as rivaroxaban, that have improved compliance for obvious reasons. Factor Xa inhibitors have fewer drug interactions than warfarin, although potent cytochrome P450 inhibitors, such as ketoconazole and clarithromycin, will augment the anticoagulant effect. They are able to be used with chemotherapeutic agents. Bleeding risks with these agents are similar to those with LMWH. Disadvantages are that they are not reversible and are highly protein bound, and therefore not dialysable, they are contraindicated in liver failure and not used in pregnancy owing to lack of information on efficacy in pregnancy and fetal safety.

Direct thrombin IIa inhibitors: argatroban, dabigatran
As the name suggests, these medications work by direct inhibition of thrombin IIa – they are able to inactivate fibrin-bound thrombin as well as free thrombin as opposed to heparin, which can only inactivate free thrombin. Perioperatively, they should be ceased at least 24 hours before standard-risk surgery or at least 48 hours before high-risk surgery, such as cardiac surgery, neurosurgery or major urological surgery. Benefits are that some orally active forms are available, including dabigatran; there are fewer drug interactions than warfarin; no routine monitoring is required; and they have a similar bleeding risk as LMWH. Disadvantages are that they are: not used in pregnancy, owing to a paucity of safety and efficacy data; they are not reversible; and should be avoided in severe renal failure.

Rivaroxaban and dabigatran are approved by the Therapeutic Goods Administration for:

- prevention of venous thromboembolism in adults who have undergone total knee or hip replacement;
- prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke; and
- treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and PE.

A shrink's shrunken guide to psychopharmacology

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As an O and G, the generalist within a specialisation, you need to know a little bit of everything: a bit of surgery, a bit of clinical medicine, a bit of anaesthesia, even a bit of psychiatry. Don't panic! Here is a simple overview of some of the medications you might find yourself running into.

Antidepressants

Despite their name, antidepressants treat a multitude of mental illnesses. They may be prescribed for a major depressive disorder, anxiety disorder, post-traumatic stress disorder, somatoform disorder or even a personality disorder. Generally, they all boost the synaptic actions of a combination of dopamine, noradrenaline and serotonin. An important point is that they all take weeks of compliance to work so it is much better to prescribe these medications early than to, for example, wait for a pregnant woman to give birth and then start treating her depression.

The major adverse effect to worry about is serotonin syndrome, particularly when combined with other medications with serotonin blockade, such as tramadol. Clinically, the patient will be haemodynamically unstable and have clonus.

Selective serotonin reuptake inhibitors

Fluoxetine, citalopram, sertraline, paroxetine

Selective serotonin reuptake inhibitors (SSRIs) are the first-line antidepressant, which you will see often. These work by blocking serotonin's reuptake into the terminal button, therefore keeping serotonin in the synapse for longer.

Pregnancy

Sertraline has the lowest placental exposure, though fluoxetine is currently preferred. SSRIs have been linked to persistent pulmonary hypertension of the neonate and cardiac septal defects, though risks are very low. Paroxetine is a higher risk of neonatal adaptation syndrome.

Lactation

Sertraline and paroxetine have the lowest secretion into breast milk.

Selective serotonin and noradrenaline reuptake inhibitors

Venlafaxine, duloxetine

Selective serotonin and noradrenaline reuptake inhibitors (SNRIs) block serotonin's reuptake, similar to how the SSRIs do. However, they also block the noradrenaline transporter that, by a complicated neurophysiological effect, increases both noradrenaline and dopamine levels in the synapse.

Pregnancy

Venlafaxine leads to an increased risk of neonatal adaptation syndrome.

Lactation

Venlafaxine is secreted in breast milk, though may be useful to prevent adaptation syndrome in newborns at risk.

Tricyclic antidepressants (TCAs)

Amitriptyline, nortriptylline, imipramine, doxepin

TCAs also inhibit serotonin and noradrenaline reuptake, similar to SNRIs. However, TCAs also hit multiple other receptors leading them to be more toxic than the SSRIs and SNRIs. They are now second-line medications owing to toxicity, which is particularly undesirable in a potentially suicidal population.

Pregnancy

Fetal exposure is high, though with no apparent adverse effects in the child long term. Amitriptyline and imipramine preferred.

Lactation

All secreted though are reasonably well studied with no apparent adverse consequences for infants. The exception is doxepin, where there have been two case reports of poor outcomes.

Mood stabilisers

These are the medications that are most risky in pregnancy and lactation. They are mostly used in bipolar affective disorder and schizoaffective disorder, though may be used in a range of mental illnesses with affective components or to augment other medications. The type prescribed depends on the predominant symptoms that the patient experiences. None of these are very safe in pregnancy or lactation, and the patient may be switched to a combination of antipsychotic and/or antidepressant medication to minimise risks.

Lithium

This medication was discovered by an Australian in the 1940s, and is particularly good at treating mania. The mechanism is unknown, with many theories proposed. Its major problem is a narrow therapeutic window, meaning that regular blood levels are required to minimise toxicity.

Pregnancy

Lowest risk mood stabiliser in pregnancy, though still has multiple risks including increased risk of Epstein's anomaly if taken in the first trimester.

Lactation

Not recommended owing to risk of neonate toxicity.

Anti-epileptic medications

Sodium valproate, lamotrigine, carbamazepine

Again the mechanisms for treating mood are mostly unknown with these drugs, though there are proposed theories. The doses required to treat mood are generally lower than those to treat epilepsy. Blood levels are still monitored, but are often more a show of compliance rather than owing to toxicity concerns. A major adverse effect to be wary of is the risk of Stevens-Johnson syndrome with lamotrigine.

Pregnancy

Avoid. Sodium valproate and carbamazepine are particularly risky for neural tube defects, with sodium valproate considered the most teratogenic. Ensure prophylactic folic acid if prescribing. Lamotrigine has been associated with cleft palate.

Lactation

Not recommended. The safest is sodium valproate, though there is a theoretical risk of hepatotoxicity.

Anti-psychotics

These are true to their name: they treat psychotic symptoms such as hallucinations, delusions and thought disorders. This is regardless of the cause of psychosis; they can be used in conditions such as delirium and depression as well as schizophrenia.

The major adverse effect to look out for is neuroleptic malignant syndrome (NMS), which is life threatening. Patients are haemodynamically unstable with a significant increase in muscle tone. They also all lower the seizure threshold.

Atypical/second-generation antipsychotics

Risperidone, olanzapine, quetiapine, amisulpride

These are much more commonly prescribed than their older counterparts the typical antipsychotics owing to their decreased motor adverse effects. However, they have increased risk of metabolic adverse effects compared with their typical counterparts. Mechanisms of antipsychotics are complex, as per the complex symptoms of psychosis. Atypicals work by blocking a combination of serotonin and dopamine receptors, controlling the amount of dopamine and serotonin in the brain.

Pregnancy

Antipsychotic discontinuation syndrome can occur in the neonate. Typical antipsychotics are safest generally. However, olanzapine and quetiapine are the safest of the atypicals, with most poor outcomes apparently associated with maternal obesity as per the metabolic adverse effects of these drugs. Avoid depot medication.

Lactation

Safest are olanzapine and amisulpride.

Clozapine

This is a type of atypical antipsychotic, but worthy of mention in its own right. This is our most risky, but also most effective antipsychotic. There are multiple serious adverse effects associated with it such as spontaneous agranulocytosis, toxic megacolon and myocarditis. If someone is prescribed clozapine they are likely very mentally unwell without it and stopping it should be avoided.

Pregnancy

Can have higher blood levels in the fetus than in the mother herself therefore theoretically putting baby at risk of the adverse effects above.

Lactation

Secreted in breast milk, avoid breastfeeding to minimise the baby suffering the serious adverse effects described above.

A final word

Please remember in regard to pregnancy and lactation, one must always balance the risks and benefits of psychiatric medications. A mentally unwell mother is unlikely to bond appropriately with her baby, leading to a possible abnormal attachment pattern in the child and future personality problems. ECT may be a safe option that will get mothers well sooner and enable them to bond with the baby earlier. Alternatively, giving a baby formula or taking the risk of continuing a psychiatric medication in pregnancy may lead to a better outcome for the baby. Getting lactation consultants on board with these plans can minimise guilt for mothers where their need for medication means that breast isn't best.

Of course, this is merely a summary of a few of our medications. Contact your friendly liaison psychiatrist or maternal mental health expert if a less common medication comes up, or if you have further questions.

Further reading

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Drugs for inflammatory bowel disease during pregnancy

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A team approach involving the obstetric service and gastroenterologist, with frequent review, is critical to the successful management of pregnancy in inflammatory bowel disease patients.

Drug therapy for pregnant women with inflammatory bowel disease (IBD) is an essential part of the management of active disease and in maintaining remission. In general, the same drug classes are used in both Crohn's disease and ulcerative colitis. With the exception of methotrexate, none of the main classes of drugs used in inflammatory bowel disease have been shown to cause birth defects or other adverse infant outcomes when used before conception, during pregnancy and during lactation.[1,2,3]

Unfortunately, many women with IBD stop their medication with the potential for a flare in disease activity. Active disease is associated with worse maternal and infant outcomes. In one study, fulminant colitis requiring colectomy during pregnancy resulted in a 50 per cent infant mortality.[4] The importance of early intervention in the event of a flare in disease activity indicates the need for a team approach with frequent review by both the obstetrician and gastroenterologist.

The five main classes of drug used in IBD to maintain remission and treat active disease are: 5-aminosalicylate drugs (5ASA); corticosteroids; thiopurines; tumour necrosis factor (TNF) antibodies; and methotrexate.

5ASA and prednisolone can be administered both orally and as a rectal foam or liquid enema. The thiopurines and TNF antibodies are immunosuppressant drugs and usually reserved for patients who have frequent or severe flares of activity or who are dependent on corticosteroids to maintain remission. In addition to these drug classes, some patients with Crohn's disease are on methotrexate to prevent relapse, an FDA category X drug that should be stopped six months before conception and for the duration of pregnancy. Antibiotics are often required during a flare of Crohn's disease and ciprofloxacin should be avoided because of its potential for cartilage damage and metronidazole avoided in the first trimester as a potential mutagen. Many patients with IBD are iron deficient and should have ongoing iron replacement therapy and monitoring. Vitamin B12 supplements may be required if there is extensive ileal disease or previous resection.

The 5ASA compounds include sulfasalazine, enteric-coated mesalazine, balsalazide and olsalazine. 5ASA has molecular similarity to salicylic acid and because it is readily absorbed from the proximal gut it needs either enteric-coating or covalent binding to a carrier molecule (sulfasalazine, balsalazide, dipentum) where it is split by bacterial action in the distal ileum and colon to release the active drug. These drugs are very important, reducing the relapse rate in ulcerative colitis by 50 per cent, and are useful in acute disease. 5ASA drugs are also used in Crohn's disease though they are less efficacious. Salazopyrin has been associated with folate deficiency (and reversible infertility in men) so folate supplementation before and during pregnancy in patients on salazopyrin is recommended. Regular blood counts are also recommended in all patients on salazopyrin in the non-pregnant population and these should continue during pregnancy.

The corticosteroids are the main therapy for acute flares of IBD, either as oral prednisone or intravenous hydrocortisone. Common mistakes during a flare of IBD are to delay the commencement of steroids, prescribe an inadequate dose and to attempt to wean off steroids too quickly. During pregnancy there is a possible small risk of cleft palate during the first trimester and excessive weight gain, hypertension and diabetes later in pregnancy. In spite of these risks, it is critical that a flare in disease be brought under control rapidly to reduce the risk of adverse fetal outcome.

The thiopurines 6-mercaptopurine (Puri-nethol) and azathioprine (Imuran) are purine antimetabolites principally affecting lymphocyte function. They have a slow onset of action over two or three months and are used to reduce the risk of relapse and to enable steroid-dependent patients to be weaned from steroids. Allergic reactions, pancreatitis and drug hepatitis can be seen early after their introduction and late side effects include pancytopaenia, increased risk of infection, skin cancer and lymphoma. Regular monitoring of blood counts is advised. Live vaccines should not be administered to patients on these drugs and the efficacy of a killed vaccine can be reduced. There is no evidence of any increased risk of teratogenicity or other side effects in neonates exposed to these drugs. There is negligible excretion into breast milk.

There are two currently available TNF blockers available for use in IBD: infliximab (Remicade) and adalimumab (Humira). These agents are generally reserved for patients who are refractory to other medical therapies although there is a trend towards earlier use in Crohn's disease in an attempt to prevent scarring of the bowel from repeated bouts of inflammation. They are powerful immunosuppressants with the main hazard being bacterial sepsis. Infliximab and adalimumab are both immunoglobulins that will be transferred across the placenta in the last trimester and, consequently, exposed infants should not be given live vaccines (such as rotavirus) up until seven months of age. There may be some reduction in efficacy to killed vaccines during this time. A risk benefit assessment should be made as to whether or not these biologicals should be continued in the third trimester. Breastfeeding is entirely safe in patients on TNF blockers.

Increasing therapy for a possible flare in Crohn's disease during pregnancy requires careful assessment. Assessment of the activity of Crohn's disease is not always straightforward and relies on history, examination, blood inflammatory markers (particularly the CRP) and imaging. Magnetic resonance imaging enterography without gadolinium is to be preferred to computed tomography (CT) scanning during pregnancy, but CT scanning should not be withheld from a patient with Crohn's disease in an abdominal crisis. Colonoscopy should obviously be avoided during pregnancy unless it would result in a critical management change. Patients with active perianal disease or previous pouch surgery are often advised to have caesarean section to avoid the disaster of perineal injury and incontinence.

In summary
Medications used in IBD – with the exception of methotrexate – should be continued during pregnancy to prevent relapse and these medications are safe during breastfeeding. A flare in disease activity should be managed promptly and aggressively to prevent poor neonatal outcome. Frequent reassurance about the safety of maintenance drug therapy is important.

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Rheumatology medications

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A summary of newer prescribed rheumatology medications, their mechanism of action and safety profile.

The treatment of rheumatoid arthritis (RA) has advanced considerably, with newer targeted therapies available if traditional synthetic disease-modifying anti rheumatic drugs (DMARD) treatment failed. The treatment goal is to achieve clinical remission, if possible, and at least low disease activity. The new class of therapies is biologic DMARDs (bDMARDs). The bDMARDs available in Australia are adalimumab (ADA), etanercept (ETN), golimumab (GOL), infliximab (IFX), certolizumab (CTZ), abatacept (ABA), tocilizumab (TCZ) and rituximab (RTX). Some of these are used in other inflammatory conditions, such as psoriatic arthritis. bDMARDs are expensive and strict guidelines apply to their use on the PBS. As rheumatoid arthritis affects one per cent of the population, these DMARDs (see Table 1 on the following page) are used for both all age groups, including those of reproductive age.

The bDMARDs are used because they are effective not only by reducing symptoms, such as pain and stiffness, but also by controlling the underlying inflammation, which had shown to reduce joint destruction. The current bDMARDs act by blocking or reducing the activation of different immune system pathways that can lead to inflammation. These include pro-inflammatory cytokines such as tumour necrosis factor (TNF), Interleukin (IL) or actions through B- or T-lymphocytes to reduce the cytokine production. Most of these bDMARDs are monoclonal antibody

Table 1. Commonly used DMARDs.

Drug	Considerations in pregnancy
Non-biologicals	
Hydroxychloroquine (Plaquenil)	Large retrospective studies show no increase in risk of miscarriage, stillbirths or congenital malformation. This is not immunosuppressive.*
Leflunomide (Arava)	Associated with birth defects, hence contraception is essential. Its major metabolites can remain in serum for up to two years and elimination of this drug can be accelerated with cholestyramine until active metabolite is <0.02 mg/dl. Watch liver function.***
Methotrexate (Methoblastin)	Contraception essential and needs concurrent folic acid supplementation, teratogenic with risk of spontaneous abortion. The likelihood of fetal malformation is dose dependent. ***
Sulphasalazine (Pyralin)	Well-tolerated, but can cause low white cell count. Does not seem to majorly increase the risk of adverse fetal outcome especially if adequate folate supplement and lower dose used.*
Corticosteroid (prednisone/solone)	Animal studies show increase oral cleft palate and there are some case reports in humans. It is safer in smaller effective dose and encourage less than 10mg if possible. **
Azathioprine (Imuran)	Malformation in animal and cohort studies showed increase in IUGR/prematurity although some data has showed no increase of poor pregnancy outcome.**
*Biologicals**	
Adalimumab (Humira)	Data are limited, animal model has not shown increase risk. Usually cease three to six months before conception.**
Etanercept (Enbrel)	Takes three weeks for the medication to be totally clear from system. Report of association with vertebral, anal, tracheal-oesophageal, renal and limbs (VACTERL) birth defects noted, but follow-up studies have not conclusively support this.**
Golimumab (Simponi)	Pregnancy data not available. Animal data shown no adverse outcome.#
Infliximab (Remicade)	Data are limited. Does cross placenta and detected up to six months in infants. Cease 3–6 month prior to conception.**
Certolizumab (Cimzia)	Pegylated Fab fragment with no Fc portion and therefore crossed placenta by slow diffusion. Level in infant has been measured <75 per cent than maternal level. No fetal harm in animal studies.#
Abatacept (Orencia)	Pregnancy data not available in humans. Shown to cross placenta and not teratogenic in animal but some alteration in the immune system with thyroid inflammation.#
Tocilizumab (Actemra)	Pregnancy data are limited. Based on animal data may cause fetal harm.#
Rituximab (Mabthera)	Pregnancy data are limited. Concentration detected in the umbilical cord. Cases report on lymphoma patient has shown no adverse outcome.#

*All drugs need to be reviewed in terms of the risk or benefit to individual patient and discussed with patient. * Minimal risk of fetal adverse outcome ** selective use allowed if benefit more than risk *** high risk of fetal adverse outcome # unknown risk of fetal adverse outcome.*

(most humanised except IFX and RTX, which are also chimeric) with some as fusion proteins (ETN).

These medications are immunosuppressive, hence the importance of screening for infections such as tuberculosis and viral hepatitis before initiating treatment. In major elective surgery, although there is little evidence to guide bDMARD therapy modification, the current recommendation is treatment cessation prior to surgery owing to some reports of increased risks of infection. The timing of the cessation interval depends upon the half life. As a general rule of thumb, this is usually about three times the half life. For example, ETN has a half life of 3.3 days, so the suggestion is to withhold this for about two weeks prior to surgery. Other bDMARD, will need to be ceased for between four and eight weeks. The medication can be restarted once wound healing is going well and there is no active infection. The bDMARDs don't usually interact with other medications, though caution is required with those that interfere by CYP450 enzyme such as warfarin. Use of simple analgesics and NSAIDs for postoperative pain control is not usually a problem.

With respect to pregnancy, the current recommendation is to cease treatment prior to pregnancy, with timing dependent on the type of bDMARD. If unplanned pregnancy occurs, the medication should be discontinued and the reported cases so far have been reassuring. Much of the risk also lays with the active rheumatoid disease itself hence this need to be controlled prior pregnancy. As always, the risk and benefit between the disease and medication use will need to be reviewed and discussed with the individual prior to pregnancy planning and decision. Some data have shown the presence of bDMARD in the newborn during first three to six months when the mother was exposed to bDMARD. As such, the recommendation is to avoid live vaccine in first six months of infancy.

Hypertension

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A summary of the main anti-hypertensive therapies, their mechanism of action, side effects and associated complications.

Hypertension is the most common condition seen in primary care, so women with gynaecological problems frequently receive concurrent anti-hypertensive therapy. Chronic hypertension is associated with serious health risks such as myocardial infarction, stroke and renal failure. For these reasons, surveillance, early detection and appropriate treatment are core components of primary healthcare.

There had been considerable variation in approaches to treatment of chronic hypertension, prompting development of the Heart Foundation Guidelines 2008 (further updated in 2010). These guidelines were written, released and endorsed by the Royal Australian College of General Practitioners (RACGP) and form the basis of therapy planning by many general practitioners.

The guidelines emphasise the importance of ongoing lifestyle modification and assessment of the individual patient's overall cardiovascular risk profile. Pharmacological management of blood pressure is recommended with blood pressure targets of less than 140/90 for most patients, less than 130/80 for patients with evidence of end organ damage, including diabetes, and less than 125/75 for patients with proteinuria.

The management guidelines suggest that using relatively low doses of individual anti-hypertensives helps to minimise side effects and, for this reason, more commonly patients will be taking several medications to manage their hypertension. The details of Heart Foundation-recommended therapies are summarised in Table 1.

Some patients may still be prescribed beta-blockers (atenolol, carvediolol, metoprolol and oxprenalol) as a secondary agent, particularly if there is established cardiovascular disease. These are no longer recommended as monotherapy, owing to adverse outcomes. In a surgical setting, their use is associated with an increased risk of bradycardia and hypotension. The necessity to cease beta-blockers perioperatively is controversial and this class should not be stopped abruptly, especially in women with ischaemic heart disease.

Table 1. Anti-hypertensive treatments in common use.

Drug class	Mechanism of action	Commonly used drugs	Common side effects	Potential effects during surgery
ACE inhibitors (ACE-I)	Block conversion of angiotensin-I to angiotensin-II, inhibit breakdown of bradykinin.	Captopril (Capoten) Enalapril (Vasotec) Perindopril (Coversyl) Ramipril (Altace)	Cough, hypotension, headache, fatigue, nausea, hyperkalaemia and renal impairment	Excessive hypotension may occur during anaesthesia and postoperatively.
Angiotensin-2 receptor antagonists	Competitively block binding of angiotensin-II to its receptors, causing vasodilation and sodium reabsorption.	Candesartan (Atacand) Irbesartan (Avapro) Telmisartan (Micardis)	Dizziness, headache, hyperkalaemia	Not to be co-administered with an ACE-I.
Calcium channel blockers (CCBs)	Block inward current of calcium into cells of vascular smooth muscle, myocardium, and cardiac conducting system.	Amlodipine* (Norvasc) Felodipine* (Plendil) Nifedipine* (Adalat) Diltiazem† (Cardizem) Verapamil† (Isoptin)	Peripheral oedema, headache, fatigue, dizziness, flushing, nausea, bradycardia, constipation *Pulmonary oedema, hypotension, and tachycardia †Associated with A-V block	Several of these are contraindicated in combination with certain antibiotics and anti-convulsants. Careful check of interactions required.
Thiazine diuretics	Moderately potent diuretics, inhibiting the reabsorption of Na^+ and Cl^- in the proximal convoluted tubule, increasing K^+ secretion and inducing vasodilation.	Hydrochlorthiazine (Microzide) Indapamide (Natrilix)	Electrolyte disturbances, orthostatic hypotension, hyperuricaemia	

Common dermatological drugs in pregnancy

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A review of the safety profile of common dermatological medicines when used in pregnancy.

Skin problems are common during pregnancy and obstetricians will encounter many patients using dermatological medicines. As with any medicine, they should only be taken if the expected benefits to the mother are greater than the risk to the mother and the baby. Equally, severe dermatological conditions should not be left untreated because of concern about taking medicines during pregnancy as the health of the mother and baby can be compromised by this. This is not an exhaustive list, but an overview of the common medications used in treating dermatological conditions.

The categories of medicines commonly used in dermatology will be discussed. Reference will be made to the Australian TGA classification for prescribing medicines in pregnancy. However, classification does not necessarily reflect risk to the fetus.

Immunosuppressants

Patients using these medications for dermatological conditions, except for topical and oral steroids, will usually be under the care of a dermatologist.

Topical steroids (Category A)

Betamethasone, clobetasol, trimacinalone, hydrocortisone, methylprednisolone, clobetasone

These are the most common dermatological medications that are used in pregnancy. Even strong topical steroids, such as clobetasol, are safe for use in pregnancy. They are prescribed for many skin conditions, such as eczema, psoriasis and papular urticaria of pregnancy.

Patients are often fearful of using these medications and will significantly under use them so that the dermatological condition does not resolve. Prolonged and extensive use should be discussed with a dermatologist or an obstetric physician.

Systemic steroids (Category A)

Systemic steroids can be used orally or intramuscularly. They are used to treat atopic dermatitis and autoimmune conditions such as pemphigoid. Pemphigoid gestsationis is treated with oral steroids. They are not teratogenic, but have other risks such as gestational diabetes and premature rupture of membranes.

Azathioprine (Category D)
Azathioprine is mainly used to treat atopic dermatitis. There is good data on use in pregnancy and it is not thought to be teratogenic.

Cyclosporin (Category C)
Cyclosporin is also used to treat atopic dermatitis and some rare conditions such as pyoderma gangrenosum. It is not teratogenic and has been used safely in thousands of transplant pregnancies.

Methotrexate (Category D)
Methotrexate should be avoided by both males and females for at least three months prior to conception. It is an abortificient and is teratogenic. Neonatal immunosuppression can occur when taken in later pregnancy.

Antihistamines

First-generation: chlorpheniramine (Category A), promethazine (Category C); second-generation: loratidine (Category B1), cetirizine (Category B2)
Antihistamines are used for treating allergic conditions, such as urticaria. They may also be prescribed in some cases of atopic dermatitis or other pruritic conditions.

Antihistamines are regarded as safe for use in pregnancy. There is more safety data available about first-generation antihistamines than second generation, but these antihistamines are non-sedating. Antihistamines may reduce milk production and can result in drowsiness of the infant so are best avoided during breastfeeding.

Antifungals

Antifungal treatments are available as both oral and topical preparations. They are used to treat fungal infections such as dermatophytes (tinea) or vulvovaginal candidiasis.

Topical antifungals such as miconazole, terbinafine and clotrimazole are safe for use in pregnancy.

Oral antifungals

Fluconazole (Category D); itraconazole (Category B3)
It is advised that oral azole antifungals should be avoided in the first trimester.

Terbinafine (Category B1)
The risks of terbinafine are currently unknown in pregnancy so avoidance is the current recommendation.

Antibiotics

Tetracyclines (Category D)
This is a very common medication used in dermatology, but is not recommended for use during pregnancy as it discolours growing teeth and may cause enamel hypoplasia.

Erythromycin (Category A)
Erythromycin may be used to treat both acne vulgaris and skin infections. It is safe for use in pregnancy.

Penicillin (Category B1)
Penicillin and flucloxacillin may be used to treat skin infections and are safe to use during pregnancy.

Antivirals

Acyclovir (Category B3)
Acyclovir is normally prescribed to treat herpes simplex or varicella zoster infections. It can be used safely in pregnancy.

Antiparasitics

Permethrin (Category B)
This is a topical insecticide used to treat scabies. It is safe for use in pregnancy.

Ivermectin (Category B3)
Ivermectin is an antiparasitic. It is used to treat severe scabies unresponsive to topical treatment. There are more than 300 reports of safe use in pregnancy in the first trimester.

Biologics

Biologics are relatively new medicines that interfere with specific components of the autoimmune response. They are used in dermatology to treat psoriasis. There are a large number of medicines in this category but the ones below are licensed for use in New Zealand. They are administered by subcutaneous injection at various intervals.

Patients on these medicines will have severe psoriasis so the risk to benefit ratio is especially important to consider. These patients will usually be under the care of a dermatologist.

As these medicines are relatively new, there is not much experience with treating pregnant women and so minimal data is available. Infection, including unusual opportunistic infection, is one of the adverse effects associated with these medicines:

- **Adalimumab Category C**
- **Ustekinamab Category B1**
- **Infliximab Category C**
- **Etanercept Category B2**

Skin cancer treatments

Imiquimod (Category B1)
Imiquimod is a topical preparation used to treat actinic keratoses and basal cell carcinomas. It has been used in pregnancy with no evidence of teratogenicity.

Fluorouracil (Category D)
Fluorouracil is used in topical form to treat actinic keratoses. Oral exposure in the first trimester has been found to be teratogenic. There are isolated reports of adverse effects with topical use. It is not recommended for use during pregnancy.

Other

Hydroxychloroquine (Category D)
Hydroxychloroquine is mostly used to treat lupus erythematosis, both cutaneous and systemic. It is not teratogenic and there have been many reports of its safe use in pregnancy.

Calcipotriol (Category B1)
Calcipotriol is a topical vitamin D derivative used to treat psoriasis. It is considered safe for use in pregnancy at recommended doses.

Dapsone (Category B2)
Dapsone is used in dermatology to treat autoimmune conditions such as dermatitis herpetiformis, which is associated with coeliac disease. It has been used extensively in pregnant women to treat malaria without adverse fetal effects.

Coal tar products
These are topical preparations used to treat psoriasis. Their safety is unclear as teratogenicity has been reported in animal studies, although not in humans. They are probably safe for second and third trimester use.

Psoralens
These are used in combination with UVA for treating psoriasis. Psoralens are mutagenic and are not recommended during pregnancy although no adverse fetal outcomes have been reported for patients becoming pregnant during PUVA treatment.

Medicines contraindicated in pregnancy

Isotretinoin (Category X)
Isotretinoin is used to treat acne vulgaris. Its teratogenic potential is well known and it is contraindicated in pregnancy.

Acitretin (Category X)
Acitretin is used to treat psoriasis. Women of childbearing age are not commonly on this medication as pregnancy should be avoided for two years owing to its slow elimination.

Complementary therapies

Very many pregnant patients will be using complementary therapies to treat various dermatological conditions. While most of these are safe in pregnancy, there is often no safety data available. Enquiry regarding these medicines is always prudent.

Summary

Women with skin conditions can and do become pregnant. Misconceptions about medications can result in poor care for women with dermatological problems. Referral to a dermatologist or obstetric physician can be helpful in the treatment of pregnant women with dermatological conditions.

Acknowledgement
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Thyroid medication

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Thyroid disease in pregnancy has long been recognised to have serious consequences for both mother and child. The management of thyroid dysfunction in pregnancy has been the subject of recent, comprehensive consensus guidelines published by the American Endocrine Society[1] and is summarised here.

During normal pregnancy, maternal thyroid hormone synthesis increases by 20–40 per cent, compensating for oestrogen-induced increases in thyroid hormone binding globulin and iodide clearance and increased placental de-iodination of thyroxine.[2] A sustained rise in serum total T4 and a fall in serum thyroid-stimulating hormone (TSH) are characteristic of the early stages of pregnancy. Structural homology exists between human chorionic gonadotropin (HCG) and TSH and there is an inverse relationship between serum HCG and TSH in the first trimester of pregnancy. Serum TSH levels decline when serum HCG levels are high and rise after 10–12 weeks gestation. The upper limit of normal for TSH in the first trimester is considered to be 2.5mU/L and in the second and third trimesters 3.0mU/L. Current guidelines recommend measurement of serum total T4 rather than direct immunoassay of serum free T4; levels of total T4 throughout pregnancy are typically 1.5-fold that seen in non-pregnant women.

Maternal T4 is the only source of thyroid hormone for the fetus before 13–15 weeks gestation. Studies of fetal development and at least one outcome study suggest early central nervous system development requires adequate trans-placental T4 transport. Worldwide, iodine deficiency is still the leading cause of preventable fetal brain damage.[3] Iodine deficiency during pregnancy also results in prolonged enhanced thyroidal stimulation and may lead to goitrogenesis in both mother and fetus. It is recommended that women increase their iodine intake to 250μg daily before conception and during pregnancy and breastfeeding. To this end, the National Health and Medical Research Council (NHMRC) currently advises pregnant and breastfeeding women to take an iodine supplement containing 150μg daily.

Overt hypothyroidism has been reported in 0.3–0.5 per cent of pregnancies and overt hyperthyroidism in approximately 0.5 per cent. Subclinical hypothyroidism (serum TSH concentrations above the upper limit of the trimester-specific reference range with normal free T4 levels) occurs in up to four per cent of pregnancies. Maternal subclinical hypothyroidism has been associated, *inter alia*, with an increased risk of pre-term delivery, placental abruption, early pregnancy loss and neonatal respiratory distress. A positive association between the presence of thyroid auto-antibodies and pregnancy loss has also been reported in euthyroid women. One randomised prospective study has documented an increase in pregnancy complications in women without evidence of underlying autoimmune thyroiditis but who have TSH levels of 2.5-5.0mU/L in their first trimester.[4] There is some evidence that correction of hypothyroidism before pregnancy can restore pregnancy outcomes to those of euthyroid women.[5] Despite this evidence, universal screening of healthy women for thyroid disease in pregnancy is not recommended because data are imperfect and conflicting results have been reported. It is recommended, however, that individuals at high risk of thyroid disease be identified before pregnancy and thyroxine treatment commenced if necessary to ensure TSH levels are below 2.5mU/L at conception (see Table 1).

Women taking thyroxine should be educated about changing thyroxine requirements in pregnancy. It is recommended that these women increase their thyroxine dose by 30 per cent until their TSH can be checked. Serum TSH and total T4 measurements should be monitored every four weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation to ensure that the requirements for thyroxine have not changed. TSH concentrations <2.5mU/L should be maintained in the first trimester and <3mU/L in the second and third trimesters. Women with autoimmune thyroiditis who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should have their TSH levels monitored every 4–6 weeks in pregnancy. If overt hypothyroidism is recognised during pregnancy, maternal thyroid function should be normalised as rapidly as possible. Following delivery, maternal thyroxine should be reduced to the pre-pregnancy dose and thyroid function monitored regularly.

If a subnormal TSH is detected during pregnancy, hyperthyroidism must be distinguished from both the normal physiological changes of pregnancy and gestational hyperthyroidism. HCG may act as a weak thyrotropin agonist given its structural homology. In the majority of normal pregnancies, the effects of HCG remain largely unnoticed and thyroid function tests mostly unaltered. Hyperemesis gravidarum (HG), however, is associated with high HCG levels and 30–60 per cent of patients with HG have elevations of serum free thyroid hormone concentrations with a suppressed TSH. Women with HG and elevated thyroid hormone levels generally do not have other clinical evidence of primary thyroid disease, such as Graves' disease. A minor proportion of these patients may have clinical hyperthyroidism, termed 'gestational hyperthyroidism'. Anti-thyroid drug (ATD) treatment should be used with caution in these patients (*vide infra*) but a short course of betablockers for symptom control may occasionally be useful. Desialylation and deglycosylation of native HCG dramatically increases thyrotropin agonist activity and in part explains the thyrotoxicosis that may be seen in women with hydatidiform mole and choriocarcinoma.

Overt hyperthyroidism in pregnancy requires treatment. Available therapy in Australia includes propylthiouracil (PTU) and carbimazole (a pro-drug of methimazole), which are equally effective. Both drugs cross the placenta. Evidence from several studies has associated methimazole/carbimazole use in the first trimester of pregnancy with an increased risk of specific congenital malformations. This has led to the current recommendations that PTU is preferred in early pregnancy.[2] Current guidelines advise changing from PTU to an equivalent dose of methimazole/carbimazole after the first trimester. When changing therapy, TFTs should be re-assessed at two weeks and then at 2–4 weekly intervals. Combined administration of ATD and thyroxine to the mother should be avoided. Trans-placental passage of thyroxine is negligible and maternal administration of thyroxine will not protect the fetus from ATD-induced hypothyroidism or potential congenital malformations. A recent Danish study has cast serious doubt on current recommendations regarding ATD use in pregnancy, reporting a significant association between early pregnancy use of both ATDs and congenital malformations.[6] Reassuringly, use of ATD therapy prior to pregnancy was not associated with congenital malformations. While more studies on the management of hyperthyroidism in pregnancy are clearly needed, until such data are available it would seem prudent to limit the use of ATDs in pregnancy wherever possible. In pregnant women with uncontrolled hyperthyroidism, subtotal thyroidectomy should be considered. The most suitable time for this is in the second trimester. Radio-iodine therapy is contraindicated in pregnant and breastfeeding women. Definitive treatment of Graves' disease in women prior to pregnancy should also be considered.

The fetal thyroid TSH receptor can respond to thyroid auto-antibodies from the second trimester. One to five per cent of neonates born to mothers with Graves' disease have hyperthyroidism owing to the trans-placental passage of stimulating maternal TSH receptor antibodies. Women with active Graves' disease, a history of Graves' disease treated with ablation therapy, a previous neonate with hyperthyroidism or who have previously been documented to have elevated TSH receptor antibodies should be screened for these between 22 and 26 weeks gestation. Women without detectable TSH receptor antibodies and who have not required ATD therapy in pregnancy have a very low risk of fetal or neonatal hyperthyroidism.

The assessment of thyroid nodules detected during pregnancy is similar to that in the non-pregnant population. Thyroid ultrasound is the imaging modality of choice. Fine-needle aspiration (FNA) biopsy should be performed on predominantly solid nodules >1cm in diameter. Nodules between 5mm and 1cm in size should be considered for FNA biopsy if there are suspicious ultrasonographic features or a high-risk history. Nodules that are thought to be hyperfunctioning should not be investigated by radionuclide scanning until after pregnancy and breastfeeding. If thyroid malignancy is detected during pregnancy, although there is no clear evidence that delaying treatment of well-differentiated thyroid cancer until the patient is postpartum worsens outcome, surgery should be offered during the second trimester. For nodules detected during the third trimester, it is reasonable to delay further investigation and treatment until after delivery, unless the nodule is suspected to be an aggressive tumour. In women with previously treated thyroid cancer, or in those with malignant nodules in whom surgery is being delayed until after delivery, it is reasonable to administer thyroxine at sufficient dose to achieve a suppressed but detectable TSH and a free or total T4 level in the upper normal range for pregnancy.

Postpartum thyroiditis (PPT) is thought to be related to the immune rebound phenomenon following pregnancy. This is accompanied by a dramatic rebound in the titre of anti-thyroid peroxidase (TPO) antibodies that reaches a maximum between three and six months postpartum. There is now general consensus that the disease occurs in 5–9 per cent of unselected postpartum women. PPT is characterised by transient hyperthyroidism and/or hypothyroidism, which may occur up to nine months following delivery. The clinical manifestations of the hyperthyroid state in PPT are not usually severe, but the hypothyroid phase may be profoundly symptomatic. Raised levels of circulating anti-TPO antibodies are detected in ten per cent of pregnant women at 16 weeks gestation. Approximately half of these women develop PPT during the first six months after delivery. Women with a history of PPT have a significantly increased risk of permanent hypothyroidism. There is currently insufficient evidence to support an association between PPT and postpartum depression and, despite its prevalence, universal screening for PPT is not recommended. There is a significantly increased incidence of PPT in patients with Type 1 diabetes, Graves' disease in remission and chronic viral hepatitis. In women with these conditions or in whom elevated titres of anti-TPO antibodies have been detected during pregnancy, TSH measurement at three and six months postpartum is recommended. Asymptomatic women with PPT whose TSH is elevated, but remains below 10mU/L, do not necessarily need thyroid hormone replacement. However, these women should be re-tested in four to eight weeks. If the TSH remains elevated at this time, thyroxine should be commenced. Patients who are symptomatic or who are planning a further pregnancy should also be treated.

Table 1. Pregnant women at risk of thyroid disease.

• Over 30 years of age
• Family history of autoimmune thyroid disease/hypothyroidism
• Presence of a goitre
• Presence of thyroid auto-antibodies
• Symptoms or signs of thyroid dysfunction
• Presence of type 1 diabetes or other autoimmune disorders
• History of infertility
• History of miscarriage or preterm delivery
• History of head and neck irradiation or thyroid surgery
• Endemic iodine deficiency

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Anti-epileptic medications

Dr Penny Gordon

A summary of commonly prescribed anti-epileptic medications, their mechanism of action and safety profile.

The management of epilepsy in women of childbearing age is an area requiring careful consideration. The interactions of anti-epileptic drug (AEDs) are numerous and are influenced by pregnancy. A fetus can be compromised from both poor seizure control and from exposure to the teratogenic effects of AEDs. Familiarisation with common AEDs will assist discussion regarding drug choice, dose adjustments and appropriate serum level monitoring.

Pregnancy

As a general principle, women of childbearing age wishing to fall pregnant should be on folic acid 5mg daily before conception and should be continued at least until the end of week 12 of gestation. Throughout pregnancy there are many metabolic changes and it is therefore very important to monitor patients with epilepsy and, in particular, to AED concentrations.

Table 1. Common medications used to treat epilepsy with a particular mention regarding pregnancy and breastfeeding.

Generic name ***Brand names*** **MoA**	**Indications**	**Side effects**	**Pregnancy**	**Breastfeeding**
Carbemazepine *Tegretol, Teril* Sodium channel blocker	Partial seizures, CTCS; can exacerbate generalised absence seizures and myoclonic epilepsy	CNS: diplopia, headache, dizziness, nausea and vomiting Skin: morbiliform rash 5-10%, erythema multiforme and Stevens-Johnson syndrome (individuals from Asian background more at risk of SJS and should be tested for HLA-*1502 before CBZ is initiated) Blood: mild hyponatraemia; mild reversible leukopenia Liver: toxic hepatitis (rare)	Associated with a slightly increased risk of dose-related congenital abnormalities	Compatible in full-term infant
Sodium valproate *Epilim, Valpro, Valprease* Acts via sodium channels as well as enhancing GABA	Primary generalised epilepsy (including absence, tonic-clonic, myoclonic and atonic seizures), and simple and complex partial (focal) seizures	Weight gain, tremor, loss or thinning of hair (usually temporary), menstrual irregularities, thrombocytopenia, acute pancreatitis, hepatitis	Risk of major malformations, which is a dose-related risk Should be avoided if possible in women of reproductive age	Compatible
Lacosamide *Vimpat* sodium channel blocker	Partial onset seizures	Side effects are dose-related CNS: dizziness, headache, diplopia (transient, dose-related) Cardiac: PR prolongation; A-V block; atrial fibrillation, flutter	No adequate data available Avoid if possible	Unknown if lacosamide is secreted in breast milk
Lamotrigine *Lamictal, Lamidus, Lamogine, Lamotrust, Reedos, Seaze, Torlemo* sodium channel blocker	Partial and generalised seizures; can exacerbate myoclonic seizures	CNS: headache, dizziness, diplopia, ataxia, tremor Skin: mild maculopapular rash; Stevens-Johnson syndrome and toxic epidermal necrolysis	Increased risk of oral clefts in 1st trimester (US Pregnancy Register) Serum concentrations fall in pregnancy up until ~32 weeks and with commencement of the OCP and therefore it may be important to monitor serum concentrations and make dose adjustments to control seizures Serum concentration rise in a few days postpartum requiring prompt dose reduction to avoid issues with toxicity	Need to monitor baby for any signs of toxicity as lamotrigine is secreted in significant amounts in breast milk
Phenytoin blocks voltage-dependent neuronal sodium channels	Partial and tonic-clonic seizures; not effective against myoclonic, atonic and absence seizures	CNS: ataxia, nystagmus, dysarthria, somnolence Skin: gingival hyperplasia, acne, hirsutism, facial coarsening	Increased risk of major malformations Increased clearance of phenytoin resulting in potential for seizures and requires regular monitoring of levels during pregnancy as well as postpartum to avoid toxicity	Compatible
Levetiracetam *Keppra, Kepcet, Kevtam, Levecetam, Levitaccord, Levitam* exact mechanism unknown; acts on synaptic vesicle protein 2A	Partial, generalised tonic-clonic, and myoclonic seizures	Dizziness, somnolence, asthenia, emotional lability, nervousness, aggression, irritability and agitation	Unknown teratogenic risk Increased clearance of drug levels during pregnancy but it is not known if this correlates with loss of seizure control	Probably acceptable in full-term neonates as levetiracetam levels secreted into breast milk result in low levels in the neonate, but neonates should be closely monitored
Oxcarbazepine *Trileptal* sodium channel blocker	Partial and generalised tonic-clonic seizures	Similar to that of carbamazepine Hyponatremia can be more severe than that with carbamazepine	Unknown teratogenic risk Increased clearance of oxcarbazepine in pregnancy	Limited available data; probably acceptable with clinical monitoring
Clonazepam *Paxam, Rivotril* Benzodiazepine	Partial and generalised seizures; usually used for refractory seizures and status epilepticus	Sedation, ataxia	No specific pregnancy risks	May cause drowsiness in the neonate; caution with abrupt cessation of breastfeeding due to risk of withdrawal in the neonate
Topiramate *Topamax, Epiramax, Tamate* Various actions on multiple targets including GABA	Absence seizures	CNS: dizziness, ataxia, headache GI: anorexia, weight loss Skin: rash, Stevens-Johnsons syndrome	Unknown teratogenic risk	Limited available data; probably acceptable with clinical monitoring

Contraception

Various antiepileptic medications (see Table 2) can induce the metabolism of oestrogens and progestins via hepatic enzyme induction and can thus decrease the serum levels of contraceptive medications. As a general principle, oral contraceptives containing 50μg of oestrogen will provide effective contraception. Levonorgestrel implants are contraindicated in AEDs, which are known enzyme inducers owing to the high failure rate.[4] There may be similar problems with the progesterone-only pill. Medroxyprogesterone injections appear to be effective, but may need to be given more frequently.[4]

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Table 2. Interactions between antiepileptic drugs and oral contraceptive.

AEDs that reduce serum levels of OC	AEDs with serum levels reduced by OC	AEDs that do not interact with OC
Carbemazepine Lamotrigine Oxcarbazepine Phenobarbitone Phenytoin Primidone Topiramate (>200mg daily)	Lamotrigine Oxcarbazepine Sodium valproate	Benzodiazepines Gabapentin Lacosamide Levetiracetam Pregabalin Vigabatrin Zonisamide

AED, antiepileptic drug; OC, oral contraceptive (Modified from Fast Facts: Epilepsy; Brodie et al 2012).

Uterotonics and tocolytics

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Medications that relax the muscle in the pregnant uterus – tocolytics – or increase uterine contraction – uterotonics – play a vital role in modern obstetric care. To understand their effects and side effects, it is important to have a knowledge of the underlying physiology of uterine muscle activity and how the different agents act on the muscle.

The pregnant uterus is essentially a bladder made of smooth muscle and in later pregnancy receives a blood supply of approximately 500ml every minute. The rhythmic contraction and relaxation of the myometrium during labour is a result of depolarisation and repolarisation of the smooth muscle membranes. These electrical discharges from muscle cells occur in bursts, with spikes of action potentials associated with muscle contractions. Although individual spikes can bring about a contraction, co-ordination of the spikes is required for sustained uterine contractions (see Figure 1). Myometrial cells do not act individually, but are coupled by gap junctions consisting of connexin proteins that group together, providing channels of low electrical resistance. For most of the pregnancy, these gap junctions are sparse, but closer to the onset of labour the number of gap junctions increases almost exponentially, allowing the myometrium to act as a co-ordinated syncytium (see Figure 2).

As the action potential spreads out over the myometrial cell surface, voltage-dependent calcium channels (VDCCs) open, allowing calcium ions to enter the muscle cell. These act on the myofilaments and initiate a contraction. There are a number of different mechanisms that influence myometrial contractility and these are summarised diagrammatically in Figure 3. The expression of VDCCs on the myometrial cell surface is controlled by progesterone. Indeed, progesterone has a number of important roles in reducing activity of the myometrial cells. Progesterone suppresses gene expression of connexins and VDCCs, it reduces synthesis of prostaglandin and up-regulates the nitric oxide (NO) system. Withdrawal of progesterone effects appears to be the major mechanism leading to the onset of labour.

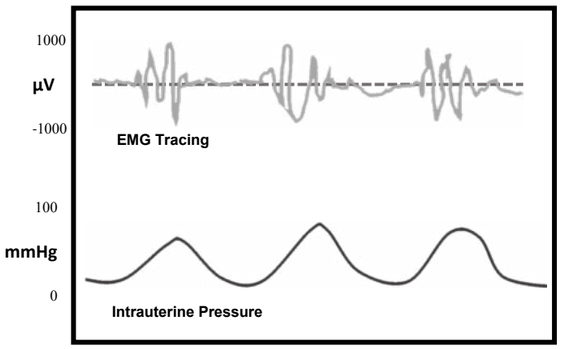

Figure 1. Myometrial action potentials and their relationship to uterine contractions in a typical labour.

Uterotonics

Oxytocin

Oxytocin is a molecule composed of nine peptides (a 'nonapeptide') that is synthesised in the hypothalamus and secreted from the posterior pituitary. It was first isolated and characterised by the American biochemist Vincent du Vigneaud, working at Cornell University Medical College, and the discovery earned him a Nobel Prize. Oxytocin attaches to a specific trans-membrane G-protein-coupled receptor and activation of the receptor initiates contraction of uterine smooth muscle. Oxytocin is very similar in structure to vasopressin and it has a similar renal effect in the kidney, reducing urine output with a potential to cause hyponatraemia.

Ergometrine

Ergometrine is one of the ergot alkaloids, closely related to lysergic acid (LSD). Ergometrine is known to act at dopamine, serotonin and α-adrenergic receptors, but its powerful effect in causing uterine muscle contraction is not associated with any one particular receptor type. It also causes contraction of smooth muscle in blood vessel walls, thus reducing blood loss from the uterus. However, this mechanism is the behind a number of side-effects: nausea and vomiting headache, dizziness and hypertension.

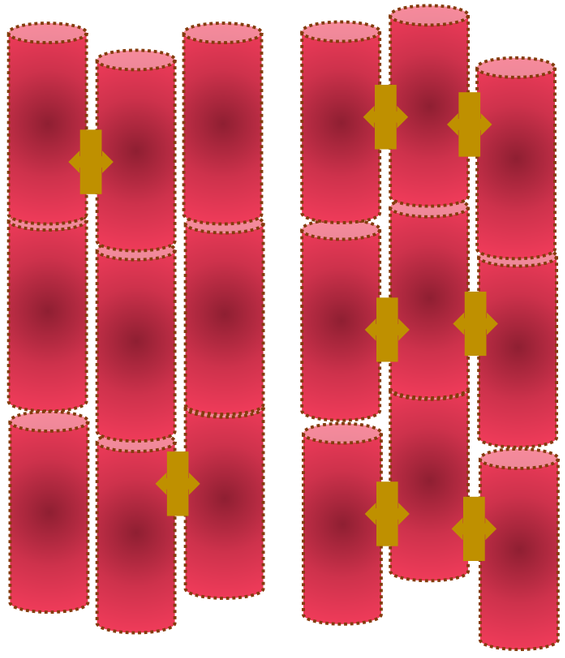

Figure 2. Gap junctions between myometrial cells: left, pre-labour – sparse gap junctions; right, labour – gap junctions form a functional syncytium.

Prostaglandins

Prostaglandins (PGs) are lipid compounds derived from fatty acid precursors. They were first isolated from seminal plasma in the 1930s, and the name 'prostaglandin' reflects their origin. The intermediate product, arachadonic acid (AA) is then metabolised by cyclo-oxygenase (COX) to various prostaglandin products, which in turn act through PG receptors that reduce cAMP in the muscle cell. Prostaglandins of the E2 class are closely associated with labour onset and are released from multiple tissues, and a likely source is the membranes and possibly decidua in labour.

Misoprostol

Misoprostol is a synthetic analogue of PGE1, and was originally developed to prevent gastric ulceration in patients using long-term non-steroidal anti-inflammatory drugs (NSAID) therapy. It acts through PG receptors to initiate uterine contractions. Because it is inexpensive and does not need refrigeration, it is a useful adjunct to other uterotonics in the management of postpartum haemorrhage, as well as early pregnancy loss.

Tocolytics

β_2-agonists

β_2-agonists, such as salbutamol and terbutaline, act on smooth muscle through β_2-adrenergic receptors. The receptors act through stimulatory G-proteins to increase levels of intracellular cAMP. cAMP acts in a number of ways to bring about smooth muscle relaxation: it decreases intracellular calcium concentrations and inactivates muscle filament actions. β_2-agonists also open calcium-activated potassium channels and change the polarisation of smooth muscle cells. The combination of all of these mechanisms leads to smooth muscle relaxation. β_2-agonists affect vascular smooth muscle causing peripheral vasodilatation, which in turn provokes tachycardia, which is one of the major adverse effects of their use. They can also induce peripheral tremors, sweating and a sense of agitation. Prolonged use of β_2-agonists in higher doses has been associated with pulmonary oedema and cardiac arrhythmias.

NSAIDs

NSAIDs act to inhibit the activity of prostaglandin synthatases, enzymes that convert the precursor arachadonic acid to prostaglandins. These enzymes are known as COXs. In pregnancy, the myometrium expresses both COX 1 and COX 2 and these are thought to play a role in the initiation of labour. Uterine muscle cells express receptors for prostaglandins, and release of prostaglandins from the membranes triggers these receptors, causing uterine contractions. NSAIDs inhibit the synthesis of prostaglandins, hence their tocolytic action. A number of studies have shown that NSAIDs are indeed effective as tocolytics, but

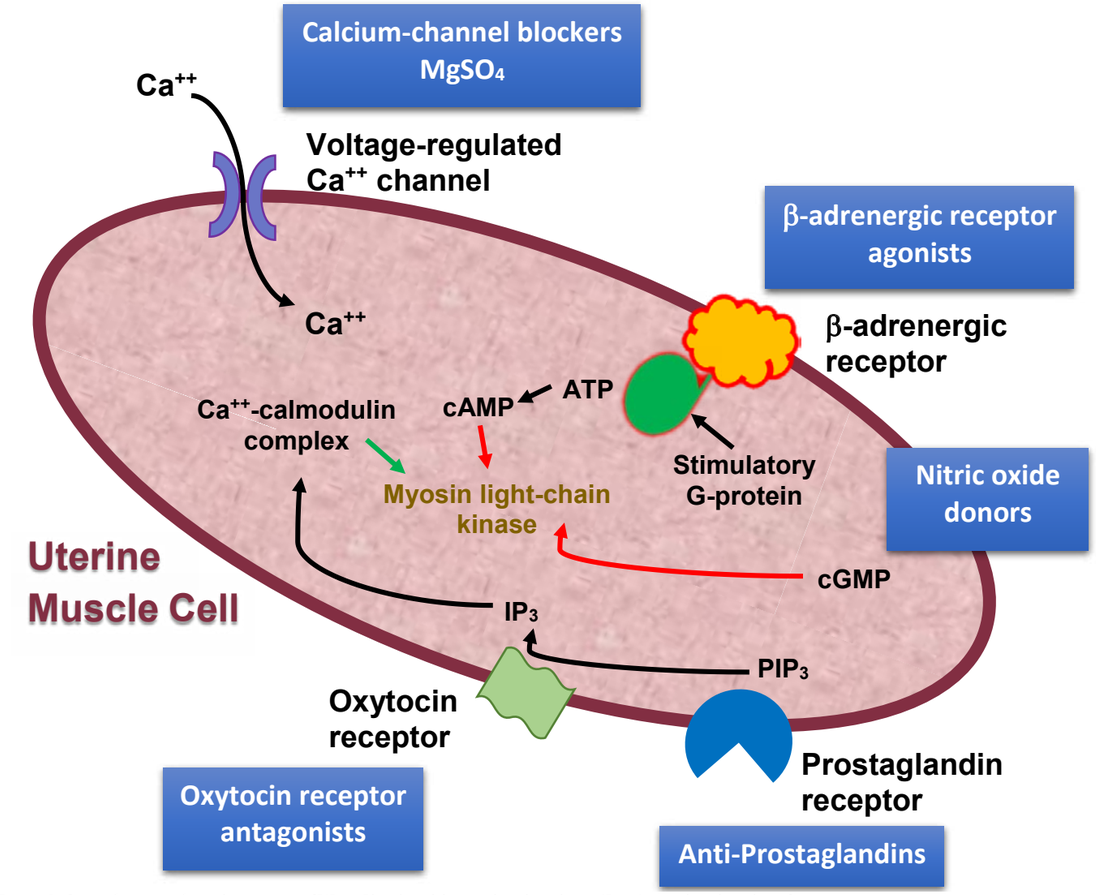

Figure 3. Sites of action of tocolytic agents. [PIP_3 – Phophatidylinositol triphosphate. IP_3 – Inositol triphosphate.]

concerns have persisted about their potential effect on the fetal ductus arteriosis, although this is likely to be a very uncommon complication of their use. Another concern has been the effect of NSAIDs on the gut blood supply and a possible association with necrotising enterocolitis, and this remains to be resolved.

Oxytocin antagonists

Atosiban inhibits oxytocin and its close relative vasopressin. It is a synthetic peptide chain that blocks production of inositol triphosphate (IP3). This action reduces the concentration of intracellular calcium in the myometrial cells and also blocks release of prostaglandins.

Calcium channel blockers

When the action potential crosses the muscle cell membrane it stimulates voltage-gated calcium channels to open, allowing calcium ions to enter the cell. The calcium binds with calmodulin and acts on myosin light-chain kinase to bring about contraction. Calcium channel blockers (CCBs) disrupt the function of the calcium channels and thus cause smooth muscle relaxation. This is obviously useful to reduce myometrial contraction, but has a number of side effects arising from the relaxation of vascular smooth muscle and cardiac muscle. CCBs selectively relax arteries and thus reduce blood pressure, though they have little effect on veins. They can also reduce cardiac output and slow the heart rate.

Glyceryl trinitrate

Glyceryl trinitrate (GTN) is a precursor to its active metabolite nitric oxide (NO), but the exact mechanism of this denitration is still unclear. It is the active metabolite NO that induces formation of cGMP which acts, through a cGMP-dependent protein kinase, to active myosin light-chain phosphatase in the muscle cell. GTN, though its effect of profound and rapid-onset peripheral vasodilatation, can cause hypotension and quite unpleasant maternal headache and these side effects tend to limit its use. However, it can be very useful in affording rapid and very safe uterine relaxation in emergency situations, and this effect is quite short-lived.

Summary

The initiation of uterine contraction is complex and multifactorial. Because there are multiple influences on myometrial function, a number of different approaches to both increasing contraction and tocolysis are available. None are perfect, and each has benefits and potential adverse effects. The selection of these therapies depends upon experience and individual patient circumstances.

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Hyperemesis gravidarum

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A brief outline of the anti-emetics that can be used for the treatment of hyperemesis gravidarum.

Nausea and vomiting of pregnancy is a common medical condition, occurring in about 85 per cent of all pregnancies. The severity can range from mild to severe, beginning between four and nine weeks and worsening between seven and nine weeks; however, up to 15 per cent of women will experience symptoms beyond 16 weeks.

Nausea and vomiting in pregnancy, regardless of severity, can have a negative impact on the overall wellbeing of pregnant women, affecting family, work and social life. The impact on quality of life is global. Women describe feelings of isolation, fatigue, helplessness, depression, anxiety and frustration. Up to 70 per cent feel their parenting abilities are affected. Therefore, it is very important to treat this condition effectively to improve the quality of life of these women.

Clinicians looking after these women are often unsure how to treat them, fearing the use of pharmacologic therapies, owing to the concerns of potential risks to the fetus. Women using anti-emetics as a rule have a better delivery outcome than other women, probably thanks to the effect of a well-functioning placenta. However, severe untreated hyperemesis can be associated with risk to the pregnancy.

Many drugs have been successfully used for the treatment of hyperemesis and are safe and effective. Greater dissemination of this knowledge may enable more women to be effectively treated by their primary clinicians and perhaps reduce referrals to emergency departments and the need for hospitalisation and the resultant anxiety. In this article we review the safety of the common drugs used in this condition.

Dietary advice, reassurance about the wellbeing of the baby, avoidance of triggers and non-pharmacologic interventions such as acupressure are good first-line measures. If these are not successful the following drugs should be considered as additional therapy.

Metoclopramide

Dose 10mg six-to-eight-hourly oral/IV/IM. Ideally, 30 minutes before a meal.

As a stomach motility agent, it may be helpful for those women who suffer from heartburn and indigestion. No evidence of embryo, fetal or newborn harm has been found in human and animal studies. In large cohort studies, metoclopramide during the first trimester of pregnancy did not result in a significant increase in risk of major congenital malformations, miscarriage or stillbirth compared with non-exposed infants. In the largest of these studies, more than 45 000 fetuses were exposed to a median of 40 doses of metoclopramide in utero, beginning at a median gestation of 57 days. Metoclopramide has been used during all stages of pregnancy.

Antihistamines

These are the oldest class of drugs used for the treatment of nausea and vomiting and work by two separate mechanisms: they directly inhibit the action of histamine at the histamine[1] receptor and indirectly affect the vestibular system. These mechanisms combine to decrease stimulation of the vomiting centre. Additionally, it has been proposed that muscarinic receptor inhibition could contribute to antihistamine antiemetic activity.[2] Commonly used antihistamines are cyclizine and promethazine. Others include mecilizine, dimenhydrinate and diphenhydramine. There is no data on using the scopolamine patch for nausea and vomiting of pregnancy.[4] The safety of antihistamines (specifically H1 receptor blockers) was affirmed in a meta-analysis that examined the association between antihistamine use and major malformation. This review of 24 controlled studies, including over 200 000 first trimester exposures, found that H1 receptor blockers appeared to have protective effect on risk of malformations (OR 0.76, 95 per cent CI 0.60-0.94). An association between exposure during the last two weeks of pregnancy to antihistamines and retrolental fibroplasias in premature infants has been reported.[3]

Cyclizine

Dose 25–50mg eight-hourly oral/IV.

This is a piperazine antihistamine. In 111 patients given cyclizine in the first trimester, no increased malformation was observed.[3]

Prochlorperazine

Dose 5–10mg oral/IV/IM six-hourly or 25mg PR twice daily.

This is a dopamine antagonist, Dopamine 2 receptors are implicated in emetic signalling through the chemoreceptor trigger zone.

Although there are isolated reports of congenital defects of children exposed to prochlorperazine in utero, the majority of the evidence indicates that this drug and the general class of phenothiazines are low risk for both mother and fetus if used occasionally in low doses.[3]

Ondansetron

Dose 4mg oral/IV six-hourly.

This is a selective serotonin 5-HT3 receptor antagonist known for its use in treating chemotherapy-related nausea and vomiting. Safety data have increased over the past few years, together with a relaxation of regulations about prescription in New Zealand, hence it is commonly used despite the cost.[1] A randomised double blinded trial was conducted comparing IV ondansetron with IV promethazine for the treatment of hyperemesis gravidarum. No difference was observed between the groups in terms of duration of hospitalisation, nausea score, number of doses received, treatment failures and daily weight. The only adverse effect was sedation in the promethazine group.

Two studies (Einarson et al, 2004 and Asker et al, 2005) found no association between the use on ondansetron and major birth defects, but their sample sizes were small. Anderka et al 2012 showed that their study concurred with the data except for cleft palate, for which a doubling of odds was observed.

Animal data on ondansetron are reassuring as to its safety in pregnancy. Human data on safety or efficacy for treatment of hyperemesis are based on case reports, small series and a historical cohort of 849 women in Denmark, exposed during pregnancy. In this large record linkage study, ondansetron was not associated with an increased risk of major congenital anomalies, miscarriage, low birth weight or small for gestational age babies when used for treatment of nausea and vomiting of pregnancy.[3]

This drug is now very popular with women owing to its effectiveness as well as its availability as a dispersible tablet (wafer form). However, it has a side effect of constipation and patients should be cautioned about this so that steps may be taken to combat it.

Owing to its cost, clinicians should consider alternatives before prescribing ondansetron, bearing in mind that there is benefit in preventing admission to hospital. Ondansetron is available on a three-month supply from retail pharmacies if prescribed by a specialist O and G and annotated that it is for hyperemesis.

Pyridoxine (Vitamin B6)
Dose 25–50mg orally eight hourly.
Is used as a first line in many countries for nausea and vomiting in early pregnancy, however, there are large individual differences in its onset and action. Studies have shown it improves mild to moderate nausea, but does not improve vomiting. In the USA it is used in combination with doxylamine, an antihistamine, and the FDA, in April 2013, approved this combination for the use in pregnancy as there are no risks to the developing fetus.

Adjunctive therapy

Acid-reducing agents

Antacids containing aluminium or calcium are safe in pregnancy and preferable to those containing bismuth or bicarbonate, which may have adverse fetal/neonatal effects. Most experience with pharmacologic acid suppressive therapy in pregnant women has been with the H2 receptor antagonists ranitidine and cimetidine, which appear to be safe in pregnancy.[4]

Vitamins and minerals

If the woman is experiencing vomiting, it is important to replenish low levels of vitamins (especially thiamine), electrolytes and minerals. Thiamine supplementation is with 50mg daily once a day.

Iron deficiency is problematic to treat in this context, if there is concern about anaemia then iron infusion may be considered past the first trimester.

Glucocorticoids

To be considered in severe hyperemesis. The mechanism is unclear and there is paucity of evidence that they are effective and there may be a small teratogenic risk.

Local guideline

A national women's hospital in Auckland has developed a guideline for the management of hyperemesis in pregnancy, based on the evidence and effectiveness of drugs, as well as cost considerations (available online at: http://nationalwomenshealth.adhb.govt.nz/Portals/0/Documents/Policies/Hyperemesis_.pdf). It covers the clinical assessment, investigations and management of hyperemesis, including the use of IV fluids and drugs. This ensures a standardised and rational approach with consistency of care for women. It is instituted at admission to the acute gynaecology area and includes a discharge plan. It encompasses a multidisciplinary approach that encourages the input of a dietician, social worker, physiotherapy and, in the case of intractable hyperemesis, an obstetric physician.

The guideline recommends metoclopramide is used as a first-line agent. Second-line agents are cyclizine, prochlorperazine and ondansetron. All women are prescribed folic acid (5mg), iodine (150μg), pyridoxine (50mg daily) and thiamine 50–100mg orally daily, or intravenously if thought to be at risk of Wernicke's encephalopathy.

Thromboprophylaxis is an important consideration as these women are at a greater risk, owing to dehydration and general reduction in activity.

Discharge planning is emphasised, to prevent readmission. A regime that is sustainable at home must be in place and effective prior to discharge. We believe this has led to safe, effective and holistic care of our women.

Although nausea and vomiting of pregnancy is a self-limiting condition, it is important that, as clinicians, we prescribe safe and effective medication for the women in our care and help them regain a good quality of life while in their first trimester of pregnancy and, for some, throughout their pregnancy.

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Pre-eclampsia

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A short review of the medical therapy for prevention and acute treatment of conditions related to pre-eclampsia.

Pre-eclampsia is a multi-system disorder, unique to human pregnancy, characterised by hypertension with involvement of one or more maternal organ systems (renal/hepatic/haematological/neurological/respiratory) and/or fetal health (growth restriction/abruption).[1] It is a leading cause of maternal and perinatal morbidity and mortality worldwide.[2]

The pathogenesis of pre-eclampsia is incompletely understood, but is related to disturbances in placentation, resulting in generalised inflammation and progressive endothelial damage.[2] Despite advancing knowledge, there is still controversy surrounding the diagnosis, screening, classification of severity and management of pre-eclampsia.[2]

The only definitive treatment for pre-eclampsia is delivery of the placenta and, while prolongation of pregnancy conveys no benefit for the mother, at early gestations this results in an improvement in fetal outcomes. However, this strategy usually results in progression of pre-eclampsia with subsequent placental insufficiency and maternal organ dysfunction, increasing the risks of maternal mortality and morbidity.[1,2] It has been estimated that up to a quarter of women with pre-eclampsia managed expectantly will develop severe morbidity, including HELLP syndrome, abruption, pulmonary oedema and eclampsia, with a mean duration of prolongation of <12 days.[1]

No conclusive evidence exists that treating mild-to-moderate hypertension in pregnancy provides any benefit with regards to critical outcomes, including progression to severe pre-eclampsia, HELLP, eclampsia and maternal or perinatal death.[2,3] The World Health Organisation has recommended treatment of severe hypertension during pregnancy with antihypertensive agents, acknowledging only very low-quality evidence for this recommendation.[2] The rationale for treating severe hypertension stems from the fact that under normal conditions, cerebral blood flow is kept constant by cerebral vasoconstriction in response to increases in blood pressure. However, when systolic blood pressure is increased above the upper limits of auto-regulation (>170mmHg), arterioles dilate creating hyper-perfusion and cerebral oedema, which increases the risks of posterior reversible encephalopathy syndrome (PRES), hypertensive encephalopathy and stroke. This needs to be balanced against the risk of treating hypertension, in particular overly aggressive treatment, with concerns that sudden, significant reduction in blood pressure may result in impaired fetal-placental perfusion resulting in fetal distress.[1] This is particularly important in the compromised fetus with grossly abnormal arterial blood flow.

Pregnancy is associated with a number of physiological changes that may influence drug absorption, distribution, metabolism and excretion. These include an increase in gastric pH, reduction in intestinal motility, increased cardiac output, increased glomerular filtration rate and reduction in plasma albumin levels, as well as modifications in gene regulation that result in changes in enzyme/

Table 1. Acute treatment of severe hypertension/pre-eclampsia.[1,2,5-7]

Medication	Dose		Route and dose	Onset of action (min)	Half-life (hrs)	Adverse effects/ Precautions
	Initial	Maximum				
Labetalol (α and β blockade)	20mg	300mg	IV bolus (over 2 min). Doses of 40–80mg every 10 min till max dose reached.	5	2.5	Bradycardia Hypotension Asthma
Nifedipine (calcium channel blockade)	5–10mg	40mg	Oral. Repeat after 45 min.	5–20	2–4	Headache Flushing
Hydralazine (peripheral vasodilator)	5–10mg	30mg	IV bolus. Repeat after 20 min.	20	0.75–3	Headache Flushing Nausea Tachycardia Hypotension
Diazoxide (peripheral vasodilator)	15–45mg	300mg	IV bolus. Repeat after 5 min.	3–5	28	Flushing Hypotension Hyperglycaemia – caution with diabetics

transporter expression and catalytic function.[4] An example of this is increased function of CYP2D6, resulting increased clearance of both clonidine and metoprolol.[4] However, as the exact magnitude of these effects are as yet unknown and there is an incomplete understanding of pregnancy-related changes on a significant number of medications, it is important to titrate medications to clinical effect rather than be exclusively guided by standard dosing regimens.

While certain guidelines may make recommendations regarding the choice of antihypertensive, there is limited evidence for such recommendations.[2] Certain medications, such as hydralazine, methyldopa, beta-blockers and nifedipine, have been extensively used and therefore are reasonable first-line choices until further evidence becomes available to guide decision-making. Certain agents, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) and sodium nitroprusside, should be avoided owing to concerns regarding their safety profiles.[1,2] ACEi use in mid-to-late pregnancy has been associated with fetal death and neonatal renal failure, and ARBs are avoided owing to their similarities to ACEi. Sodium nitroprusside may cause profound hypotension, methaemaglobinaemia, cyanide and thiocyanate toxicity and transient fetal bradycardia, although many of these reactions are related to prolonged infusions.[1]

The choice of agent and route of administration should be guided by the experience of clinician with the medication of choice, its cost and local availability, and indications and/or contraindications specific to the patient and clinical situation.[1,2] Tables 1 and 2 outline medication options, pharmacological parameters, precautions and contraindications to a number of antihypertensive agents for both acute management of severe hypertension and more prolonged control of hypertension, respectively.

Eclampsia is characterised by the manifestation of generalised seizures, not attributable to other causes, in women with pre-eclampsia and complicates approximately one per cent of cases of pre-eclampsia in developed countries.[1,2]

The aetiology and pathology of eclampsia remains incompletely understood, but is related to central nervous system ischaemia and vasogenic oedema resulting in confusion, seizures and visual loss, with MRI findings typically showing symmetrical white matter oedema

Table 2: Chronic treatment of severe hypertension/pre-eclampsia.[1,2,5-7]

Medication	Dose	Onset of action (hours)	Half-life (hours)	Drug metabolism	Adverse effects/precautions
Methyldopa (centrally acting anti-adrenergic agent)	250–750mg TDS	12–24	1.75	Bioavailability 50% Predominant renal excretion	Sedation Dry mouth, blurred vision Contraindicated in depression Caution in renal impairment
Labetalol (α and β blockade)	100–400mg TDS	1–2	6–8	50% protein bound Metabolised hepatically Metabolites excreted in urine	Bradycardia Headache Bronchospasm – caution in obstructive lung disease
Oxprenolol (β blockade with sympatomimetic activity)	20–160mg TDS	1–2	1–2	Variable bioavailability (20–70%) Metabolised hepatically Metabolites excreted in urine	Bradycardia Headache Bronchospasm – caution in obstructive lung disease Fetal growth restriction
Nifedipine SR (calcium channel blockade)	20–60mg BD	1.5–4	6–11	Hepatically metabolised	Headache Flushing Tachycardia Peripheral oedema Constipation Elimination half-life increased with liver impairment
Hydralazine (peripheral vasodilator)	25–50mg TDS	1	0.75–3	Significant first pass metabolism Low oral bioavailability (35%) Metabolised hepatically Metabolites excreted in urine	Flushing Headache Nausea Lupus-like syndrome Clearance reduced with renal impairment
Prazosin (α blockade)	0.5–5mg TDS	1–3	2–3	Variable bioavailability (40–85%) Metabolised hepatically – some metabolites active	Orthostatic hypotension (most marked after first dose) Clearance reduced in liver impairment
Clonidine (Centrally acting vasodilator)	75–300μg TDS	1–3	5–25	50% hepatic metabolism Excreted renally	Dizziness Dry mouth Constipation Sleep disturbance Clearance reduced in renal impairment

Table 3. Medical therapy for prevention and acute treatment of eclampsia.[1,2,5-7]

Medication	Dose	Mode of action	Onset of action (hrs)	Half-life (hrs)	Adverse effects/precautions
Prevention					
Magensium sulphate	4g IV over 15-20 min followed by infusion (1–2g/hr)	Blocks neuromuscular transmission and reduces the amount of acetylcholine released at the end-plate by the motor nerve impulses	Immediate	(Effect lasts 30 min after IV bolus)	Overdose can cause respiratory depression and bradycardia. Contraindicated in myasthenia gravis and heart block. Caution in renal impairment.
Phenytoin	Loading dose 1g. Maintenance 250mg daily	Anticonvulsant. Inhibits spread of seizure activity in the motor cortex	0.5 – 1	10–15	Metabolised in the liver. Contraindicated in patients with bradyarrhythmias.
Acute treatment					
Diazepam (IV)	2mg/min. Repeated doses every 10 mins to max 10mg	Acts at limbic and subcortical levels of CNS – anxiolytic, sedative, skeletal muscle relaxant and anticonvulsant effects	Rapid	20–40	Sedation. Tolerance. Cross the placenta – may cause hypotension, hypotonia, respiratory depression and hypothermia in the newborn as well as withdrawal if prolonged exposure.
Clonazepam (IV)	1–2mg over 2–5 min				

in the posterior cerebral hemispheres, particularly the occipito-parietal regions. While changes may initially be reversible with treatment, infarction is the end result if untreated.[2]

Table 3 outlines the agents for preventative and acute abortive treatment of eclampsia. Parenteral magnesium sulphate is the drug of choice for preventing eclampsia and, compared with placebo or no anticonvulsant, has been associated with a significant reduction in the risk of eclampsia, with no difference in terms of risk of maternal death, serious maternal morbidity, stillbirth or neonatal death.[2] It is clearly indicated to prevent recurrent eclamptic seizures and is also used as primary prevention in cases of severe pre-eclampsia, especially in the setting of uncontrolled hypertension or neurological symptomatology.

Magnesium sulphate is more effective in reducing the risk of eclampsia than phenytoin, however, phenytoin has a therapeutic role in those patients where the use magnesium sulphate is contraindicated. Magnesium sulphate is renally excreted and its use in patients impaired renal function should be undertaken with caution, with monitoring of serum magnesium concentrations, aiming for levels between 2 and 4mmol/L.[1]

Eclamptic seizures are usually self-limiting, and the use of abortive treatment may not always be required if seizures are witnessed, self-limiting and of short duration. Where seizures are unwitnessed and duration of seizure is unclear, abortive treatment with benzodiazepines (diazepam/clonazepam), while preparing administration of magnesium sulphate, is indicated.[1,2]

Conclusion

Familiarity with the medications used to prevent and treat pre-eclampsia and eclampsia in the maternity patient is essential, including their dosing, pharmacokinetics and potential adverse effects. The information provided, in particular with regard to dosing schedules, is meant as a guide and should be used in conjunction with local guidelines and clinical judgement.

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Magnesium sulphate

The small molecule that is making a big difference.

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As molecules go, magnesium sulphate ($MgSO_4$) had a pretty glamorous start. The story goes that early in the 17th century in the district of Epsom in England, a local farmer found that his cattle were refusing to drink from his well. The farmer tried the water himself, noted that it was bitter and found that the springs all around the Epsom region shared this bitter taste. However, Epsom spring waters were thought to possess healing powers and the town became a spa town. Chemist Nehemiah Grew found that boiling down the spa water yielded a salty residue he named 'Epsom salt', for which he obtained a Royal patent. In 1755, Sir Humphrey Davey isolated and identified Epsom salt as magnesium sulphate, naming the element magnesium after the region of Magnesia in Thessaly, Greece.

> 'Incredibly, after a century of use in obstetrics, the exact mechanism of action of magnesium sulphate remains unclear.'

We now know magnesium is one of the most abundant substances in the body, participating in literally hundreds of metabolic processes, from glucose metabolism to DNA synthesis. Our intake is from green leafy vegetables, wholegrains and nuts, and magnesium is excreted renally. Magnesium homeostasis is closely linked to that of potassium and calcium. During pregnancy, measureable levels of magnesium may vary markedly. The physiological haemodilution of pregnancy and changes in the volume of the extracellular space can reduce magnesium concentrations in serum and this can be further altered with nausea and vomiting in pregnancy, resulting in gastrointestinal losses.

Use of magnesium sulphate in obstetrics

A century ago, eclamptic seizures were relatively common in countries such as the USA. Few therapeutic options were then available for treatment of convulsions and the use of intraspinal magnesium sulphate had already been popularised in the treatment of status epilepticus. Taking a lead from this, obstetricians in the USA adopted the use of intravenous magnesium sulphate to treat eclamptic seizures and noted its effectiveness and dramatic falls in the mortality of the condition. During that era, magnesium sulphate was often used as part of a cocktail of medications deployed to manage eclampsia and it was not until after the Second World War that research was done to establish the fact that it was good for managing eclampsia, but not so good for management of hypertension.

The oral absorption of magnesium sulphate is notoriously unpredictable, so parenteral routes – either intravenous or intramuscular – are the only reliable methods of administration. Standard solutions contain 50 per cent magnesium sulphate as a heptahydrate in sterile water, with five grams of magnesium in 10ml of the solution. The absorption is rapid, with peak serum levels achieved within one hour of intramuscular injection, and almost immediately following intravenous use. Owing to its pharmacology, it must be used with extreme caution in patients with heart block and myasthenia gravis.

Incredibly, after a century of use in obstetrics, the exact mechanism of action of magnesium sulphate remains unclear. Magnesium is a calcium antagonist at the motor endplate of nerves in many types of muscle, including cardiac muscle. Calcium is thus integral to smooth muscle contraction and calcium inhibition results in muscle relaxation, including that of the myometrium. Increased magnesium levels appear to disrupt the balance between calcium and magnesium ions, altering muscle action. As well as its peripheral effects, magnesium sulphate blocks N-methyl-D-aspartic acid (NDMA) receptors in the central nervous system and this appears not only to reduce involuntary muscle action, but also to reduce nerve excitability and possibly seizure activity. It also has an effect on catecholamines, causing arterial vasodilation and thus reducing blood pressure.

Safety of magnesium sulphate

Magnesium sulphate is, in general, a safe medication to use, and it is rare to induce any serious adverse consequences administering a bolus dose to control an acute eclamptic seizure. Pre-eclampsia is a state of vasoconstriction and the powerful vasodilatory effect of magnesium sulphate is likely to be one of the main mechanisms of its effect in eclampsia. However, with continued use, magnesium sulphate has the potential to cause a neuromuscular blockade and resulting respiratory depression. Fortunately, simple assessments of respiratory rate and the patellar reflexes provide a sensitive guide to the degree of neuromuscular blockade and predict impending overdose and toxicity.

Noting the well-recognised effects of magnesium sulphate on smooth muscle activity, early researchers conducted experiments using strips of myometrial muscle excised at caesarean sections, immersing them in solutions with varying concentrations of magnesium sulphate. As might be predicted, the higher the concentration of magnesium in the solution the greater the effect to inhibit myometrial muscle contraction. These results, coupled with clinical observations, led many clinicians in the USA to use prolonged courses of high-dose magnesium sulphate as a tocolytic in women with threatened preterm labour. What was not readily appreciated was that the cumulative doses required to provide tocolysis, doses that were much higher than required for seizure management, were associated with a greater incidence of adverse side effects and subsequent trials demonstrated that other methods of tocolysis were safer.

Magnesium sulphate for neuroprotection

The widespread use of magnesium sulphate and the number of large studies in which it was used, meant that a great deal of data were available about neonatal outcome after its antenatal use. A number of researchers noted that, although it was not usually a primary outcome in studies, there seemed to be fewer children delivered preterm who were subsequently diagnosed with cerebral palsy when magnesium sulphate had been administered in the peripartum period.

There was a reasonable body of evidence to underpin this, providing a possible mechanism of action. The competition between magnesium and calcium inhibits NMDA receptors, and it was known that activation of NDMA receptors with resulting calcium influx into neurons seemed to cause irreversible neuronal injury. Treatment of adult patients with magnesium sulphate was already known to reduce cerebral excitability and increase cerebral blood flow. Magnesium sulphate also seemed to have an anti-inflammatory action, presumably owing to blockage of reactive oxygen species and other pro-inflammatory cytokines.

Since magnesium sulphate is a small and simple molecule, it crosses the placenta essentially unhindered, meaning the fetal serum concentration of magnesium will closely approximate the maternal concentration. This led researches to question whether fetal exposure to magnesium sulphate might induce similar protective effects on the vulnerable developing brain.

Nelson and Grether published the results of a case-control study, comparing children of low birthweight who developed cerebral palsy, compared to similarly small babies who did not. They found that the mothers of the children without cerebral palsy were much more likely to have been treated with magnesium sulphate during pregnancy, a finding that supported the hypothesis that transplacental magnesium sulphate did indeed have a neuroprotective effect.

Despite some worrying results from the relatively small Magnesium and Neurological Endpoints Trial (MagNET) study, the much larger Australian-coordinated Australasian Collaborative Trial of Magnesium Sulphate ($ACTOMgSO_4$) randomised over 1000 women who were likely to deliver within the next day, where the pregnancy was not beyond 30 completed weeks. All of the adverse neonatal and childhood outcomes occurred less frequently in the magnesium sulphate treatment arm, though they did not reach statistical significance. Importantly, the distribution of other adverse outcomes was similar in the two groups. When the results of the Australian and other similar prospective trials were assessed in systematic reviews, it became clear that antenatal use of magnesium sulphate shortly before birth in very preterm babies reduces the risk of cerebral palsy.

Summary

What an amazing story this is, from a farmer who couldn't get his cattle to drink bitter water contaminated with Epsom salts, to the realisation that those same salts – magnesium sulphate – can cross the placenta and protect the developing brain. To make things even more interesting, despite the use of this remarkable little molecule in obstetrics for many decades, the exact mechanisms by which it exerts its amazing effects remains still remain to be learned. Who says the days of wonder have gone?

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Prostaglandins

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Prostaglandins are a diverse group of substances we use therapeutically on a daily basis. In other circumstances we use drugs to block their effects. An understanding of their biochemistry, physiology and pharmacology will only enhance our obstetrics, gynaecology and general practices.

Hardly a day passes in our practices where we don't utter the word prostaglandin, use prostaglandins (PG) therapeutically or block their effect with drugs. The term 'prostaglandin' was coined in 1935, before anything was known of their structure. In 1961 there was one published report on them in the medical literature, by 1973 there were over 1000 and today Google comes up with 1 280 000 entries in 0.10 seconds.

Yet what do we know about these mysterious substances? After all, many of us would never have received a single lecture about them in medical school. What are they; where are they and how do they exert their effects? This article will hope to shed light on this for you.

History

In 1930, two New York gynaecologists Kurzrok and Lieb, while studying the effects of human semen on strips of human uterus (as you do), noticed that the muscle contracted and relaxed. Later, in the mid-1930s, Goldblatt, an Englishman, and Ulf von Euler from Sweden independently reported the smooth muscle contracting effects of sheep seminal fluid. Von Euler named this lipid-soluble acid 'prostaglandin' for obvious reasons.

Years passed, but in 1964 Bergstrom and von Dorp, also independently, were able to synthesise prostaglandin E2 (PGE2), the active ingredient of Prostin, from arachidonic acid (AA). By 1971 it was discovered that aspirin and related drugs inhibited prostaglandin synthesis. In 1975, 1976 and 1983, thromboxane A2, prostacyclin (PGI2) and leukotrienes were respectively discovered.

The term 'prostaglandin' has turned out to be a misnomer as these substances are found in small amounts in all human tissues except erythrocytes. Their effects are protean and often paradoxical.

Synthesis and biochemistry

PG are also known as eicosanoids, in other words autocoids, from eicosatrienoic acid (dihomoλlinoleic acid), which is an essential 20 carbon omega 2 fatty acid. All prostaglandins are 20 carbon molecules. The linoleic acid is converted enzymatically to AA (see Figure 1) , the father of all prostaglandins, thromboxanes and leukotrienes.

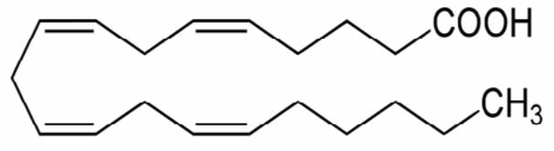

Figure 1. The chemical structure of arachidonic acid.

Once synthesised, AA is stored by esterification to the phospholipids of cell membranes and other complex lipids.

The concentration of free AA in cells is very low. The biosynthesis of eicosanoids is dependent upon the availability of this important precursor. It has to be released from the cell membrane for use either by the enzyme phospholipase A2 or an influx of calcium ions. These are released in response to physical, chemical and hormonal stimuli.

Once released, AA is metabolised rapidly (see Figure 2) to oxygenated products, including prostaglandins, by a ubiquitous complex of microsomal enzymes such as cycloxygenases (COX 1 and 2) and lipoxygenases. Essentially, there are two pathways. AA is metabolised to PGs and thromboxanes by COXs and to leukotrienes by lipoxygenases. Both prostaglandins and leukotrienes are proinflammatory and released in times of stress.

COX 1 and 2 initially convert AA to PGG2 (prostaglandin G2). This rapidly morphs non-enzymatically into the chemically unstable PGH2, which has three main metabolic pathways depending on the specific tissues and their requirements at the time. Firstly, it can be converted to the obstetrically famous PGE2 by an isomerase enzyme or by a reductase to PGF2α, also familiar to all readers.

Endothelial cells are rich in prostacyclin synthase and this enzyme converts PGH2 to PGI2 (also known as prostacyclin) which is a potent vasodilator and inhibitor of platelet aggregation. Like all prostaglandins it has a typically short half life of three minutes. In direct juxtaposition to this are platelets, which have abundant thromboxane synthase. This enzyme converts PGH2 to thromboxane A2 (t1/2 30 seconds), a very potent vasoconstrictor and platelet aggregator. All of this is important in order to be able to understand non-steroidal anti-inflammatory drugs (NSAIDs), their function and controversies.

The leukotrienes are proinflammatory and produced in most white cell types as well as alveolar cells and are important in the pathophysiology of asthma. A leukotriene receptor blocker called montelukast (Singulair) is used as an asthma prophylactic, especially in children. These important substances will not be discussed further in this article.

Physiology of prostaglandins

Prostaglandins sustain homeostatic function within cells and mediate pathogenic mechanisms including the inflammatory response. They are not endocrine hormones, they are autocrine or paracrine. In other words, they are produced locally and either act on the cells they are produced by (autocrine) or surrounding cells (paracrine). The interesting thing about prostaglandins is, unlike most enzymes, they are not proteins, but lipids.

Their effects are mediated by a number of distinct receptors, all with specific prostaglandin agonists. Ten receptors have been described to date. Their nomenclature is not relevant to daily clinical practice.

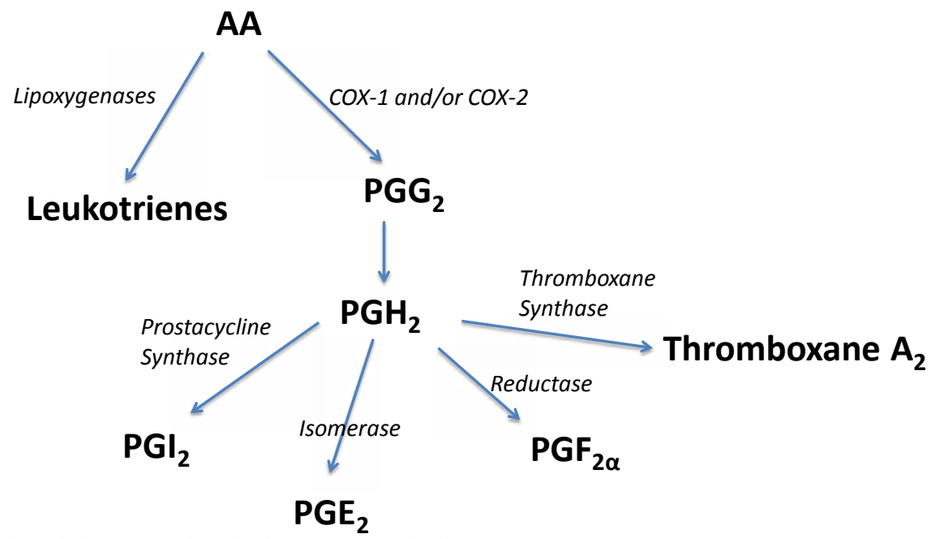

Figure 2. Conversion pathways for the common prostaglandins.

Stimulation of these receptors either results in facilitation or inhibition of adenyl cyclase and hence the concentration of cyclic AMP and the relevant protein and enzyme production.

They are metabolised and their effect terminated by prostaglandin dehydrogenase on first pass through the lungs hence their super short half lives. Their metabolic effects are diverse and dependent upon which prostaglandin and which tissue is involved. Their effects on platelets and vascular smooth muscle have already been alluded to. Table 1 summarises the effects of the more important prostaglandins to our specialty.

An important effect of prostaglandins is their action on the stomach. They are able to protect the stomach lining by a number of mechanisms including the inhibition of gastric acid secretion and an increase in gastric mucus production. Hence the prostaglandin analogue misoprostol (cytotec) relieves ulcer pain and promotes ulcer healing with an efficacy approaching that of omeprazole. Unfortunately, the side effect of diarrhoea limits its usefulness, but it has a niche where it is used in people who have to take NSAIDs despite a predisposition to peptic ulcer disease.

Effect of prostaglandins on reproduction and parturition

In obstetric and gynaecology practice the effect and use of prostaglandins are integral. Firstly, it is thought they may have an important role in fertility, especially with regards to fertilisation. Their high concentration in semen and efficient vaginal absorption is suggestive of this with demonstrable effects on the uterus, fallopian tubes and sperm transport.

With regards to menstruation, it has been found that there are high concentrations of prostaglandins in the menstrual fluid. They have a role in causing uterine contractions, increased gastrointestinal peristalsis and sensitisation of afferent pain fibres. All these factors contribute to dysmenorrhoea. It is for this reason that NSAIDs (COX inhibitors) work well for period pain and are more effective than narcotic-based analgesics.

Table 1. A summary the effect of prostaglandins more relevant to our specialty.

Prostaglandin type	Major sites of synthesis	Major biological activities
PGD2	Mast cells, eosinophils, brain	Inflammation Bronchoconstriction
PGE1	Most tissues	Vasodilation Platelet aggregation
PGE2	Kidney, spleen, heart, uterus	Vasodilation Platelet aggregation Uterine contraction Maintains patency of ductus ateriosus
PGF2α	Kidney, spleen, heart	Vasoconstriction Bronchoconstriction Uterine contraction
PGI2 (Prostacyclin)	Heart, endothelial cells	Platelet and white cell aggregation Vasodilation

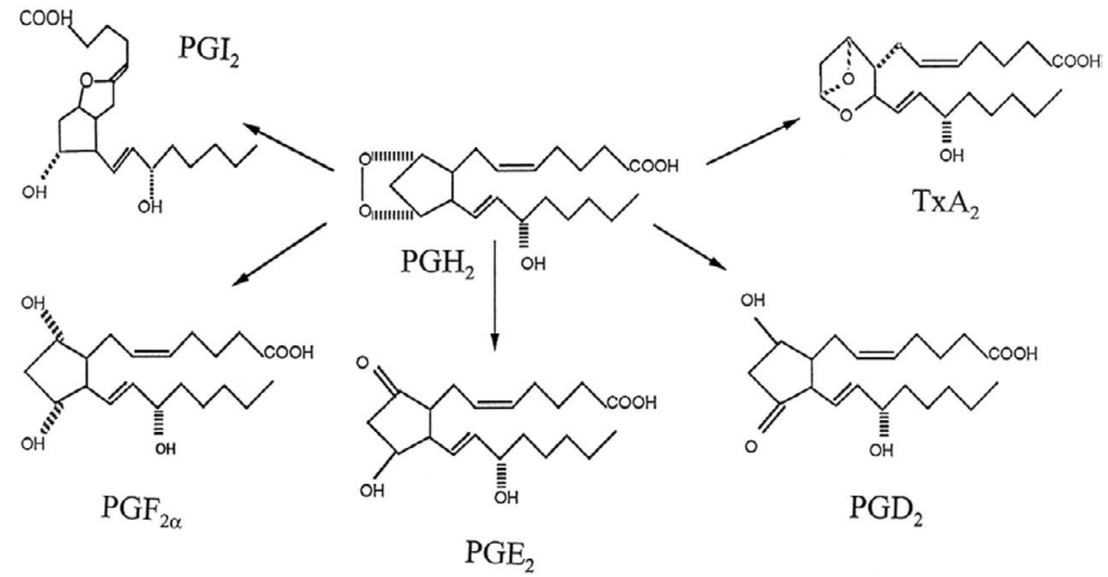

Figure 3. Chemical structures of the common prostaglandins.

During pregnancy, the ability of the fetal membranes to elaborate prostaglandins rises progressively and during labour the concentration of prostaglandins in the blood and the amniotic fluid is elevated. The significance of this is uncertain as is how much the onset of labour is determined by prostaglandins. Of all the prostaglandins, the E and F series result in uterine contractions with E being much more uterine selective and certainly more superior in cervical ripening. One of the therapeutic advantages of prostaglandins is that prostaglandin receptors are always present in the myometrium whereas oxytocin receptors develop during pregnancy, not peaking till the last part of pregnancy and even during labour. This allows prostaglandins to be used earlier in pregnancy for instance in induction of labour for fetal death in the second trimester when oxytocins would never work.

Therapeutics

Because prostaglandins affect all tissues, their therapeutic uses are diverse. Blocking their action is also therapeutic as they cause inflammation that is often pathological, such as in osteoarthritis. As we saw earlier, they are also useful in period pain.

Options

Agonism

1. Induction of labour – PGE2 (Dinoprostone or Prostin), misoprostol.
2. Therapeutic termination of pregnancy – PGF2α (Dinoprost), misoprostol (usually with mifepristone).
3. Treatment of postpartum haemorrhage (PPH) – misprostol, intramyometrial prostaglandin F2α.
4. Management of miscarriages (including missed miscarriages) – misoprostol.
5. Maintenance of patency in cases of patent ductus arteriosus (PDA) – PGE1 (Prostin VR).
6. Impotence – PGE1 (Caverject).
7. Gastric cytoprotection – misoprostol (Cytotec).
8. Treatment of glaucoma – latanoprost (Xalatan).

Antagonism

1. NSAIDs – non-selective COX inhibitors, for example, indomethacin, naproxen, diclofenac, ibuprofen and aspirin; or selective COX 2 inhibitors, for example, celecoxib and meloxicam.

Selected examples relevant to O and G

Agonism

1. Prostaglandin E2 chemical name dinoprostone (trade names Prostin, Cervidil): this is used in medical inductions to ripen the cervix in an attempt to get the patient into labour. It is inserted as an intra-vaginal gel (Prostin 1 or 2mg) or as a 10mg pessary attached to a tape (Cervidil). It acts by dissociating collagen fibrils and altering the mucopolysaccharide composition of the cervix. It promotes cervical ripening by softening and effacing. It has a pharmacological half life of less than one minute and its primary metabolite less than ten minutes, though this is half as potent as the original PGE2. It promotes a more natural labour than artificial rupture of the membranes and oxytocin.
2. Misoprostol (Cytotec): this drug is a prostaglandin E1 analogue and comes as a 200μg tablet. Originally developed for peptic ulcer treatment, it is now used off label for a variety of indications in obstetrics and gynaecology. These include medical abortion, management of miscarriage, induction of labour, cervical ripening before medical procedures and the treatment of postpartum haemorrhage (PPH). It has a number of advantages. It is low in cost, doesn't need refrigeration, has a long shelf life and can be used orally as well as rectally, vaginally, sublingually and buccally.
3. Gemeprost (trade name Cervagem): this drug is a PG analogue, probably 10–200 times more potent than PGE1, PGE2 or PGF2α. It comes as a 1mg pessary. Its main effect is to act locally with minimal systemic absorption to soften and dilate the cervix. It can be used prior to intrauterine operative procedures in the first trimester of pregnancy, but is mainly used for therapeutic termination in the second trimester of pregnancy, often for death in utero.
4. Prostin F2α injection (trade name Dinoprost): this comes in a 5m/ml injection. It used to be used extra-amniotically for mid trimester termination, but has been surpassed by newer drugs. It is now used mainly as an intra-myometrial injection for severe treatment-resistant PPH.

Antagonism

NSAIDs act by blocking, either reversibly or irreversibly, COXs, which are the first enzymes in the prostaglandin synthetic pathway. There are two: COX 1 and COX 2. COX 1 is the constitutive form of the enzyme found everywhere in most tissues such as blood vessels, stomach, uterus and kidney. COX 2, however, is induced in settings of inflammation by cytokines and other inflammatory mediators. This enzyme is inhibited by corticosteroids as well as NSAIDs and, more particularly, the COX 2 inhibitors.

All NSAIDs have analgesic, anti-pyretic, anti-inflammatory and to a less extent anti-platelet properties. They reversibly bind to COX enzymes and their action lasts as long as the half life of the drug. Most of them are non-selective.

Aspirin was the original drug in this group and is slightly unique in its action. It irreversibly binds to both COX 1 and 2. It covalently acetylates the enzymes by binding to serine. Its effect is as long as the enzyme lasts in that particular tissue. In platelets this is about seven to ten days. That is why patients need to be off aspirin for this length of time before surgery.

The ideal dose of aspirin as an anti-platelet agent is uncertain, but is thought to be about 160mg. If this dose is exceeded by too much it will block prostacyclin production as well as thromboxane synthesis hence losing its antithrombotic effect.

As COX 2 is only produced in sites of inflammation, blocking this enzyme selectively is advantageous. It is able to block the inflammatory affects without blocking the important functions such as gastric protection. That is the theoretical advantage of drugs like celecoxib (Celebrex). One downside is that COX 2 is a major source of PGI2 (prostacyclin) production so blocking this enzyme may have some theoretical prothrombotic tendency. This may have been a contributing factor to Vioxx being taken off the market.

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Anaesthetics

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An outline of some of the more commonly used drugs in current obstetric anaesthetic practice.

This article is intended to outline some of the commonly used drugs in current obstetric anaesthetic practice. It is not comprehensive, but will hopefully give the non-anaesthetist some insight into why particular drugs are used, their pharmacology and potential unwanted effects. Most drugs are not licensed for use in pregnancy and anaesthetic agents are no exception. Obstetric anaesthetists have historically tended to eschew newer agents and use drugs that have been around for a long time and therefore have a well established safety profile for use in pregnancy.

Induction agents

As their name suggests, these drugs are used to rapidly induce anaesthesia when given by intravenous injection. Unlike anaesthetic gases, which act relatively slowly and are sometimes poorly tolerated by patients, they generally cause unconsciousness in one arm-brain circulation time (20–40 seconds).

Propofol

Seeing an anaesthetist holding a 20ml syringe of white liquid will be a familiar sight to many and with good reason; introduced into clinical practice in the late 1980s, propofol has become the dominant induction agent used today. The drug is water insoluble and hence has to be mixed with soya bean oil and given as an emulsion, giving its trademark appearance.

It induces anaesthesia by enhancing inhibitory neuronal transmission. Its popularity rests on its rapid redistribution and therefore quick offset of action, which results in brisk wake up with minimal 'hangover'; its suppression of airway reflexes, which facilitates airway manipulation; and significant anti-emetic properties. Downsides include myocardial depression and vasodilatation (common to most anaesthetic agents), pain on injection and prolonged infusions can precipitate a progressive, sometimes fatal, metabolic acidosis. Transfer across the placenta is fast and some studies have shown poorer Apgar scores compared with thiopentone.[1,2] However, other studies have shown no difference in neonatal outcomes.[3,4]

Thiopentone

This barbiturate used to be the standard choice of induction agent for the obstetric anaesthetist, but its use has declined in recent years. It is a very old drug, having been developed in the 1930s, and has a long established safety profile in obstetrics. It is a potent anaesthetic and anticonvulsant and works by enhancing inhibitory GABAergic neuronal transmission. It is unstable in solution and thus has to be dissolved in water before use, which has cost, time and safety implications. Problems with its manufacture have resulted in a recent difficulty securing supplies. Like propofol, it is a myocardial depressant and vasodilator and will reduce cardiac output in a dose dependent manner. It is highly irritant and accidental intra-arterial injection can cause necrosis. Anaphylactic reactions are rare, but severe when they do occur. Thiopentone readily crosses the placenta, however, plasma levels in the fetus are rarely enough to cause neonatal depression.

Ketamine

Ketamine finds occasional use on the delivery unit when inducing anaesthesia in the profoundly shocked patient. Structurally related to phenylcyclidine ('angel dust'), it works as an antagonist at NMDA receptors and has both anaesthetic and analgesic actions. Although still a myocardial depressant, it stimulates the sympathetic nervous system, causing an increase in circulating catecholamines that maintains cardiac output and blood pressure when given. Its side effects of hallucinations and nausea limit its more widespread use. When given epidurally it prolongs the effect of local anaesthetics by three-to-four times.

Volatile anaesthetics

These gases (technically vapours) are usually used to maintain anaesthesia once the patient has been put to sleep with an intravenous drug. The most commonly used agents are sevoflurane, isoflurane and desflurane. The concentration of the gases breathed out by the patient is used to gauge the depth of anaesthesia as it is assumed to be in equilibrium with the concentration of the agent in the brain. This offers a distinct advantage over an intravenous agent, the concentration of which cannot currently be measured directly. Lower amounts of the volatile anaesthetics are needed in the pregnant patient, probably a central effect of progesterone. Their precise mechanism of action remains elusive despite intense interest in this area. It seems likely that multiple mechanisms are at play. They all tend to reduce arterial blood pressure and uterine tone in a dose dependent fashion. They readily cross the placenta and neonatal depression can occur. This is not usually a problem as most instances of their use is during emergency lower segment caesarean section and delivery occurs before a significant amount of drug is able to reach the fetus.

Nitrous oxide

Nitrous oxide (N_2O) is the single most commonly used anaesthetic in obstetric practice, though to give a general anaesthetic with N_2O would require it to make up 104 per cent of the inspired gas! N_2O has the important attribute of providing analgesia as well as sedation. While N_2O is known to inhibit methionine synthetase (an important component in the synthesis of DNA) there is no evidence that short-term use in clinically relevant concentrations has any adverse impact on mother or fetus. Prolonged exposure to concentrations >50 per cent has been shown to be teratogenic during early pregnancy in animals.

N_2O has fallen from favour in anaesthesia for several reasons including an increased risk of nausea and vomiting, environmental concerns (it has a greenhouse gas effect 300-times that of carbon dioxide) and an increased incidence of myocardial infarction when used in general anaesthesia.[5] Despite this, it still has a definite role in obstetrics and is often still used in caesareans performed under general anaesthesia. It has the dual benefit in this situation of providing analgesia, and thereby limiting the opioid exposure to the fetus, while having no effect on uterine tone.

Vasopressors

Hypotension is a relatively common feature of anaesthesia and is usually owing to vasodilation. During neuraxial block for caesarean it is nearly universal owing to vasodilation and sympathetic block and women will invariably need blood pressure support through the procedure. This can be effected by stimulation of either α1 receptors, causing vasoconstriction, or β1 receptors, producing an increase in heart rate. Phenylephrine is a pure α1 agonist and produces vasoconstriction, directly opposing the vasodilation seen after a spinal or epidural anaesthetic. This rise in blood pressure, owing to constriction of arterioles and veins, produces a reflex drop in heart rate. Ephedrine has both α1 effects and β1 effects so no bradycardia is seen. There is evidence that the use of phenylephrine results in a slightly higher fetal pH than ephedrine; however, this is not associated with any Apgar changes.

Muscle relaxants

Neuromuscular blocking drugs (NMBDs) do not generally cross the placenta as they are very ionised, and so do not cross membranes easily. They can be divided into depolarising, those that cause muscle contraction before paralysis, and non-depolarising. Suxamethonium is still the only depolarising NMBD in widespread clinical use. It has rapid onset, is used for rapid sequence induction and is rapidly metabolised over several minutes by plasma cholinesterases.

Non-depolarising muscle relaxants do not cause muscle contractions and include vecuronium, rocuronium (**r**apid **o**nset vecuronium) and atracurium. These drugs generally have a slower onset, though high doses of rocuronium have comparable onset times to suxamethonium. This was traditionally associated with a very prolonged block time, but a new drug, sugammadex, binds up rocuronium specifically and can be used to essentially 'turn off' the block seen with rocuronium.

All NMDBs act by binding to the acetylcholine receptor at the neuromuscular junction of skeletal muscle and preventing its activation by the body's own acetylcholine, which would normally result in muscle contraction. Non-depolarising NMBDs can be reversed through the use of neostigmine, which decreases the metabolism of the body's acetylcholine thereby increasing its levels. As acetylcholine levels rise, the NMDBs are displaced from the receptors and skeletal muscle contraction returns.

Opioids

As well as analgesia, opiates are used in anaesthesia to blunt the profound increase in blood pressure and heart rate seen in response to endotracheal intubation. Opiates work on a variety of opiate receptors centrally, but are distinguished clinically more by their variable pharmacokinetic profiles.

Morphine is the prototypical opiate and still the most commonly used for intraoperative and postoperative analgesia. It is metabolised to an active metabolite that is then cleared renally. In renal failure this metabolite can accumulate and cause sedation. Morphine also increases the tone of the bladder sphincter and can cause urinary retention.

Pethidine has fewer emetogenic effects and more euphoric effects than morphine and is one-tenth as potent, so 10mg of pethidine is equivalent to 1mg morphine. The main metabolite is norpethidine, which can also accumulate in renal failure and lower the seizure threshold. Pethidine has interesting effects including an increase in uterine contraction amplitude and a mild anti-cholinergic effect that can increase the heart rate.[6]

Fentanyl is a potent mu opioid receptor agonist 50–100 times more potent than morphine. It is notable for its rapid onset and offset compared to other opiates. This is owing to a high lipid solubility causing it to pass across the blood-brain barrier quickly, it then rapidly redistributes throughout the body, which reduces the concentration of the drug at the receptors. However, at high doses or with prolonged infusions it will accumulate within the body.

Remifentanil has gained increasing use as an analgesic in labour in place of epidurals if these are not available or are contraindicated. The reason for remifentanil's popularity is its extremely rapid onset and its consistency in offset time regardless of duration of use. Remifentanil's remarkable consistency is owing to it being broken down in the plasma itself by non-specific plasma and tissue esterases, and not relying on a saturable system such as a particular organ. In theory this provides for a drug with rapid onset, but which should breakdown and not accumulate between contractions. The reality is that the effect is not perfectly matched to contraction time and there appears to be a degree of maternal sedation and desaturation.

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Endometriosis

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Before any discussion can be had about what is in the 'drug cupboard' for endometriosis, it is imperative that we know what and who we are dealing with.

At the outset, it must be emphasised that the diagnosis of endometriosis must be made surgically. The best tool at our disposal for this purpose is the laparoscope, in the hands of an experienced operator, ideally in a team setting. The pre-operative work up should include a directed history, a vaginal examination and, more importantly, imaging of the pelvis using a trans-vaginal ultrasound or magnetic resonance imaging (MRI). Imaging is especially useful to exclude deep infiltrating endometriosis, recto vaginal septum endometriosis and endometriomas. MRI is becoming increasingly more useful for ruling out adenomyosis. Tumour specific markers add dimension to this plan.

To begin
Firstly, let me start by describing why I do not use two specific drugs at all and have not done so for almost 20 years. Depo Provera (a progesterone), approved as a contraceptive, can be, and has been, widely used. However, for significant endometriosis, the frequency of injections is far greater (MIMS Annual) than that used for contraception and the number of side effects, including significant weight gain, fluid retention, mood change and thin, dry vaginal mucosa, puts this drug at the bottom of my list. There is also a long washout period for this drug, which is important if pregnancy is planned.

Similarly, danazol (Danocrine), which is highly efficacious, has unacceptable side effects, including weight gain in the order of 10kg, acne and possible irreversible hair growth. It is imperative to discuss these side effects with young fertile women. Invariably, in my practice, the response from the woman is 'no thanks'.

Moving forward
Having discarded two previous main contenders, we are left with the pill in various guises: progesterones; the Mirena intrauterine contraceptive device (IUCD); the Nuvaring; the two GnRH analogues (Zoladex and Synarel); and newer drugs that have potential for clinical use in the future. Rather than approach this task by simply describing each drug, I am going to describe the various clinical situations in which each drug might be used, alone or in combination.

The teenager with endometriosis only
Laparoscopic diagnosis and treatment is undertaken with the aim of surgically removing all endometriosis at the first operation. Provided the patient has reached her full height potential, and with parental consent, the combined oral contraceptive pill is used. Ideally, I use Brevinor 1 (Norimin 1) supplemented with a small dose of Primolut N if spot bleeding is a problem. The problems here can be weight gain, depression, fluid retention and acne. I switch to Diane 35 (or similar) if acne becomes a problem. Adequate counselling needs to be given to teenagers and their parents about the need to take this medication on time, to continuously cycle packets (skipping the sugar pills) and to avoid antibiotics where possible.

I try to avoid the use of the Mirena and GnRH analogues in this very young age group with endometriosis. The 'crampy' pain in the developing uterus when the Mirena is added to the mix often means that the four months needed for the Mirena to settle in is just not reached.

The older teenager with adenomyosis
This is where a pre-operative workup with an MRI scan is imperative. A good endometriosis unit must be backed up with a radiologist who is aware of the fact that adenomyosis should no longer be a disease where the diagnosis is made at hysterectomy in the 40-year-old woman! I commonly see adenomyosis in teenagers and young women and the patient may or may not have peritoneal endometriosis (personal experience of over 500 unpublished MRI scans over eight years in teenagers).

In my practice, I offer the teenage or young patients a pre-operative MRI with the sole purpose of discussing, before surgery, whether a Mirena should be inserted at the time of the first surgery. If a Mirena is to be inserted, adequate counselling of the patient as well as her parents is mandatory. The likelihood of the patient needing even more pain relief in the first few months needs to be discussed. Of course, the need for safe sex is also an imperative discussion because of the increased risk of chlamydia infection in this age group.

Once over the three-to-four month hump, improvement is more likely than not if adenomyosis has been minimal (infiltration of the junctional zone limited to less than 1.4cm into the myometrium and no adenomyomas).

Mirena
A Mirena device contains 52mg of levonorgestrel and initially releases 20µgs every 24 hours. Levonorgestrel is a potent progesterone that also has anti-oestrogenic properties resulting from modification of peripheral oestrogenic effects as opposed to binding to oestrogen receptors. Levonorgestrel is also used in combined oral contraceptive pills and progesterone only pills. The advantage of the Mirena IUCD delivery system is that it allows delivery of the drug directly to the target organ, in other words the endometrium. After five years, the daily delivery halves to 10µgs.

Because a Mirena allows high levonorgestrel concentrations in the endometrium, oestrogen receptors are rendered insensitive to oestrogen (MIMS Annual 2013).

Women in their 20s not yet wishing to conceive
Again, pre-operative work up with a vaginal ultrasound scan and MRI will allow planning for adequate surgical excision at the first attempt. For Grade III/IV endometriosis, deep infiltrating endometriosis or endometriosis in association with MRI-proven adenomyosis, I prefer a combination of the Mirena and a high progesterone pill or a Mirena and a GnRH analogue (usually Zoladex) in an attempt to eradicate the maximal amount of disease possible. My reasoning here is that in Australia, the patient gets only one six-month subsidised course of Zoladex paid for in her lifetime. Therefore, it is my belief that we should maximise drug and surgical treatment early on and not wait for disease to progress before bringing in the big guns. Once a course of Zoladex has been completed, I then add in a combined oral contraceptive pill (COCP) with a high dose of progesterone for two reasons. Firstly, there is a reduced risk of the patient bleeding with a higher dose of progesterone and secondly, to avoid the 11 per cent risk of large painful follicular cysts that comes with Mirena use.

Zoladex
Zoladex is a 3.6mg implant of goserelin acetate. It is injected subcutaneously, biodegrades over at least 28 days and is used for endometriosis and adenomyosis as well as breast and prostate cancers. Goserelin acetate is a decapeptide analogue of LHRH/GnRH. There are two phases to its action. Initially, within the first week, there is a flare reaction leading to a transient rise in serum LH and FSH concentrations. This is followed by the chronic phase in which potent inhibition of gonadotropin production occurs, leading to dramatically reduced levels of oestradiol and thus regression of endometriosis and adenomyosis.

Gonadal (and therefore oestrogen) suppression is sustained for as long as administration continues. Oestrogen levels diminish within 21 days and are comparable with postmenopausal levels, hence patients must be warned that they will suffer temporary, iatrogenic, menopausal symptoms. Similarly, bone mineral density should be measured in at-risk patients before therapy. Most patients tolerate the hot flushes, headaches and/or vaginal dryness well and only seldom is add-back HRT required. The company's product leaflet warns that bioavailability may be variable, which may explain why some women continue to bleed while on the treatment.

Pre-treatment of endometriosis for fertility
In 2011, a paper in *ANZJOG* discussed the effect adenomyosis can have on pregnancy rates with IVF.[1] I have adopted a policy of pre-treating all my MRI-proven adenomyosis patients with a minimum of three months of Synarel nasal spray before commencing FSH injections for IVF cycles. I also start prednisolone 15mg on day seven of the FSH injections as recommended by this same article.

Treatment of patients undergoing a hysterectomy
Either Zoladex or Synarel (nafarelin, another GnRH analogue) can be used on patients who elect to have a hysterectomy for their endometriosis. Often, adenomyosis co-exists with the endometriosis, but this, of course, is treated surgically by the hysterectomy itself. I adopt a surgical approach in removing any visible peritoneal disease at the time of the laparoscopic hysterectomy. Even if an abdominal hysterectomy is performed, I remove any additional peritoneal disease laparoscopically. I then post-treat the woman with three months of either Synarel or Zoladex, followed by the option of a COCP in those patients wishing to retain their ovaries.

Lipiodol ultra fluid
Delivered as a sterile ethyl ester of poppy seed oil (with an iodine content of 480mg/ml), Lipidol was originally used as a radio-opaque fluid for diagnostic hysterosalpingography. With the development of ultrasound-visible agents, Lipiodol has recently rarely been used in gynaecology. However, evidence indicates that flushing the uterine cavity with Lipiodol significantly increases fertility for a period of up to six months, but only in endometriosis patients. In Australia, Lipidol must be applied for on a case-by-case basis.[2]

The problem with drugs
Just as surgical procedures have known risks and limitations, so do drugs. I often say to my patients 'endometriosis is a bit like rheumatoid arthritis. If there was one drug that worked 100 per cent of the time, we would use it!' The use of medical treatments for endometriosis is restricted by limited efficacy of the drugs, side effects, patient compliance and recurrence of the disease after a course has come to its end.

The problem of side effects is perhaps made worse by the internet and 'Dr Google' who so many patients will consult prior to starting medical therapy. In my opinion, patients sometimes have a biased opinion towards their treatment after consultation with their cyber physician, which possibly makes compliance worse and may exaggerate their experience of side effects. Danazol suffered such a plight. I have virtually stopped prescribing Danazol because of the perceived risk of severe side effects in the community, which is not completely unfounded of course. The GnRH analogues suffered a similar plight because patients hear they cause menopause. Their perception is that menopause symptoms will be life-long and make them old.

Careful patient counselling is of paramount importance if we are to have any hope of good compliance. Patients need to be educated about the need for drug treatment after surgery to decrease recurrence rates and avoid, where possible, too many surgeries.

Future prospects
Given females represent only 50 per cent of the population, only five-to-ten per cent of women suffer from endometriosis, those women are affected for perhaps three decades only and only a proportion of affected women will respond to any particular drug, any pharmaceutical company that wishes to 'invest' in a new drug for this disease will do so at a huge expense for a rather limited reward. Any new drug development programs must also bear in mind possible teratogenic risks. Potential treatments for the future include anti TNF alpha, a monoclonal antibody, which may offer hope for women suffering from painful deep deposits of endometriosis, where surgery has failed. Other possibilities include aromatase inhibitors, selective progesterone receptive modulators and new oral GnRH antagonists.

Certainly, of all the treatments we have, the progesterones are cheap, effective and relatively well tolerated. Perhaps any new treatments should be compared to them. For the foreseeable future, a surgical diagnosis, followed by excisional surgery, histological confirmation and, where possible, immediate follow-up drug therapy aimed at ceasing menstruation and limiting recurrent disease, forms the backbone of treatment for endometriosis.

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Recurrent miscarriage

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New pharmacological approaches to a difficult problem.

Recurrent miscarriage, or recurrent pregnancy loss (RPL), is an uncommon, but very distressing problem, for couples. Using the definition of three or more consecutive first-trimester pregnancy losses, without a live birth, it is generally estimated that between one and three per cent of women are affected.[1] Using a population-wide estimate of the rate of early pregnancy loss as about 15 per cent for any given pregnancy, then the statistical probability of three such losses in a row is 0.34 per cent ($0.15 \times 0.15 \times 0.15 = 0.0034$). The observed proportion is much higher, suggesting that a group of couples will have a true underlying pathology and this is not just bad luck.

There are a number of well-recognised risk factors for recurrent miscarriage (see Box 1). Most of us will initiate investigations to determine if any of these risk factors are present in younger women after they have three miscarriages, but often earlier (perhaps after only two miscarriages) in older women who do not have the luxury of time. The majority of couples with recurrent miscarriage do not have any underlying pathology detected, despite thorough investigation. This is a distressing situation.

When a definite (or likely) cause for an early pregnancy loss is discovered, therapy is commonly initiated. For example, when an inherited thrombophilia is diagnosed, treatment with anticoagulants (heparins or aspirin) is often commenced. Frustratingly, while anticoagulation seems to have an intuitive theoretical underpinning, randomised trials of low-dose aspirin, low molecular weight or unfractionated heparin have not produced convincing results.[2] This is a nuisance, since as many as one woman in five who has recurrent miscarriage will screen positive for a thrombophilia and large numbers of studies have now been reported. Fortunately, the evidence seems to be clearer for anti-phospholipid syndrome (APS), a condition identified in as many as 15 per cent women with recurrent miscarriage: the risk of pregnancy loss can be halved by judicious use of a combination of aspirin and heparin.[3]

In a similar way, the other clinical entities that might predispose to recurrent miscarriage can be dealt with, though not necessarily easily. Anatomical abnormalities of the uterus, including uterine septae or fibroids, may or may not require surgical correction. Balanced translocations in the parents, though accounting for a very small number of recurrent miscarriage cases, may respond to either conservative management or, in selected cases, to the use of pre-implantation genetic screening of embryos with genomic hybridisation techniques in IVF. Good glycaemic control can be sought in women with previously poorly controlled diabetes. And so it goes.

The major challenge occurs in managing those couples where a very thorough investigation has revealed absolutely no pathology that might explain recurrent pregnancy loss. Unfortunately, this is the most common situation that faces us. Older longitudinal studies suggest that the most likely outcome for a couple who have had recurrent miscarriages, and in whom no underlying abnormality has been found, is an ongoing pregnancy next time.[4] That said, recurrent miscarriage seems to be a common reason for seeing a specialist, and most of us will be faced with distressed couples in this situation.

No obvious aetiology: a pharmacological solution?

Couples with recurrent miscarriage are often concerned and keen for action, and although it can be difficult to subject 'tender loving care'[1] to clinical trials, reassurance and regular contact definitely play a vital role in management.[5] Beyond this, a number of pharmacological therapies are in common use. Aspirin, for example, is an empirical therapy that is often tried. Unfortunately, there is no evidence that aspirin provides any benefit for women with unexplained recurrent miscarriage.[6] Similarly, empirical use of heparins in the hope of treating undiagnosed low-grade inflammation or thrombosis in the placental bed does not seem to provide any benefit either.[7]

'Immunotherapy' is a broad term for treatments that aim to modulate a supposedly abnormal maternal immune response to the implanting embryo. These include such treatments as intravenous immunoglobulin (IVIg) infusions, trophoblast cell infusions, paternal cell immunisations and other related therapies. Again – and unfortunately – the evidence for such treatments is weak at the moment.[1]

One area that might be promising is the use of progesterone in early pregnancy. A recent systematic review of the use of progesterone in women with a history of recurrent miscarriage provided some support, reporting a statistically significant reduction in the rate of subsequent miscarriage in this group.[8] The reviewers commented on the small number of women in the four trials included – only 225 in all – and the 'poor methodological quality' of the studies, including the fact that oral, intramuscular and vaginal routes of administration were all used.

Box 1. Known risk factors for recurrent miscarriage

- Increasing maternal age
- Increasing paternal age
- Obesity
- Anti-phospholipid syndrome
- Lupus anticoagulant
- Anticardiolipin antibody
- Anti-B2 glycoprotein-I antibodies
- Parental aneuploidies
- Congenital uterine abnormalities
- Inherited thrombophilias
- Poorly controlled diabetes

The dialogue between embryo and endometrium

It seems clear that embryo implantation and early fetal growth are not simple processes. Studies in which decidualising endometrial stromal cells (ECSs) and blastocyst-stage embryos were cultured together clearly point to a complex biochemical 'conversation' between the embryo and the cells of the endometrium, with abnormal embryos seeming to inhibit the secretion of implantation-promoting factors.[9] The interesting conclusion from such studies is that the endometrium seems to be able to detect an abnormal embryo and that decidualisation does not occur so that abnormal embryos are much less likely to implant.

Armed with the knowledge that the human endometrium has the ability to differentiate between normal and abnormal embryos, elegant experiments have been undertaken by Weimer and colleagues using endometrial cell monolayers obtained by biopsy from women of normal fertility and women with a history of recurrent miscarriage.[10] When abnormal embryos were placed with the endometrium of normally fertile women, implantation did not occur, as expected. However, the endometrium of women with recurrent miscarriage was receptive to both normal and abnormal embryos. The authors duly concluded that endometrial cells in normally fertile women discriminate between high- and low-quality embryos, whereas the cells from women with recurrent miscarriage don't discriminate at all. This is clearly a new paradigm.

Moderators of the endometrial-embryo dialogue

Natural killer cells resident within the uterus (uNK cells) appear to be quite different to those found in peripheral blood, whose role is to deal with viral infections and tumours, for example. The uNK cells seem instead to release cytokines involved in angiogenesis, and are likely to play a leading role in the immune function of the endometrium during embryo implantation.[11] Studies suggest that women with recurrent miscarriage have greater numbers of uNK cells in the endometrium during the luteal phase[12] and high concentrations of uNK cells appear to be associated with lower levels of 11β-HSD1 and decidualisation.

What does all of this mean? There is now experimental evidence that some women with otherwise unexplained recurrent miscarriage are almost 'hyperfertile' – their endometrium is receptive to implantation for a long time, and does not appear to be too selective, allowing abnormal embryos to implant. This would explain the common description of women who become pregnant easily, but lose their pregnancy early.

Prednisolone and recurrent miscarriage

There is experimental evidence that prednisolone therapy reduces the concentration of uNK cells in the endometrium[13] and trials of prednisolone therapy are underway across Europe. Prednisolone is the active metabolite of prednisone, and prednisone is a synthetic form of cortisol. Cortisol is a steroid released from the adrenal gland, its functions to suppress the immune system and to act on metabolic pathways so as to increase blood glucose levels, hence the term 'glucocorticoid'. Glucocorticoids down-regulate interleukin receptors, dampening humoral immune responses. Prednisolone binds with glucocorticoid receptors (GRs) and the bonds are irreversible – the resulting complexes migrate into the cell nucleus and strongly influence cell functions.

Prednisolone therapy has been used for women with recurrent miscarriage for two decades, for most of that time without a clear theory of the basis of its action. It has only been in the last few years that the possible link between uNK cell numbers, endometrial hyper-receptivity and recurrent miscarriage has been explored in detail with the realisation that prednisolone may improve pregnancy outcomes by suppressing cytokine production and uNK cytolysis.[14]

Meta-analysis of the relevant trials concluded that, although corticosteroids do not impart a strong risk of teratogenesis, their use does increase the risk of oral clefts with an increase in risk from about 0.1 per cent to between 0.3 and 0.4 per cent.[15] A subsequent prospective study did not report any teratogenic effect from systemic corticosteroid use in the first trimester.[16] While corticosteroid use may increase the risk of preterm delivery, gestational diabetes and hypertension in pregnancy, such effects appear to be restricted to women taking steroids in high dose after the first trimester and use in the first trimester only does not appear to increase any of these risks.[17,18]

Conclusions

Recurrent miscarriage is a distressing condition to deal with, yet it is something that demands action. Investigation will reveal possible causes in less than half of couples, meaning that the majority of women in this situation will not be given a satisfactory explanation for what seems a devastating problem. In these circumstances, empirical treatments such as low-dose aspirin, heparins and various 'immunotherapies' have not been shown to provide any real benefit at all. The possibility is open that progesterone treatment might help, but this needs more work.

The true revolution has been the realisation that women with recurrent miscarriage might actually be 'hyper-fertile'. There is evolving and intriguing experimental evidence that women with otherwise unexplained recurrent miscarriage have an endometrium that is overly receptive and receptive for a longer time to abnormal embryos. Hence the common clinical story of a couple who become pregnant quickly and without problems, only to miscarry each time. There is mounting evidence that uNK cells play a role, perhaps by affecting the decidualisation and by interfering with the endometrial-embryo chemical 'dialogue'. The use of glucocorticoid treatment – of prednisolone in particular – might well alter this balance, restoring the normal receptivity and selectivity of the endometrium and restricting implantation to healthy embryos. The results of these trials are keenly awaited and perhaps might provide new hope to desperate couples.

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The safety of drugs in pregnancy and breastfeeding

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A practical approach to how to deal with counselling women regarding some commonly used medications during pregnancy and breastfeeding.

There is a general perception that any medication exposures during pregnancy pose a potential risk to the fetus. Despite this fear about the safety of medications during pregnancy, several studies from around the world (including Australia) showed that over 90 per cent of women use some form of prescribed or non-prescribed medication during pregnancy.[1,2]

Thus, despite all their concerns, women are exposed, either intentionally or inadvertently, to a large number of substances during pregnancy and somewhat surprisingly there are relatively few drugs that are considered to be major teratogens and are absolutely contraindicated in pregnancy.

The Australian Categorisation of Drugs in Pregnancy (A-X found in MIMS and other prescribing references) should only be used as a guide to prescribing and should not be used to counsel women about the safety or otherwise of medications in pregnancy. It is also important to remember that the categorisations are not applicable to breastfeeding.[3]

It is important that all couples considering their reproductive options are informed and understand that for any pregnancy there is a background (population) risk of between three and five per cent of having a baby with a major birth defect or other neurodevelopmental problem that may not be apparent at birth. The risk or otherwise of any exposure needs to be related back to this background risk and the couple must be counselled whether or not a specific exposure has increased their risk of having a baby with an abnormal outcome above the background risk. Overall, the risk for any individual birth defect, such as neural tube defect (NTD), is low (around one per 1000 live births). Even if the relative risk of a defect such as NTD is increased tenfold (RR=10) by a medication such as carbamazepine, the absolute risk for this defect following this particular exposure is still only one per cent.

For practical teratology counselling purposes, pregnancy can be divided into three periods:

1. 'All-or none' period (2–4 weeks amenorrhoea). This is the first two weeks after conception; the time from conception to the first missed period. It is generally believed that exposures during this time do not cause malformations as the conceptus is a mass of dividing stem cells with minimal contact with the maternal circulation and which have not yet differentiated into organs.
2. Embryonic period (4–10 weeks amenorrhoea). The embryonic period or period of organogenesis is the most critical period of development, during which time exposures can cause structural birth defects such as NTDs, cardiac defects and orofacial clefting. Most teratogens exert their teratogenic effects during a relatively small window of time during this period. For example, thalidomide caused limb defects following exposure between 20 and 35 days post conception.
3. Fetal period (from ten weeks amenorrhoea). During the fetal period, exposures cannot cause malformations (as the organs have already formed), but may cause disruption of normally formed organs by various mechanisms. Usually these effects are owing to the drug's recognised pharmacological actions, for example, NSAIDs and ACE inhibitors/angiotensin receptor antagonists can impair fetal renal function and thereby decrease fetal urine production and amniotic fluid volume (oligohydramnios) that causes fetal joint contractures and pulmonary hypoplasia.

Counselling regarding exposures during pregnancy

Clinically timing of the exposure is the most important factor. An agent can only cause a problem if exposure occurs during a critical period of embryonic or fetal development. Thus it is vital to establish the timing of the exposure in relation to the pregnancy and the most accurate way is by early dating ultrasound. In many cases, a woman may be reassured about an exposure of concern simply by having an ultrasound that dates the exposure and having occurred either prior to pregnancy or during the all-or-none period. One exception to this is the major teratogen, isotretinoin, as there have been reports of anomalies in babies exposed in the all-or-none period.

Women with chronic conditions – such as asthma, inflammatory bowel disease, depression, rheumatological conditions, thyroid disease and epilepsy – may well require ongoing medication prior to and during pregnancy as well as while breastfeeding. These women often benefit from face-to-face counselling, ideally before conception, to discuss ideal management of their condition so as to optimise mother and baby's health before during and after pregnancy. In many conditions, the risks of untreated or under-treated conditions will be higher than any potential risks of medication. This pre-conception consultation is also an important opportunity to address other general health issues including diet, smoking, alcohol use, folic acid/multivitamin supplementation, ensuring immunity to rubella and varicella and exploring potential genetic and other risk factors.

When pregnant women seek advice about past or ongoing exposure to drugs, chemicals or other environmental agents there is often a high level of anxiety. Some women may consider terminating the pregnancy because of information received about potential fetal risks. Counselling must be non-directive and information should be given in a way that a woman (and her partner) can understand the implications of the exposure, assess the risks and make a decision

Table 1. Examples of some drugs of choice for common conditions during pregnancy.[4]

Condition	Drugs of choice	Other suitable agents	Comment
Allergic rhinitis	Topical agents: nasal irrigation, saline sprays, sodium cromo-glycate and corticosteroids Systemic anti-histamines, pheniramine, dimenhydrinate, loratadine, cetirizine	Topical decongestants Phenylephrine, oxymetazoline, xylometazoline	Topical decongestants should be used according to directions.
Cough/cold	Paracetamol Throat lozenges Codeine Dextromethorphan Bromhexine Guiafenesin	Pseudoephedrine, phenylephrine	Pseudoephedrine and phenylephrine as well as other sympathomimetic agents are used in many cough /cold compounds and nasal sprays. Because of concerns about their vasoconstrictve effects, they should be used with caution especially in the first trimester but women should be reassured after inadvertent exposure.
Constipation	Dietary fibre, docusate, bisacodyl, psyllium, paraffin	Lactulose, cascara, senna	Stimulants such as cascara, senna should not be used on a regular basis but occasional use is safe.
Haemorrhoids	Laxatives (see above treatment of constipation)	Haemorrhoid preparations contain some of the following ingredients Hydrocortisone and prednisolone Lignocaine and cinchocaine (local anaesthetics) Witch hazel (hamamelis), aluminium acetate and allantoin: reduce inflammation. Zinc oxide: protective. Peru balsam and benzyl benzoate: mild antiseptic and anti-itching action	Many ointments and suppositories which help relieve symptoms of haemorrhoids are available over the counter. Although there have been no studies confirming the effectiveness of topical haemorrhoid preparations, they are widely used and not considered to increase risks to the baby at any stage of pregnancy. These products help relieve the itch or discomfort of haemorrhoids, but do not treat the underlying varicose veins.
Fever	Paracetamol	aspirin NSAIDs	Some data suggest aspirin and NSAIDs may be associated with increased miscarriage risk in 1st trimester. Aspirin and NSAIDs should be avoided in 3rd trimester because of premature closure of ductus arteriosus.
Nausea and vomiting of pregnancy	Ginger, pyridoxine (vitamin B6) and doxylamine	metoclopramide, prochlorperazine, ondansetron	Doxylamine and vitamin B6 in combination should be used as first-line treatment for NVP.
Heartburn/reflux	Antacids, simethicone H2 antagonists	omeprazole and other PPIs	Recent studies from Europe and North America have shown that omeprazole is not associated with an increased risk of birth defects or other adverse pregnancy outcomes.
Pain	Paracetamol, codeine, morphine, pethidine	NSAIDs, aspirin	Concerns about maternal tolerance and dependence as well as potential neonatal withdrawal following use of opioids in late pregnancy.

based on as much evidence-based data as possible. Information must be individualised for a woman's particular situation, in other words, the gestational timing of the exposure/dose/route of administration and the underlying medical condition for which she is taking the medication. It is also important to address what the patient already knows – information she may have received from other sources (lay people, the internet and other healthcare providers).

Drugs of choice during pregnancy

Usually, there are several medications available to treat common conditions and there are some medications which are felt to be safer than others for use in pregnancy.

When choosing therapy in pregnancy the usual considerations of efficacy and side effects should be considered in addition to specific fetal safety concerns. Just as in the non-pregnant population, the lowest effective dose of any drug should be used and polytherapy should be avoided wherever possible. However, it is pointless to prescribe medication at sub-therapeutic doses in order to minimise fetal risks. In fact, this is the worst possible strategy as the mother is being inadequately treated while her baby is still being exposed to medication.

Conditions that may need medication during pregnancy can be broadly grouped into the following:

1. common conditions that can affect pregnant women, in other words, pain, fever, cold and flu, hayfever and allergies
2. conditions related to or exacerbated by pregnancy, such as nausea and vomiting of pregnancy (NVP), heartburn and gastro-oesophageal reflux, constipation, thrush and hypertension; and
3. chronic conditions where women may require ongoing medication, such as depression, epilepsy, rheumatoid arthritis and inflammatory bowel disease.

Table 2. Some known teratogens: drugs to be avoided during pregnancy.

Drug	Comment
Isotretinoin (Roaccutane)	Major teratogen causing craniofacial, ear, cardiovascular and limb defects as well as structural CNS anomalies and neuro-developmental problems. Unfortunately inadvertent exposures in early pregnancy continue to occur due to increasing prescribing rates for relatively minor acne.
Valproic acid	Fetal valproate syndrome including neural tube defects, cleft palate, cardiac anomalies and minor facial dysmorphism as well as increased risk of neuro-developmental problems. Risks greater with polytherapy and with doses >1000mg/day.
Warfarin	Oral anticoagulant. Use between six and 12 weeks gestation associated with warfarin embryopathy characterised by nasal hypoplasia and stippled epiphyses. Increased risks with doses >5mg. Use later in pregnancy may result in fetal CNS haemorrhage.

With the majority of drugs, a higher dose within the normal dosing range does not increase the teratogenic risk. Some exceptions to this rule include lamotrigine, warfarin and valproic acid (increased risks of teratogenicity with daily doses >200mg, 5mg and >1000mg, respectively).

In trying to minimise fetal risks, drugs that have been widely used for many years are preferable to newer alternatives. Although the latter may have fewer maternal side effects there is generally less human pregnancy safety data available and thus they should only be used if there is no therapeutic alternative.

Older drugs are also more likely to have longer term follow-up data available. The older anti-epileptic drugs, carbamazepine and lamotrigine, have reassuring long-term neurodevelopmental data available and although newer anti-epileptic drugs, such as gabapentin, are being increasingly prescribed for other indications (such as chronic pain) and because they are often better tolerated there are no long-term neuro-developmental follow-up studies available and thus caution should be advised especially when being used for off-label indications.

Women with conditions such as hyperlipidaemia may take medication to prevent long-term sequelae of their condition. In these situations, the need for medication during pregnancy needs to be balanced with possible fetal risks, especially when the reason for treatment is prevention of long-term complications. Therefore lipid-lowering statins are not generally recommended for use during pregnancy and breastfeeding.

Drugs in breastfeeding

The benefits of breastfeeding in terms of infant nutrition, immunity and maternal bonding are well known. Many breastfeeding women will require medication to treat either a chronic medical problem, such as depression, or an acquired problem, such as mastitis. However, there is relatively limited data about the milk concentration of many medications used by breastfeeding mothers. Because of this dearth of information and the theoretical concerns about the effects of these maternal medications on the breastfed infant, many clinicians err on the side of caution and advise their breastfeeding patients either to avoid taking needed medication while breastfeeding or to stop breastfeeding temporarily (but, unfortunately, this may become permanently).

As with pregnancy, most product information regarding breastfeeding is relatively discouraging, as drug companies are reluctant to recommend the off-label use of medication in this patient group. Performing a literature search or looking at pharmacokinetic parameters such as oral absorption or protein binding data is often more helpful than looking at product information. It is also important to remember that many of the drugs with little breastfeeding data are actually given to the paediatric population (at doses far greater than those found in breast milk) and this may also help in counselling women where there is minimal breastfeeding data available. In fact, there are relatively few drugs that are absolutely contraindicated in breastfeeding. These drugs include cytotoxic agents, iodine-containing drugs, such as amiodarone, and recreational drugs, such as cocaine and ecstasy. Radiocontrast agents are also contraindicated, but most have a very short half-life so that breastfeeding need only be stopped for a very short time.

There are useful online resources for clinicians to access information about medication safety in breastfeeding including Lactmed.[5]

In conclusion

Information regarding exposures in pregnancy and breastfeeding needs to be up-to date and relevant and given to a woman in a non-directive way that empowers her to make rational decisions and optimise her treatment options. It is far better to delay giving information to a pregnant woman to ensure that it is correct rather than give negative or alarmist advice (even including suggesting termination of an otherwise wanted pregnancy) that is then extremely difficult to undo or unsay. Obstetric drug information services such as MotherSafe can provide information and counselling to healthcare professionals and/or consumers.[6] It is therefore vital that obstetricians are aware of the resources that are available so that they can inform their patients of the risks or otherwise of their medications and thus help guide them to make rational decisions and optimise their treatment during pregnancy and breastfeeding.

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Perinatal mental health

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Anxiety and depression in association with pregnancy, childbirth and the postnatal period remains poorly diagnosed and undertreated.

There is significant morbidity and mortality associated with mental health disorders in pregnancy and the puerperal period. Antenatal anxiety occurs frequently, overlaps with depression and increases the likelihood of postnatal depression.

Up to 80 per cent of mothers experience the 'baby blues' three-to-five days after giving birth. This period of emotional liability is transient and self-limiting, usually dissipating within ten days.

Australian research suggests that around 40 per cent of new parents experience adjustment disorders. Furthermore, up to ten per cent of women experience antenatal anxiety and/or depression, increasing to 16 per cent of women experiencing postnatal anxiety and/or depression with about one-third of fathers also experiencing a depression or anxiety disorder. Puerperal psychosis, which is considered a psychiatric emergency, affects around one in 1000 women. Bipolar disorder is at greater risk of reoccurring postpartum and women with severe psychiatric disorders (bipolar, schizophrenia, major depression) have a 70-fold increased risk of suicide in the first postnatal year.[1]

Suicide has become one of the leading causes of maternal deaths in Australia.[2] The presence of maternal mental health conditions can also have an adverse impact on the growth and development of the fetus/infant and the wellbeing of other family members. The psychological wellbeing of pregnant women and new mothers should therefore be considered as important as their physical health and included as part of routine antenatal and postnatal care.

The first Australian Clinical Practice Guidelines surrounding the detection, management and treatment of perinatal mental health disorders were established in 2011. The beyondblue Clinical Practice Guidelines were endorsed by the National Health and Medical Research Council (NHMRC) and recommend universal antenatal and postnatal mental health screening.[3] Appropriate screening includes administering a depression screener (for example, the Edinburgh Postnatal Depression Scale[4] [EPDS]) and a psychosocial assessment to evaluate psychosocial risk (for example, the Antenatal Risk Questionnaire[5]), and assess for past psychiatric or abuse history, supports, stressors and so forth.

The Diagnostic and Statistical Manual of Mental Disorders V, 2013 lists criteria for the diagnosis of major depression[6]:

- depressed mood and/or anhedonia (lack of interest or pleasure or enjoyment);
- significant change in weight or appetite;
- markedly increased or decreased sleep;
- psychomotor agitation or retardation;
- fatigue or loss of energy;
- feelings of worthlessness or guilt;
- reduced concentration; and/or
- recurrent thoughts of death or suicide.

In addition, these symptoms must be accompanied by significant impairment in capacity to engage and function in usual activities.

Symptoms more specific for perinatal anxiety and depression can include:

- inability to enjoy the new baby;
- concurrent anxiety or panic attacks – physical symptoms of anxiety such as heart palpitations, constant headaches, sweaty hands associated with fears they may unwittingly harm baby or something bad will happen to the baby;
- can't rest even when the baby is sleeping; and/or
- have thoughts of harming themselves or the baby (infanticide).

Management

Apart from the adverse consequences for women becoming depressed when they are going through demanding physical and social changes, there are additional concerns. There is the possible negative impact of pregnancy depression on perinatal outcomes[7], while perinatal maternal depression may impact on the relationship between mother and child and on the child's emotional, behavioural and cognitive development.[8] Primary prevention and early intervention strategies (for example, through routine screening) are potentially important in view of the frequent contact pregnant women, new mothers and infants have with health services, but the effectiveness of these strategies needs to be tested.[9]

There is no evidence to suggest that pregnant or postnatal (perinatal) women require different psychotherapeutic recommendations than other psychiatric patients. Thus, psychological interventions that are effective in the general population will also work in perinatal women:

- For mild-to-moderate anxiety and depression, cognitive-behavioural therapy (CBT) without medications has been shown to be effective. Interpersonal psychotherapy (IPT) without medications can reduce depressive symptoms in perinatal women with depression.
- Because poor marital relationships are consistent psychosocial predictors of anxiety during pregnancy and postpartum depression, recommend family or marital therapy when appropriate.
- For women with a history of childhood trauma (abuse or neglect), more in-depth psychotherapy will be needed.

Medication

Pregnancy influences the pharmacokinetic processes of drug absorption, distribution and elimination. As the glomerular filtration rate usually increases during pregnancy, renal drug elimination is generally enhanced, whereas hepatic drug metabolism may increase, decrease or remain unchanged. A mean increase of eight litres in total body water alters drug distribution and results in decreased peak serum concentrations of many drugs. The placental and fetal capacity to metabolise drugs may influence the fetal exposure to the drugs taken by the mother. However, overall fetal exposure may be very substantial. Because of the changes in pharmacokinetic and drug metabolism as well as increased maternal weight, remaining on the same dose of medication as pregnancy progresses is ostensibly the same as reducing the dose.

In contrast, for most psychotropic drugs the amount ingested by the infant is rarely greater than ten per cent of maternal levels and is thus considered 'safe'. The only exceptions are lithium and lamotrigine, which are lipophilic and may be found in much greater quantities in breast milk.

Ideally, decisions about psychotrophic medication use during and after pregnancy should be made before conception. The use of a single medication at the lowest effective dosage is preferred over multiple medications and those with fewer metabolites and higher protein binding are also preferred. While pharmacotherapy during pregnancy should be minimised, it is important not to undertreat psychiatric illness. Most women with a mood or other serious psychiatric condition will relapse if treatment with an antidepressant or mood-stabilising medication is stopped periconceptually.

All couples have a baseline risk of around three per cent of having a baby with a major birth defect and this may be as high as five per cent if neuro-developmental problems, which may not become apparent until after the first year of life, are also included.

Antidepressants

Around four per cent of Australian women will be on an antidepressant at conception. When choosing an antidepressant or anxiolytic for pregnant or breastfeeding women, prescribers should bear in mind that the safety of these drugs is not well understood. All antidepressants carry the risk of adaptation problems (withdrawal or toxicity) in neonates; in most cases the effects are mild and self-limiting, but may be more severe in sick or premature infants and infants exposed to multiple psychotropic medications.

Tricyclic antidepressants are used to treat depression, particularly in patients requiring sedation, for example dothiepin and in patients with chronic pain syndromes. The data are reassuring regarding both short- and long-term safety. Postural hypotension and constipation in the mother are potential side effects.

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently used antidepressants during pregnancy, but this has caused some controversy because of the lack of consistency in the literature about associations with adverse outcomes. Although further studies are needed to accurately determine the benefits and harms of individual SSRIs, several large meta-analyses examining thousands of offspring exposed to SSRIs indicate that these are not linked with adverse obstetric outcomes such as increase in miscarriage, low birthweight or prematurity[10] or malformations[11] apart from a small association with paroxetine and septal ventricular defects (most of which spontaneously resolve).

SSRIs taken after 20 weeks gestation appear to be associated with a small increased risk of persistent pulmonary hypertension (PPHN) in the neonate.[12] Stopping SSRIs in the third trimester has been suggested to reduce the potential for PPHN and neonatal withdrawal symptoms, but this is not proven. However, the absolute risk of any baby developing PPHN is extremely low. Furthermore, the mother is placed at risk of exacerbation of her symptoms at a critical juncture in her pregnancy, delivery and early parenting.

The longer term, subtler neurodevelopmental outcomes of infants exposed to SSRIs need a lot more evaluation, but so far the best study available does not suggest major adverse consequences in children followed up to six years of age.[13]

SSRI molecules do pass into the mother's milk, owing to their low molecular weight, but the infant dose remains less than 5–10 per cent. Citalopram and fluoxetine are present in breast milk at higher levels than sertraline, which is the least. However, women should not switch SSRIs on breastfeeding safety grounds alone.

Other psychotropics

Benzodiazepines (such as diazepam for panic attacks) use in the first trimester was thought to be associated with an increased risk of cleft palate, but a more recent meta-analysis does not support this earlier report. The main concern with chronic use of benzodiazepines is tolerance or dependence in the mother. There is no evidence for long-term neurodevelopmental delay. Benzodiazepines use later in pregnancy may be associated with floppy baby syndrome, neonatal drowsiness and respiratory depression and seizures.

Mood stabilisers for bipolar disorder

Valproate should be avoided as much as possible in pregnancy. Neural tube defects (such as spina bifida and anencephaly) have risk raised from around one in 1000 to 1–2 per cent; with an absolute risk of birth defects, including cardiac defects, cleft lip and palate and facial dysmorphism, of between eight and 12 per cent. There are known risks of neurodevelopmental sequelae, even with valproate monotherapy.[14]

Lamotrogine is being increasingly used to treat mood disorders and, overall, has not been associated with an increased risk of birth defects, although some studies have suggested a slightly increased risk of cleft lip/palate with doses greater than 200mg/day. As opposed to valproate, long-term neurodevelopmental data are reassuring.

Women whose mental health is stable with lithium should not necessarily be advised to cease or change their treatment. They should be counselled about the small risk of cardiac malformations in the fetus and potential neonatal toxicity during breastfeeding (because of the high levels in breast milk). However, in most patients stable on lithium, the benefits to the mother outweigh the small risks to the baby.

Antipsychotics

There is very little safety information available on antipsychotics, which are used to treat psychosis but also, increasingly, in the short-term management of anxiety and mood disorders. So far, small studies suggest no risk of birth defects, but there are no long-term neurodevelopmental data available. Atypical antipsychotic medications are associated with maternal weight gain, subsequent glucose intolerance and other associated obstetric risks.

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Further Reading

CG45 Antenatal and postnatal mental health: full guideline
NICE National Institute for Health and Care Excellence
http://guidance.nice.org.uk/CG45/Guidance

Beyondblue Clinical Practice Guidelines for Depression and Related Disorders – Anxiety, Bipolar Disorder and Puerperal Psychosis – in the Perinatal Period. A guideline for primary care health professionals. Available at: www.beyondblue.org.au/index.aspx?link_id=7.102&tmp=FileDownload&fid=1626 .

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www.tresillian.net
www.whatwerewethinking.org.au/
www.ngala.com.au/

National Perinatal Depression Helpline 1300 726 306 (Monday to Friday 10am–5pm AEST).
Behind the Mask; The Hidden Struggle of Parenthood. Trailer: www.youtube.com/watch?v=FjqOqJLkyFs .
Beyond the Baby Blues; The complete perinatal anxiety and depression handbook (2011) Knox, C, O'Reilly, B, Smith, S.

MotherSafe

www.mothersafe.org.au
MotherSafe is a free telephone advisory service on exposures in pregnancy and lactation for the women of NSW and their healthcare providers, based at the Royal Hospital for Women, Randwick.

Menopause pharmacology

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A review of the pharmacology of clinically proven treatments for the common symptoms of menopause.

The menopause, defined as the permanent cessation of ovarian follicular activity, or, in practical terms as the absence of menses for more than 12 months in a woman who has not undergone hysterectomy, normally occurs within a ten-year window from age 45–55, with a mean age of 51.5 years in the Australian population.

The menopause is associated with a variety of short- and long-term symptoms. The commonest acute symptoms are the vasomotor symptoms of hot flushes and night sweats, followed by joint and muscle pains, insomnia, vulval symptoms and poor memory. Figure 1 illustrates common menopausal symptoms with differences in incidence experienced around the world. Interestingly, these differences are seen within different national and ethnic subgroups as well. Long-term consequences of the menopause include osteoporosis, with increased risk of associated fracture, and cardiovascular disease. These symptoms have one common thread; they are owing to withdrawal of oestrogen in a previously oestrogen-primed woman.

Vasomotor symptoms are the most common presenting symptom in Western women. Core body temperature is controlled by a temperature control centre within the medial pre-optic area of the hypothalamus.[1]

In premenopausal women physiological levels of oestrogen maintain endorphin levels within the hypothalamus, but when oestrogen declines after the menopause there is a resulting release of noradrenergic activity from its tonic inhibition. This leads to increased hypothalamic release of noradrenaline and serotonin, leading to a lowering of the sweating threshold in the thermoregulatory centre. Post-menopausal women who experience hot flushes have a greater narrowing of the thermoregulatory zone than those women who are symptom free and are, therefore, more sensitive to small increases in core temperature.[2] Studies have confirmed that oestrogen administration widens the thermoregulatory zone.[3]

Menopausal arthralgia has been reported in more than 50 per cent of Australian women, with an even greater percentage following surgical menopause and in Asian women. The same symptoms are commonly seen following the initiation of aromatase inhibitor therapy.[4] Oestrogen withdrawal is clearly the cause and the mechanism of action appears to be related to the

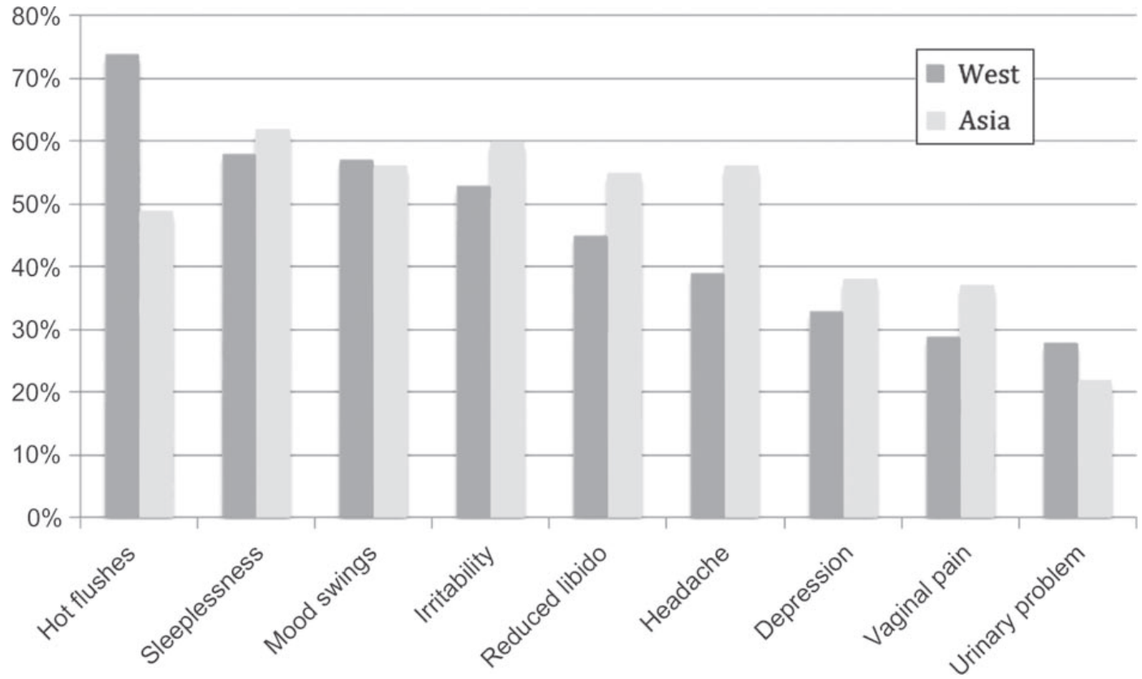

Figure 1. Prevalence of menopausal symptoms in Asian and European women. From Baber R East is east and West is west: perspectives on the menopause in Asia and The West. Climacteric *2014;17:23-28 (reproduced with permission).*

actions of sex hormones on pain processing pathways, immune cells and chondrocytes.

Vulval symptoms are also very common and result from the effect of the hypo-oestrogenic state on the vulval and vaginal epithelium. These changes result in vulval and vaginal dryness and itchiness, as well as superficial dyspareunia and sexual dysfunction.

Oestrogen

Oestrogen withdrawal is at the heart of menopausal symptoms thus, not surprisingly, oestrogen replacement has proven to be the most effective treatment. Oestrogen exerts the majority of its effects in a traditional endocrine manner, via genomic [transcriptional] effects mediated by hormone binding to the oestrogen alpha and beta receptors.

The effect of oestradiol on vasomotor symptoms is genomically mediated, is dose dependent and has proven to be the most effective treatment of vasomotor symptoms.[5] The effects of oestrogen on the cardiovascular systems are also largely genomic, however there are some non-genomic actions resulting from the recruitment of signalling pathways that are often associated with cell membrane receptors, ion channels or enzyme linked receptors. The complex interplay of transcriptional and non-transcriptional mechanisms results in increased production of nitric oxide, with resultant rapid vasodilatation of blood vessels, blocking the vessel wall's response to injury and decreasing the development of atherosclerosis.[6] Similarly, in studies of the effects of oestrogen on bone, while the major effects are mediated via ERs found on osteoclasts, non-transcriptional effects have also been found, resulting in a net response of increased bone density.

The route of administration of oestrogen may affect the side-effect profile, with increasing evidence that topical oestrogen patches are associated with a reduced risk of venous thromboembolic and cerebovascular events compared to oral oestrogen, probably owing to the former bypassing hepatic first-pass metabolism.[7]

Local oestrogen treatment of vulval symptoms is extremely effective, and there was no increase in incidence of endometrial hyperplasia when compared to placebo in a Cochrane meta-analysis.[8] However, the rate of systemic absorption is variable and topical oestriol may be preferable to topical oestradiol, as the receptor binding affinity of oestriol is 80 times weaker than that of oestradiol.

Progestogens

Progestogens are a group of C21 carbon structures containing a pregnane skeleton that bind to progesterone receptors. They include naturally occurring progesterone and the synthetic progestins.

The principal role of progestogens is to protect the endometrium from oestrogenic stimulation, as unopposed oestrogenic stimulation of the endometrium will lead to endometrial hyperplasia, atypical hyperplasia and endometrial cancer. Numerous studies have shown that administration of a progestogen for ten to 14 days per month will induce secretory change in the endometrium and prevent hyperplastic change. This action is mediated genomically via the progesterone receptors PR a and PR b.

While natural progesterone and the retro progesterone dydrogesterone bind mainly to the progesterone receptors, the synthetic progestins not only bind to the progesterone receptor but also bind to other steroid receptors including glucocorticoid, mineralocorticoid, androgen and oestrogen receptors. This can give rise to unwanted side effects including the apparent increase in risk of breast cancer seen with long-term use of oestrogen combined with synthetic progestins compared to natural progesterone or dydrogesterone.[9]

Therefore, progestogens should only be used in women with an intact uterus or in women receiving HRT for debilitating menopausal symptoms shortly after surgical treatment of endometrial cancer.

Testosterone

Testosterone is produced in the adrenal cortex and the ovary. Levels decline following the menopause and are more pronounced following a surgical menopause. There is no level of testosterone below which a woman can be described as androgen deficient. However, several randomised clinical trials of testosterone in doses appropriate for women have shown significant benefit in the treatment of hypoactive sexual desire and arousal disorders.[10] Testosterone exerts its primary effects genomically via testosterone receptors; however, it is important to note that aromatase also converts testosterone to oestrogen. Therefore, without testosterone women cannot produce oestrogen and testosterone supplementation will inevitably result in some oestrogen production as well.

Tibolone

Tibolone is a synthetic compound exerting oestrogenic, progestogenic and androgenic properties. The parent compound has only weak activity, but is metabolised in the gut into two hydroxylated metabolites that exert their clinical effects primarily by binding to the oestrogen receptors. A Delta 4 isomer acts as a weak progestogen, exerting its effect via the progesterone receptors, and the parent molecule also exerts a weak androgenic effect via the androgen receptor. Tibolone and its metabolites also inhibit the action of a breast specific sulphatase enzyme and 17-beta hydroxy steroid dehydrogenase type 2, resulting in reduced oestrogenic stimulation of the breast. Thus although tibolone alleviates vasomotor symptoms, improves bone density and reduces fractures it does so via a combination of metabolic, enzyme-mediated and receptor-mediated actions.[11]

Non-hormonal treatments

SSRIs and SNRIs

Perhaps the most commonly used non-hormonal prescription treatments for hot flushes are the antidepressants, usually in doses much lower than those required to treat major depressive illness. Selective serotonin re-uptake inhibitors (SSRIs) are potent inhibitors of serotonin re-uptake. Serotonin noradrenaline re-uptake inhibitors (SNRIs) are potent inhibitors of serotonin and noradrenaline re-uptake, although in many cases low-dose SNRIs will block only serotonin re-uptake and high-dose SNRIs will block re-uptake of serotonin, noradrenaline and also dopaminergic neurotransmission. As mentioned earlier, the mechanism underlying hot flushes appears related to a disorder in thermoregulation triggered by oestrogen withdrawal and mediated by either adrenergic or serotonergic neurotransmission.[12] Given that SSRIs inhibit only serotonin re-uptake and low-dose SNRIs act principally via the same mechanism, it seems most likely that alleviation of vasomotor symptoms is via the effect of the drugs on serotonin.

Perhaps the most widely used is venlafaxine in doses of 37.5–75mg. The active metabolite of venlafaxine, desvenlafaxine[13-16], in doses of 50–100mg daily has also proved effective, as have escitalopram[17] and citalopram.[18] Unlike the treatment of depressive symptoms, alleviation of hot flushes with these treatments is usually rapid, within one or two weeks. Side effects are typical of all antidepressants, but usually mild because of the low doses used. Paroxetine has also been shown to be effective and was recently approved by the FDA in a very low dose of 7.5mg daily.

Some SSRI/SNRIs have the potential to interfere with tamoxifen metabolism. Paroxetine and fluoxetine are potent inhibitors of CYP2D6 in vitro, while venlafaxine, desvenlafaxine, citalopram and escitalopram have little or no effect. Therefore, the latter should be preferred in women receiving tamoxifen therapy. A randomised cross-over trial of gabapentin and venlafaxine showed a similar reduction in hot flushes, but women preferred venlafaxine.[19]

Clonidine

Clonidine stimulates alpha 2 adrenoreceptors in the brain stem resulting in reduced sympathetic outflow from the central nervous system and decreased peripheral resistance, heart rate and blood pressure.[16] Normal postural reflexes are unaffected. Clonidine's principal indication is to treat hypertension but it has been demonstrated to have a modest impact on vasomotor symptoms. The mechanism for this action remains uncertain, but may be owing to reduced catecholamine production or alternatively to reduced peripheral vasodilatation.

Doses used are usually 50μg twice daily and in those doses side effects are generally mild and include dry mouth, constipation, drowsiness and dizziness. As with most interventions, an improvement in symptomatology should be seen within four to six weeks.[20]

Gabapentin and pregabalin

Gabapentin and pregabalin are analogues of gamma aminobutyric acid (GABA) and were originally developed to treat epilepsy and neuropathic pain. Gabapentin, in particular, has also been shown to be effective, in a dose-dependent manner, in the treatment of vasomotor symptoms of the menopause.

The mechanisms of action of gabapentin and pregabalin remain unclear. Despite their origins, neither drug has activity in the GABAergic neurotransmitter system. Gabapentin increases the concentration and probably the rate of synthesis of GABA in the brain, it binds with high affinity to a novel binding site in the brain associated with voltage-sensitive calcium channels, it appears to modulate certain types of calcium current, it reduces the release of several monoamine neurotransmitters and it increases serotonin concentrations in human whole blood.

Not surprisingly, the mechanism of action of gabapentin in alleviating hot flushes has not been fully elucidated. Gabapentin inhibits neuronal calcium currents in vitro, binding to alpha 2 gamma voltage-gated calcium channels. This binding site is substantially up-regulated in response to peripheral nerve injury and may be similarly up-regulated in response to oestrogen withdrawal leading to increased activity of neurotransmitters in the hypothalamus.[21]

In randomised controlled trials, gabapentin in doses of 900mg per day has been shown to be significantly better than placebo in the treatment of hot flushes.[22] Dizziness and somnolence are the commonest side effects and both are dose dependent as well as reversible.

Summary

Although oestrogen (in combination with progestogen for endometrial protection) is the most effective way of treating vasomotor symptoms, there are many non-hormonal options available. There is increasing evidence that the route of oestrogen administration may change the side-effect profile and topical oestrogen is an effective way of treating postmenopausal vulval symptoms.

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Saved by fetal surveillance

Dr Will Twycross
DRANZCOG

Massive perivillous fibrin deposition is a rare placental condition with a high rate of fetal demise. It usually presents in women who are otherwise well, unlike the common maternal conditions associated with placental compromise. This leads to a high risk of it going unrecognised in nulliparous patients.

Patients may travel or holiday in late pregnancy, leading to delivery in a facility other than that in which they are booked. We report the case of a nulliparous woman on holiday near term, who presented to a small rural facility with two days of decreased fetal movements. Booked at a tertiary facility, she had no apparent medical complications of pregnancy. CTG findings of surprising severity precipitated the need for urgent delivery on site. Placental histopathology confirmed a rare placental condition of unknown aetiology with a high rate of fetal demise.

Mansfield is a small rural town in north-east Victoria. It has a large influx of visitors on weekends, mainly for recreational and adventure tourism. The local hospital delivers an average of 90 babies annually. The obstetric unit has an operative delivery capacity that has been maintained because the nearest referral hospital, at Wangaratta, is 90 minutes by road. The Melbourne tertiary hospitals are three hours by road. Midwifery, medical and theatre staff participate regularly in continuing professional development (including RANZCOG's Fetal Surveillance Education Program and simulation training) and the team approach is strengthened by a shared model of antenatal care. The only blood available for emergency cases is two units of O-negative and the town and hospital have no pathology laboratory. On Australia Day, 2014, the Mansfield District Hospital A&E and wards were busy. Theatre staff had performed an emergency caesarean section at 5am that morning. In the mid-morning, a 42-year-old nulliparous (G5P0) woman presented to A&E concerned about two days of decreased fetal movements. She was at 37+2 weeks in her only pregnancy to reach viability, and was booked for delivery at a tertiary facility in Melbourne. The A&E nurse triaged her to a midwife who applied a CTG and took her history. Her four previous miscarriages had been investigated at a tertiary recurrent miscarriage clinic, with two equivocal findings, a weakly positive (1:320) ANA titre and a factor XII of 49 (ref 50-150). Duloxetine 60mg bd had been taken throughout the pregnancy owing to a past history of severe depression.

On examination, the patient was clinically well. She was afebrile, normotensive not hyper-reflexic, had no peripheral oedema and clear urinalysis. The fundus was a 34 week size, (clinically small for dates), the presentation was cephalic and there were no palpable contractions. The CTG showed three prolonged deep decelerations, two following weak (unfelt and not palpable) Braxton-Hicks contractions (see Figure 1). A decision was made to proceed to emergency caesarean section and consent obtained. While theatre staff were arriving, antenatal notes faxed from the Mercy Hospital in Melbourne revealed a normal pregnancy until that time. It was noted that there was no bleeding or bruising during IV insertion.

In theatre, deep decelerations continued during spinal insertion (see Figure 1). Delivery occurred two hours after presentation, with the liquor having been noted to be clear and the maternal surface of the placenta unusually and almost uniformly white in appearance (see Figure 2). Apgars were 6 (at one minute) and 8 (at five minutes) and the male baby's birth weight was 2580g (13th percentile).

Bleeding/clotting during the procedure was normal and the overall operative loss was 500ml. The baby was noted clinically to be under-nourished and, when put to the breast, fed poorly. His blood sugar level dropped to 1.4 after four hours. It was corrected with complementary feeding every three hours up to 90ml/kg/day. He subsequently fed well on the breast and on discharge, on day six, had gained 46g. As is customary in the country for Australia Day, he appeared on the front page of the local paper beside the (much larger) baby delivered earlier that morning. He has subsequently thrived (personal communication).

The placenta was re-examined and photographed postoperatively (see Figure 2). It was firm to the touch, with a predominantly yellow-white maternal surface (80 per cent of surface). Subsequent pathological and histological analysis showed 'massive perivillous fibrin deposition (MPVFD) with secondary infarction' (see Figures 3 and 4).

MPVFD is a rare, but serious condition and, unlike the common ischaemic placental pathologies, usually presents in women who are clinically well, making its onset likely to go undiagnosed. The term is used interchangeably in the literature with 'maternal floor infarction'.[1,2] The striking macroscopic appearance conforms exactly with the histological appearance, the densest fibrin deposition being in the basal (maternal surface) layer.


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OUR NEWEST AUSSIES:

AUSTRALIA Day will always be special for these two tiny babies – born at Mansfield District Hospital on Australia Day 2014. (right) the first child for arrived shortly after 5am, while the yet un-named and early arrival for and arrived at 12.59pm.

For full details on both babies, turn to page 2.

A moment of fame, the two babies born on Australia Day were front-page news in the town.
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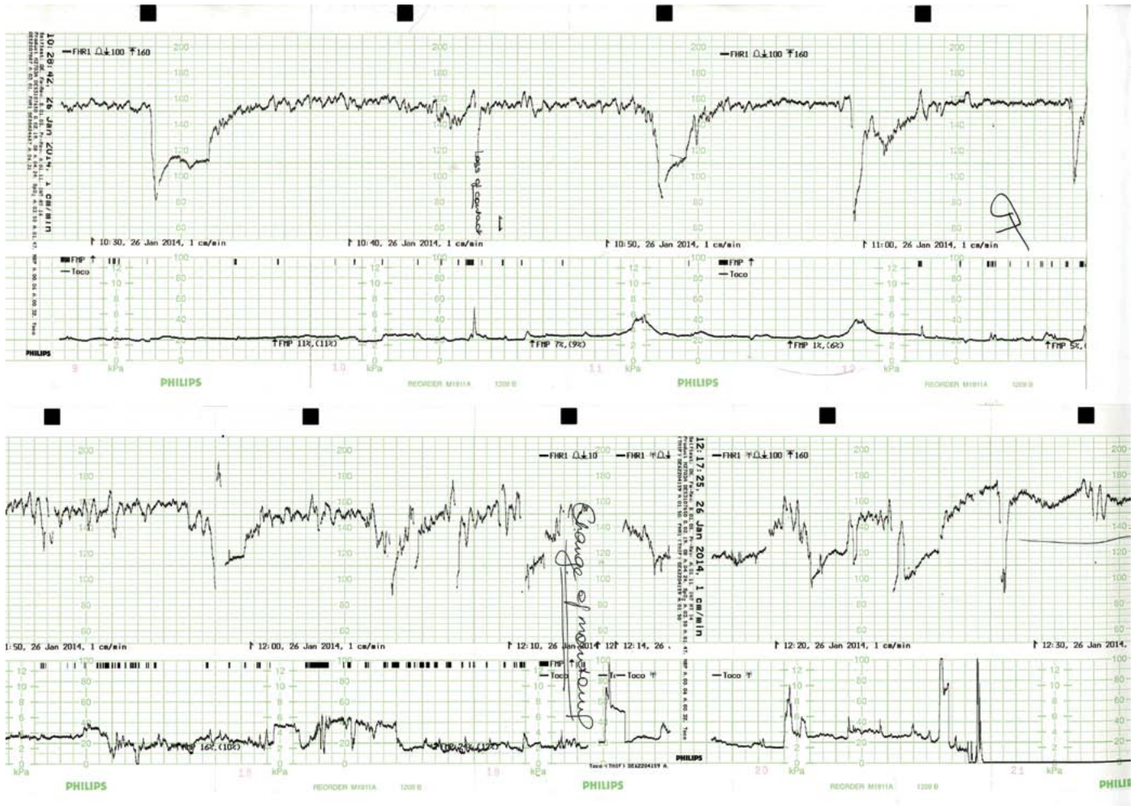

Figure 1. Maternal CTG on presentation and during spinal anaesthetic insertion.

RANZCOG releases latest edition of the Intrapartum Fetal Surveillance Clinical Guideline

RANZCOG has recently published the third edition of the Intrapartum Fetal Surveillance Clinical Guideline.

The principal aim of Intrapartum Fetal Surveillance (IFS) is to prevent adverse perinatal outcomes arising from fetal hypoxia and metabolic acidosis related to labour. In combination with continuing education, training and credentialing, this Guideline has been developed to help reduce adverse perinatal outcomes related to inappropriate or inadequate IFS.

This Guideline is intended for use by health care professionals, including obstetricians (specialist or general practitioner), midwives, physicians, trainees and allied health professionals providing care to women in established labour in Australia and New Zealand. Given the diversity of practice and the unique geography of Australia and New Zealand, the College believes this Guideline should be the preferred guideline, as it has been written with these considerations in mind.

To support the implementation of best practice in IFS, RANZCOG also runs a range of face-to-face education programs across Australia and New Zealand. These programs are based on the IFS Clinical Guideline and underpinned by a range of educational resources, including online programs and a reliable assessment tool (www.fsep.edu.au).

This third edition of the Guideline is available for download from the College website, under Statements and Guidelines: Fetal Surveillance.

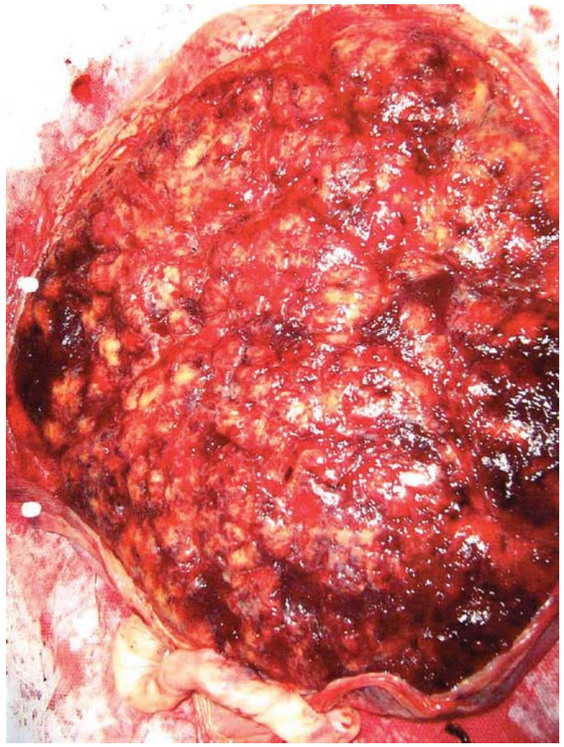

Figure 2. Placenta: maternal (basal) surface taken ten minutes after birth.

MPVFD results in high rates of interuterine growth restriction (IUGR), perinatal morbidity and mortality and recurrence. The literature agrees that the aetiology is currently unknown, and multifactorial. In a recent comprehensive pathological review, Ona et al[2] postulate: 'The microscopic features of MPVFD are highly suggestive of either direct damage to the syncytio-trophoblast and/or disturbances in the balance of dually derived intervillous procoagulant/ anticoagulant factors necessary to maintain the fluid state of the blood in the maternal space.' Possible causes of syncytio-trophoblast injury include hypoxic, toxic, infective, allo-immune and auto-immune pathologies and, with respect to clotting disorders, the anti-phospholipid syndrome has been confirmed in a number of cases.[3] A retrospective controlled study of the serum of ten MPVFD patients[4] has shown that a subset of patients with MPVFD have immunological markers consistent with maternal anti-fetal rejection. The term 'fibrinoid' is sometimes used, rather than fibrin as immunohistochemical analysis shows the deposition matrix appears to contain fibrin from both the maternal coagulation cascade and an extra-cellular fibrinoid substance derived from the trophoblast[2], making the condition's complex pathogenesis even more intriguing. It is thus likely the condition has numerous possible causes involving either/or syncytio-trophoblastic damage or coagulation disturbance in the intervillous space, each or both leading to the final common pathway of fibrinoid deposition.

The largest retrospective histological analysis, (47000 deliveries between 1991 and 1998) in northern Dublin[5], was enabled by the fact that in Rotunda Hospital, the placenta is examined histologically and slides kept in all cases with an abnormal antenatal course or outcome. It found 13 cases (11 mothers), an incidence of 0.028 per cent. The fetal mortality rate was 31 per cent, delivery was pre-term in 33 per cent and all fetuses showed IUGR. Only one of the 13 was delivered by lower segment caesarean section, implying that only one was detected clinically or was detected as distressed prior to delivery (CTGs were not reviewed). Re-examination in 2002 of the placental slides with an electron microscope showed the condition to involve sclerosis of the villi by 'true fibrin'. This led the authors to question the term maternal floor infarction, as the condition involved sclerosis of the chorionic villi as the primary process, rather than infarction. The argument that the use of the term infarction is inaccurate is supported by the more recent review of the pathological process, quoted above.[2] All the fetal postmortems in the Dublin series showed definite histological evidence of hypoxia. In this series, the condition also had a high

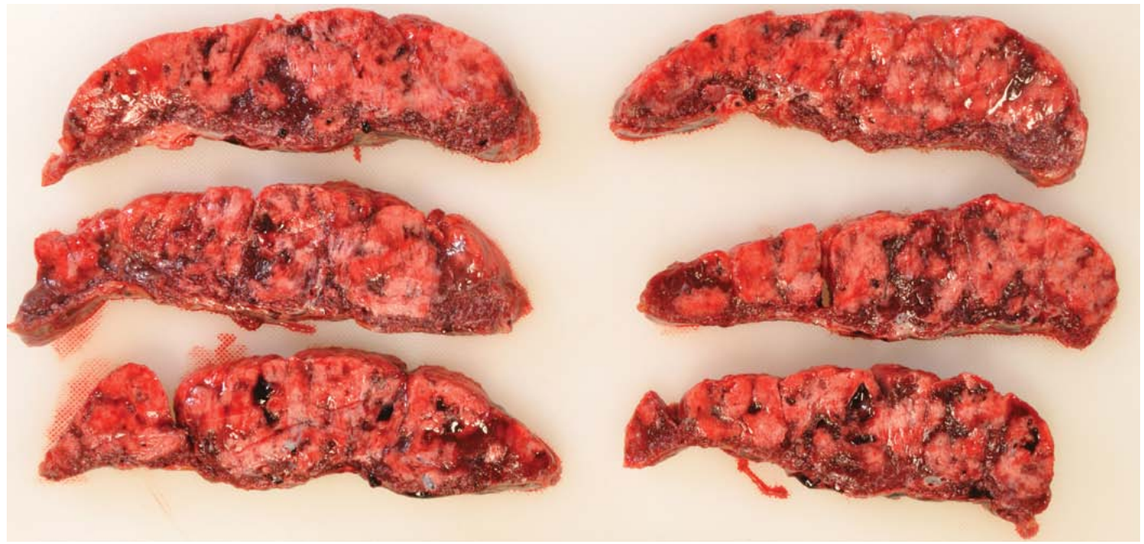

Figure 3. Placenta: cross section. (From another case: Courtesy Dr Nick Manton, Consultant Pathologist, SA Pathology.)

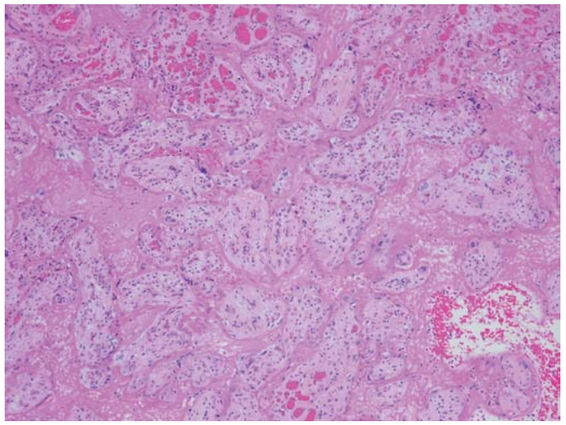

Figure 4. Placenta: H&E section showing eosinophilic fibrin deposition in intervillous space, surrounding degenerate chorionic villi. (From another case: Courtesy Dr Nick Manton, Consultant Pathologist, SA Pathology.)

recurrence rate (18 per cent). The study acknowledges the possibility that another population may show different characteristics with respect to MPVFD.

The clinical prenatal correlations of MPVFD are difficult to study, but the ultrasound triad of IUGR, low AFI and a dense hypoechogenic placenta would correlate with declining placental and fetal renal function, and the fact that dense fibrin depositions appear anechoic or hypo-echoic on ultrasound. This has led some researchers to emphasise the condition's preventable nature, particularly where possible predisposing factors such as recurrence or recurrent miscarriage are present.[6]

Despite these possible clues receiving commentary in the early 1980s, the large Dublin series confirms that during the 1990s, the condition remained rarely recognised antenatally, which is hardly surprising considering its rarity. The Mansfield case is interesting as an example of being able to correlate a clearly abnormal GTG trace with this rare placental pathology. Five consistent ante- and postnatal factors correlate in this case: the mother's (life-saving) observation of decreased movements; a severely compromised CTG; a placenta which was macroscopically over 80 per cent compromised; histological confirmation of the pathology; and the delivery of a poorly nourished baby whose clinical course confirmed diminished glycogen stores.

Small rural hospitals whose booked obstetric case load is 'low risk', may still need to have the ability to perform emergency caesarean section safely, especially if they are a long way from the nearest referral hospital. Occasionally, operative delivery will also prove life saving to visitors to the district, as it was in this case, or as in another recent case at the same hospital where a classical caesarean section was performed at 29 weeks for a patient with an abruption. In both of these cases, a good outcome was enabled by the presence of medical, nursing and theatre staff capable of dealing with operative obstetric emergencies.

This case highlights the need to urgently investigate a mother's report of decreased fetal movements and for high levels of vigilance in patients with a history of recurrent miscarriage. While the mother felt in later written communication that the life of her baby was saved at the hospital, it was her own action in reporting this change which was the most crucial step in a timely and successful outcome. She subsequently sent a significant donation to the maternity unit, raised by her family in Melbourne.

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Journal Club

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

Endometrial polyps

Endometrial polyps are a common gynaecological problem with the normal treatment being polyp removal, commonly as a day surgery procedure. Polyps may be removed blindly with polyp forceps, resected with an operating hysteroscope or be removed with a mechanical hysteroscopic morcellator.

Smith et al report a multicentre single blind randomised controlled trial comparing hysteroscopic morcellation with a 2.9mm rotary morcellator, with a disposable bipolar hytseroscopic electrosurgical system. All procedures were performed in the office setting without general anaesthesia or conscious sedation. Women were excluded from the study if they wished to be treated under a general anaesthetic, or if they were considered by the surgeon to be unable tolerate an office polypectomy. In all, 121 women were randomly allocated to the two groups.

Women in the morcellation group had a significantly higher rate of complete removal of the polyp, a significantly shorter procedure time and a significantly lower pain rating during the procedure, but not afterwards. A significantly higher number of women rated the morcellation technique as totally acceptable; however, only one woman rated either technique as totally unacceptable. The authors concluded that office hysteroscopic morcellation of endometrial polyps is faster and less painful than electrosurgical resection. It is a modality that warrants consideration when dealing with this common problem.

1 Smith PP, Middleton LJ et al. Hysteroscopic morcellation compared with electrical resection of endometrial polyps. *Obstetrics and Gynecology* 2014; 123:745-751.

Caesarean section and endometriosis

The rate of caesarean section (CS) continues to rise, with the Australian Institute of Health and Welfare reporting a rate of 32.3 per cent in 2011.[1] One possible long-term complication is endometriosis. While endometriosis in the caesarean scar is well-known, this Swedish study[2] seeks to answer whether the risk of pelvic endometriosis is increased by CS. Andolf et al performed a prospective cohort study linking ICD diagnoses of endometriosis from the Swedish Patient Register with mode of delivery data from the Swedish Medical Birth Registry. Women were included in the study if they gave birth to their first child between 1986 and 2004, for a total of over 700 000 women. Of these, 3110 were treated as inpatients for endometriosis between 1987 and 2005 when the data were retrieved for analysis.

The rate of endometriosis in the CS group was 0.6 per cent while in the vaginal delivery group it was 0.4 per cent. Women who had vaginal deliveries before CS were included in the CS group after that delivery, while women having a vaginal birth after CS remained in the CS group. The authors report a significantly increased risk for endometriosis after CS compared to having all vaginal deliveries (hazard ratio =1.7; 95 per cent CI 1.7-1.9). They also report that there would be one extra case of endometriosis over ten years for every 325 CS performed. Merits of this study include the large numbers; however, association does not necessarily mean causality and their results require further study.

1 Li Z, Zeki R, Hilder L & Sullivan EA 2013. Australia's mothers and babies 2011. Perinatal statistics series no. 28. Cat. no. PER 59. Canberra: AIHW National Perinatal Epidemiology and Statistics Unit.
2 Andolf E, Thorsell, Källen K. Caesarean section and risk for endometriosis: a prospective cohort study of Swedish registries. *BJOG* 2013; 120: 1061-1065.

Mammography and breast cancer mortality

This Canadian paper[1] has received considerable publicity and debate since its publication. We should be aware of its main findings and of the lessons that may be learned for gynaecological screening programs. Miller et al report a randomised screening trial comparing mammography to no mammography over a 25-year period in Canada. Nearly 90 000 women aged 50–59 were enrolled into the trial between 1980 and 1985 and over five years received either annual mammography screens or no mammography. Women aged 40–49 in the mammography arm and all women aged 50–59 in both study arms received annual physical breast examinations, while women aged 40–49 in the control arm received a single physical breast examination before being returned to normal care in the community. Diagnoses of breast cancer and deaths attributed to breast cancer were ascertained from linkage to records including the Canadian Cancer Registry and the Canadian national mortality database.

The results found, during the five-year screening period, in the mammography arm there were 666 diagnoses of invasive breast cancer and 180 deaths from breast cancer (over the entire follow-up period), while in the control group there were 524 diagnoses and 171 deaths. The rate of mortality was not significantly different between the two groups.

Over the whole study period, there were 3250 diagnoses and 500 deaths from breast cancer in the mammography group, and 3133 diagnoses and 505 deaths in the control group. The authors also conclude that 22 per cent of screen-detected breast cancers were over diagnosed. The conclusion of the study was that mammography did not significantly reduce mortality from breast cancer compared to physical breast examination or usual care when adjuvant therapy for breast cancer was freely available. This result has been predictably controversial. A similar Swedish study on breast screening in 2011[2] reported a 31 per cent decrease in mortality in the screening arm. Criticism since the publication of the Miller et al study has also included discussion of better screening results from more modern imaging technology; however, it raises important questions of the evaluation of screening programs. In the case of breast cancer, improved treatments may have altered the value of mammography over time. In gynaecology, we will see a similar debate regarding the effect of the HPV vaccine on cervical screening. Both programs are expensive and governments will be keen to spend their health budget optimally.

1 Miller AB, Wall C et al. Twenty-five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomized screening trial. *BMJ* 2014; 348: 366.
2 Tabar L, Vitak B et al. Swedish two-county trial: Impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology* 2011; 260: 658-663.

Q&a

Q&a attempts to provide balanced answers to those curly-yet-common questions in obstetrics and gynaecology for the broader *O&G Magazine* readership, including Diplomates, Trainees, medical students and other health professionals.

Q *'I have a patient whose routine morphology ultrasound, performed at 19 weeks, revealed normal morphologic appearances, placental position and liquor volume, but measurements suggesting the fetus was symmetrically small, about two weeks smaller than the dates. The dates are very certain and she had an ultrasound at 12 weeks (with a low-risk NTS result). How should I handle this and what should my plan be?*

Dr Chris Wilkinson
FRANZCOG, DDU, CMFM, MPH

a The unexpectedly small fetus is a puzzling problem and can cause great distress to women. Of course, the commonest cause of a fetus that is morphologically normal, but symmetrically small is simply wrong dates. In this case, the dates appear to be accurate, but it is always worth reviewing the earlier imaging to make sure that measurements from the nuchal translucency scan were accurately taken. It is also useful to re-check the PAPP-A result, if it was done, to see whether it was low and might be associated with very early-onset growth restriction, and to review the maternal medical history.

Assuming that the dates are accurate and that the nuchal translucency screen yielded a low-risk result, then an assessment of the parents is the next step. It may seem obvious, but a very petite mother and small father can have a small baby. If the liquor volume is normal and the Doppler waveform of the uterine arteries is normal, it is worth checking for congenital infection. This includes the 'TORCH' serology – toxoplasmosis, rubella, cytomegalovirus and herpes.

It is definitely worth having a second pair of eyes check the 20-week scan, (in particular the heart and outflow tracts), by having a second opinion from another skilled and experienced imaging specialist, such as a maternal-fetal medicine subspecialist or obstetric ultrasound subspecialist. At the time, an amniocentesis or non-invasive prenatal testing (NIPT) could be discussed, particularly if there are any soft signs or suspicious anatomic features elicited – an appropriate quantitative PCR can also be undertaken for congenital infection on the specimen of liquor.

Whatever the outcome of these investigations, serial ultrasound is important. In this case, I would repeat the ultrasound in two weeks to assess growth velocity, dopplers (umbilical artery, ductus venosus and middle cerebral artery), amniotic fluid volume and to see if any structural abnormalities with the fetus become more evident (such as a reduction in limb growth velocity, suggesting skeletal dysplasia). Timing of ultrasound assessment afterwards depend on the hypothesised cause, as appropriately timed premature delivery as prompted by fetal surveillance with ultrasound (and CTGs after 26 weeks) may reduce the risk of stillbirth in an otherwise normal baby with placental insufficiency.

Intrapartum care in Kiribati

Carmel Walker
Asia Pacific Services
Senior Co-ordinator

In January 2014, the College delivered its new RANZCOG Intrapartum Care workshop program in Kiribati. This was the first time that RANZCOG had conducted training workshops for doctors, midwives and medical assistants in Kiribati.

The RANZCOG Intrapartum Care (IPC) program, developed and delivered since 2013 through the Australian government (formerly AusAID) Pacific Island Project, is administered by the Royal Australasian College of Surgeons, but facilitated and coordinated by RANZCOG. Pilot workshops were conducted in Fiji in April 2013, led by Prof Glen Mola, with responses indicating that the workshop could be a valuable contribution to local efforts to improve intrapartum care by kick-starting the introduction of new practices and skills. Building on the pilot workshop series, the RANZCOG Educational Development Unit has further developed the program. This ensures it is underpinned by a robust, quality educational framework, including stakeholder buy-in to ensure quality data collection for short-term and longitudinal analysis of changes and improvements in the delivery of intrapartum care in the sites where the workshops have been held. The RANZCOG team that went to Kiribati consisted of Prof Rajat Gyaneshwar, obstetrics and gynaecology consultant from Fiji; Bronwyn Robinson, educational development senior coordinator; and the author.

The IPC workshops were well supported by the Minister of Health in Kiribati, Dr Kautu Tenaua, himself an obstetrician/gynaecologist, who still works a one in three roster in the labour ward, as well as attending to his demanding ministerial responsibilities.

Skills station, IPC workshop Kiribati, January 2014.

Dr Ioanna Beiatau demonstrates shoulder dystocia at the IPC workshop.

'We were very appreciative of the RANZCOG team's visit to Kiribati for onsite training in the management of labour. From the workshops, I learned that there are many gaps in the knowledge of some of our midwives and some misunderstandings, which have led to inappropriate management of women in the third stage of labour, women with prolonged rupture of membranes and general identification of problems during admission to labour ward. The training we received to develop and improve our obstetric protocols will build the capacity of our staff to better manage the care of women in labour, both in our hospital and in our outer islands, and at the same time meet the needs of a more knowledgeable and informed population, as is the case everywhere. Training is particularly important for our new interns who have now returned to Kiribati, having just graduated in Cuba last year. The interns will require guidance and supervision and the guidelines as discussed in the workshops will assist the transition of the interns in to our health service and improve quality of care for our patients,' said Dr Tenaua.

'The other major development for us is that we now have our newly qualified Head of obstetrics and gynaecology at TCH, Dr Ioanna Beiatau, who has just completed her specialist training at Fiji National University College of Medical Nursing and Health Sciences (FNU CMNHS) in 2013. I was relieved and proud when Ioanna graduated and returned from Fiji, but am aware that as a new young specialist she will continue to need mentoring and support with professional, surgical and management skills from more experienced colleagues. For RANZCOG to take up a supportive role in mentoring and onsite training for Dr Beiatau and the labour ward staff would be invaluable, and I am confident that the strong bond we have formed with RANZCOG over the years and now through the IPC workshops will continue,' said Dr Tenaua.

Dr Tenaua was Head of obstetrics and gynaecology at the TCH from 1990–2003 before going on to become Minister of Health in 2007 to the present time. He has attended WHO meetings in Geneva since 2007, representing the Pacific Island Countries (PICs), and has twice delivered the keynote address at the WHO General Assembly.

'The Pacific has many challenges with our diverse cultures, geographical, environmental and ecological issues. With regard to the provision of health services in the Pacific, an isolated practitioner faces many difficulties professionally and personally. I, myself, have operated on my wife, my two sisters and many friends – not an ideal situation for any practitioner – however, sometimes there is no choice, and no one to consult with professionally. When the Pacific Society for Reproductive Health (formerly known as the South Pacific Regional Obstetrics and Gynaecology Society SPROGS), was formed in 1993, the enthusiasm and anticipation of the small Pacific island was tremendous. We knew it was the beginning of a more positive and proactive approach to supporting us in our small PICs and this has indeed been the case,' said Dr Tenaua.

Left to right: His Excellency George Fraser, High Commissioner to Kiribati, Dr Kautu Tenaua, Minister of Health, and Prof Rajat Gyaneshwar, representing RANZCOG at the Induction Ceremony for New Interns, Kiribati.

Left to right: His Excellency George Fraser, Australian High Commissioner to Kiribati, His Excellency Anote Tong, President of the Republic of Kiribati, Ms Carmel Walker, His Excellency Mike Walsh, New Zealand High Commissioner to Kiribati, and Prof Rajat Gyaneshwar.

Dr Tenaua is one of two Pacific Ministers of Health who has trained and worked as a specialist obstetrician gynaecologist, the other is Dr Neil Sharma, Minister of Health in Fiji.

'Having two senior Pacific Health Ministers with a specialist obstetrician background is beneficial for all the Pacific islands, in that it brings women's health to the forefront of strategic planning and setting health policy at the highest level,' said Prof Gyaneshwar. 'Women's and family health has, at last, risen on the health agenda, with strategic thinking about innovative approaches to Millennium Development Goals 4 and 5 as we approach 2015. Beyond that time it is likely that a new and broader agenda for development goals encapsulating non-communicable diseases and public health will seek to achieve better successes in global health.'

'Collaboration between governments, NGOs, specialist medical colleges and organisations, including the Pacific Society for Reproductive Health, FIGO, AOFOG and other partners will produce better healthcare outcomes for the Pacific community in the long term, if there is a strong commitment to change, improvement and empowerment. This commitment is needed at every level, and this was clearly demonstrated by our participants in the IPC workshops in Kiribati,' said Prof Gyaneshwar.

How to get involved

The RANZCOG IPC program will continue to be offered to PICs during 2014, through the Pacific Islands Project. Workshops were held in Vanuatu during February and March 2014. Fellows wishing to mentor isolated specialist obstetrician gynaecologists in the Pacific, should contact Carmel Walker, Asia Pacific Services Senior Co-ordinator, at: cwalker@ranzcog.edu.au .

About Kiribati

Kiribati is a country of around 104 408 inhabitants. It is a group of 33 low-lying coral atolls (undersea volcanoes protruding above sea level) in the Pacific Ocean, stretching across the Equator and covering the Gilbert, Phoenix and Line island groups. The land mass is 811 square kilometres, but only 2.47 per cent of the land is arable.[1] Of the population, around 44 000 live in the capital, Tarawa, which is now experiencing socio and environmental problems associated with overcrowding. The Tungara Central Hospital (TCH), in the main town of Narawerewere in the densely populated South Tarawa region, was built in 1991, and now has a capacity of 140 beds, with 20 of these in the labour and postnatal wards. There are five or six births per day in the TCH labour ward.

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1 CIA World Factbook www.cia.gov/library/publications/the-world-factbook/rankorder/2002rank.html?countryname=Kiribati&countrycode=kr&regionCode=aus&rank=102#kr accessed 3 April 2014.

The Skyline's the limit

A recent auction, held as part of the social program at the RANZCOG New Zealand Annual Scientific Meeting, raised a substantial sum for the Mercia Barnes Trust.

One of the stunning views from Skyline that greeted the auction attendees on arival.

The Mercia Barnes Trust Auction at Skyline was a highlight of this year's Annual Scientific Meeting in Queenstown, New Zealand. With one of the most amazing views in the world as a background, incredibly generous guests and a talented auctioneer, the event raised more than $26 000 to go to the Mercia Barnes Trust to provide opportunities for young researchers in our specialty.

With a trip up the gondola, bubbles in hand, guests were welcomed by the beautiful view of Queenstown and then headed out to the balcony to mingle before the auction began.

The night was great fun: there was great food, plenty of wine and many acts of generosity from members of the College, delegates and exhibitors. There were some stand-out moments, many of which were created by our enthusiastic auctioneer Hamish Lane, who gave us his time and who used his skills (as a stock auctioneer) to great effect.

One highlight was a friendly bidding war between keynote speaker Matthew Barber and Fellow Mike Stitely that ended with Mike as the winner only to give his win to Matthew, who then reciprocated by giving Mike a gift later in the night. Another highlight came at the end of the evening when the New Zealand Committee won the late Prof Gerald Duff's RNZCOG gown, kindly donated by his wife Gaynor

Special thanks go to Phyllis Huitema, a Mercia Barnes Trustee, whose fundraising skills made the auction such a success; our entertaining auctioneer Hamish Lane, who donated his services; College staff; and our generous exhibitors and delegates, who donated and purchased items.

The Mercia Barnes Trust was initiated in 1994, by the Royal New Zealand College of Obstetricians and Gynaecologists (RNZCOG) in honour of Dr Mercia Barnes, who died that year just after completing her four-year term as President of the RNZCOG. The aim of the trust is to assist and promote New Zealand-based research in the area of women's and reproductive health. The recent focus has been to support young researchers.

Award-winning journalism

Jo Chandler's article 'Builder Barry Kirby's labour of love in PNG', first published in the *Weekend Australian Magazine*, won the second annual RANZCOG Media Award for Excellence.

It was midnight and Barry Kirby had been at the wheel for almost seven hours, nudging his 4WD 200km down a goat-track of bog, fog and yawning ravines in some of Papua New Guinea's most inhospitable back country, when he experienced his epiphany.

Later, friends would gently suggest he was overthinking a garden-variety midlife crisis. He was a prime candidate – 40, a loner, a searcher; a carpenter by trade and adventurer by nature, nearing the end of a defining four-year posting in a lost corner of PNG. 'People would talk about "change of life" and other stupid things,' says Kirby, ever the plain-spoken Australian tradie. 'But I kept getting these messages.'

That night on the road in 1990 he was hauling building materials back to the village of Menyamya, where he'd lived for the past four years, when his headlights fell on what looked like a hessian sack. Kirby climbed out of the cabin to investigate and found a woman curled under a cloak of beaten bark. People appeared on the roadside, drawn out of the rainforest by the Toyota's lights. Language doesn't necessarily translate from one valley to the next in PNG, but Kirby learnt that the woman had been cast out as a witch. She had two dead husbands. She also had chronic diarrhoea and, on later reflection, very likely HIV-AIDS.

Kirby asked the villagers to help him bundle her into the passenger seat. The smell was beyond bad. 'She was sitting there and I'm driving along – I couldn't talk her language, she couldn't talk mine,' Kirby recalls. 'She had lovely white teeth, I remember.' She huddled deep in the folds of her bark 'malo'. At the health centre Kirby looked for the doctor, but he was away. So he put the woman to bed, fetched some water and tracked down someone who promised to watch over her. 'I went back to see her in the morning and she was dead,' Kirby says. 'You walk away and you think, 'F..k. That's preventable. She died because no one went to see her and put a line in.'

He made a decision that night – or rather, he yielded to a mad, nagging notion he'd been slapping away like a bothersome fly throughout his time in Menyamya, where he'd too often witnessed the grief from PNG's understaffed and failing health network. 'I sort of gave up fighting this feeling, just gave in.' Barry Kirby, a Northern Rivers farm boy who had never been much of a student, would become a doctor.

On a good day, Dr Barry Kirby wakes to benign conditions on Milne Bay, beyond the easternmost tip of mainland PNG. In flat water he can coax 33 knots from the outboard of his borrowed banana boat as he commutes the luminous avenues between palmfringed Pacific islands. It looks for all the world like paradise, but he knows better. He will be met by gatherings of heavily pregnant women waiting in the shade of tumbledown health clinics, fanning themselves with copies of their Buk Bilong Ol Meri, the precious record of their antenatal visits. On the best days he might deliver a baby into the arms of a healthy mother. After a difficult labour, he's as exultant as she is exhausted. On the worst days he treks up to a village hidden in the jungle to find the sister, mother or husband of a woman who has died in childbirth, and will add her story to his overflowing archive of similar sorrows.

His crossings into this hidden landscape, where all that separates birth and death is luck, obsess and distress him. It's why he's making a special trip to Normanby Island, one of the larger rocks in the archipelago where he conducts his medical rounds. There's another story waiting for him to collect before the forest swallows it up and the lessons are lost.

With the boat moored in a shallow cove, we wade over the litter of bleached and broken coral to unload supplies of drugs and equipment for the clinic. Dr Barry is in foreman mode. He has the tradesman's swagger of capability as he strides around the health centre at Sehulea station. For the moment his hard-won doctoring credentials are less useful than his old childbirth tools. He's trying to fix the plumbing, because there's no water coming down from the tanks up on the hill and the single solar-powered light in the delivery room is on the blink. Water is the priority. The nurses are well accustomed to birthing babies by lamplight, but as the ordinarily unflappable resident midwife Sister Dorcas John laments, they can do nothing without a clean water supply. Two women who have made the journey to the clinic from their villages several hours' walk away wait patiently on the veranda, though it provides little relief from the midday heat.

Kirby strips off his sweaty clothes, washes in a shallow dish of precious water and emerges from Sister Dorcas' little house in crisp collared shirt and shorts, transformation completed by the stethoscope draped around his neck. The doctor is in. His first patient, Clara, is ripe to bursting and a week overdue, assuming her dates are right. He stretches a tape measure over the mountain of her belly, drops his head and listens intently to the baby's heartbeat. He closes his eyes and gently travels his hands. The baby's head is still floating high, not engaged as it should be by now for imminent delivery. It's her second baby, but there's no record of whether the first was also late, or even when it was born. 'How many Christmas' since the first baby?' he asks. Two. 'Is your husband here?' Yes, he's around. Kirby tells Clara she must stay close to the clinic, not go home to her village. If the baby hasn't budged by morning she'll ride back with us in the boat to Alotau, four hours away on the mainland, where he'll admit her to the provincial hospital.

Next patient is Malika. She's not due for a couple of weeks but her tiny frame staggers under an even more spectacular belly. Kirby goes through his routine again, feeling for clues. 'Is there a lot of kicking, lots of movement?' She nods vigorously. This time around 'it's gotta be twins', Kirby concludes, but without an ultrasound he can't be 100 per cent sure. His questions trip more alarms. Malika's

husband has a history of violence towards her and has left her for another woman. She's marooned in his village, so she won't have much, if any, help when her time comes. He tells her to send word to summon her mother from her garden in the island's interior. Malika will certainly be coming back with us to Alotau and she will need a guardian to look after her at the hospital. The boat's beginning to look a little crowded on the return trip.

If all goes to plan, Kirby won't be relying on the weary outboard to service his far-flung country practice much longer. He's finalising a deal to buy a seaplane, which he will pilot himself once he has finished updating his licence – the relic of another previous life. Milne Bay is about to get its own 'flying doctor', specialising in on-call emergency obstetrics retrievals, a first for PNG. The seaplane rescue service is the centrepiece of an ambitious, largely self-funded experiment trialling strategies that have emerged from Kirby's own research – his painstaking collection and analysis of the stories of dead women – and which he hopes will claw back the death toll of PNG's escalating maternal health emergency. 'There are moments,' he reflects later, nursing a beer on the deck of the Alotau boatshed he calls home, 'when I've got my head up a perineum, stitching it up, and I look back and think, 'How the hell did I get here?''

Young Barry Kirby never much enjoyed city life or schoolrooms, and pined for weekends out on the family farm. He scraped through St Laurence's in Brisbane, a middle-rung Catholic boys' college, then got a job as a trainee accountant on the seventh floor of the BP building in Sydney ('how boring was that'). He lasted less than 12 months before following his father Frank's footsteps and getting an apprenticeship, finding satisfaction in craftsmanship and freedom in the unfettered life of a journeyman carpenter.

He was also taking his father's lead when he signed up for the job in PNG. Frank Kirby had served with an Australian artillery unit that fought an ugly campaign to dislodge the Japanese from Shaggy Ridge, near Madang. He rarely spoke of the war, but many times he told his son of the warmth of the people of PNG and the wild splendour of its landscape.

Kirby discovered these for himself when, after his building business in Alice Springs went bust, he took the job in Menyamya to build a high school and student boarding house with Australian aid money. He immersed himself in a community where men decorated themselves with cassowary bones, women wore grass skirts, and bows and arrows were carried in earnest. The history books recount many blood-curdling tales of white men's encounters with the local Kukukuku tribe – infamously fierce warriors. 'Magnificent people – once you get to know them,' Kirby says.

By 1990, the school project was almost complete and Kirby was mulling over whether to accept an offer to stick around or return to Australia when he found the dying woman in his headlights and his destiny became clear. It took him 12 years and the sale of all he possessed to pay his way through medicine – the long way, via the University of Technology Sydney, Griffith University and the University of PNG. He was 52 and had $50 to his name when he emerged as a rural obstetrics specialist.

It was during his final phase of training at Alotau Hospital in 2002, working 24/7 on local wages of $250 a week, that a plan started to form. After a further three years' preparation for exams, Kirby qualified for Australian registration and started to pick up locum work in the bush and lucrative short contracts overseas, stashing away his earnings and pursuing his last academic requirement for rural obstetrics practice – a research project digging deep into some of the casualties of PNG's maternal mortality crisis. Women die during or soon after childbirth at a rate of 733 per 100,000 births in PNG – a rate that has doubled in a recent decade. (In Australia, the figure is about eight, unless you are Aboriginal, when it is about 21.) Analysis of World Bank and PNG Demographic Health Survey data puts the lifetime risk of dying from pregnancy in PNG at one in 28, compared to one in 10,000 in Australia, says Professor Glen Mola, head of obstetrics and gynaecology at the University of PNG. Mostly, mothers bleed to death for want of basic medical attention. Kirby's research told how, where and who, honouring the casualties with identity.

I came across Kirby's work in 2010 while researching news stories on the woeful fallout of PNG's collapsing health system. Mola had forwarded the investigation his then postgraduate student had compiled tracking the deaths of 31 mothers in Milne Bay province. The report was intriguing – and not just for the surprising provenance of its author. It contained an excruciating litany of case studies, true tales animating the well-worn statistics.

Take the story of Lispa, Case #26, and the valiant efforts of her husband Isaac to save her. Isaac raced over a mountain to borrow a dinghy and beg fuel to ferry Lispa to help after the umbilical cord broke while delivering their fifth child. 'Placenta is too hard for me to push out,' she told Isaac's sister. She was bleeding badly by the time they reached the remote aid post – only to find the health worker had no drugs or equipment. She suckled her baby until she died.

Kirby's tone showed little regard for the conventions of the dispassionate, distanced, disembodied academic voice. He put himself squarely in the picture, explaining the travails of access across wild seas and jungle, realities that would have to be tackled if health services were ever to improve. He prefaced the report with a dedication to 'the brave Milne Bay women who have given up their lives for the sake of giving life'.

Of PNG's 200,000-plus births a year, more than 120,000 are unsupervised. As Professor Mola tells it, these women deliver in the bush or their villages 'on a dirt floor, with no skilled attendants, no equipment, no capacity to get somewhere if something happens, and many die'. Despite years of talk and promises, little has happened to improve a health system that one former PNG health minister described as 'bloody useless'. With Kirby gearing up to trial his crazybrave ideas at half a dozen remote island sites, I wrote him a note, eventually wangling an invitation to come and see what he was doing.

We ride into Alotau in the doctor's battered Land Cruiser, half a million miles on the clock, avoiding dogs and chickens, pigs and potholes, and women carting babies, food and wood. He crunches the gears as we crawl up the winding avenues. His routine is to ride his bike up here most mornings; at 62, there's a lot to do before he gets 'too decrepit'. We pass simple, tidy shacks draped with long lines of flapping laundry, frangipanis sprinkled with pale blossom and broad African tulip trees, boughs blazing with crimson spikes. We slow at a vantage point above the turquoise bowl of the bay. The sea and sunshine have nurtured happier and gentler cultures around this idyllic coast than some of the more punishing landscapes of the interior. Nonetheless life is hard in Milne Bay. Cash is scarce since copra (dried coconut flesh) prices crashed and depleted stocks forced the closure of the lucrative beche-de-mer (sea slug) harvest. Women bear the brunt of it. At local markets they might earn just 10 cents for a hand of bananas or a paw paw.

One of the things women told Kirby, when he surveyed them about why many didn't come into the health centres, was that they couldn't afford the 5–10 kina ($2.25-$4.50) fees. So he's lobbying provincial authorities to scrap the charge and in the meantime subsidising it for mothers at his trial sites. They also told him they were embarrassed they had no clean clothes for their newborns and no soap to wash them with. Hence the busy enterprise we find when Kirby pulls up at his boatshed. Four local helpers are loading dozens of plastic baby baths filled with tiny singlets and plastic pants, nappies and towels, talc and baby oil, mosquito nets and bright loincloths. Midwives distribute these 'baby bundles', worth about 60 kina ($27) each, as a reward to women who come in from their villages – sometimes many hours' walk away – to deliver their babies at the health centres. It's proving a powerful lure. In the six months they've been offered at his sites, supervised deliveries have risen sharply and deaths have fallen away. More than 600 bundles have gone out. Sehulea health centre used to average 60 to 70 supervised births a year, but there have been more than 90 in the six months since the bundles have been distributed.

Other initiatives include extra staff training, drug supplies, equipment and a bonus for health workers – 20 kina ($9) for every baby above the previous year's average. The incentives payment is based on a successful program in Cambodia that Mola was keen to see trialled in PNG. (He's supported it with funding through 'Send Hope Not Flowers', an initiative of Australian obstetricians who encourage their patients to ask for donations in lieu of congratulatory bouquets.) In a context where health workers are overburdened and unsupported, some are also notoriously cranky and rough with their patients. The 'baby bonus' encourages them to refine their bedside manner.

The next phase will be a radio network to the farflung aid posts and the seaplane rescues. Kirby has founded a fledgling charity to run it, tentatively called The Hands of Rescue Foundation. His role model is another maverick medico, the late Fred Hollows.

Kirby cheerfully admits he's fixated. There's room for little else in his life. He was married once, to the first girl he ever asked on a date, but it didn't last long. Other romances, and the opportunity for children of his own, were sacrificed first to Menyamya and later to pursuit of his medical degree, which absorbed most of his time and all his money and passion. 'Once you have the knowledge, how can you walk away? You've witnessed it. You have to do something about it. You won't be happy with yourself unless you do.'

He doesn't subscribe to much of the Catholic orthodoxy of his upbringing but the baggage is harder to shake. Kirby was raised in a household where faith and social justice were central to identity and conscience, and the search for meaning – vocationally and spiritually – remains a powerful motivator. Along with, perhaps, a dash of redemption. 'I've got some skeletons in my closet,' he declares. 'Some of them I don't want to say anything about. I've been an arsehole at times. No risk about that.' That conversation is closed.

We trek up into Normanby Island's lush hinterland, following the vague contours of a jungle path past clusters of huts and cooking fires. Kirby sets a cracking pace; I'm trailing, drenched in sweat. The last time he was on Normanby, about three months back, Kirby was interviewing the families of two women who had died in childbirth when the meeting was interrupted with news that there had just been another death, not far up the track. He found Catherine Pindo with 'the most peaceful look on her face,' Kirby recalls. 'Almost beatific.' With her clan gathering and wailing, this was no time to ask questions.

We've come back to find out why she died. She was 23. Her sister Marita is waiting at the abandoned hut where Kirby last saw Catherine laid out on the floor. Marita is nursing Catherine's sleeping son, John Bosco, named for the 19th century Italian priest who founded the Salesian order. The missionaries did their work thoroughly in these parts. We sit in the shade of a hut decorated with icons of the Virgin Mary to talk to Marita and a cousin, Flora, who was also present when Catherine died.

Kirby settles with his notepad and pen, launching into his practised posthumous ritual, a kind of verbal autopsy. Did Catherine go to school? Yes, to grade nine. Was this her first baby? Yes. Her husband, Ronald, was he a good husband? Yes. Did he beat her? No, never. Did he take her to the health clinic for checkups? Yes. Who helped the baby come out? Our mother. Questions and answers go back and forth in Tok-Pisin and Tok-Ples (local language) and English. There are 82 of them on Kirby's standard checklist.

Flora describes Catherine's last moments. The labour was long, a day and a night, but she had seemed well the morning after her son finally arrived. Then she went down to the river to toilet, and when she returned she said she was dizzy and hot. She lay down and there was froth at her nose and mouth. 'She said, 'Mummy, you tell Marita to feed the baby',' Flora says. 'She said, "I'm going to leave you". And then she said thank you to the Lord. And then she died.' For long moments the doctor's pen is still and his head is bowed over his notebook. The only sound is the wavelike cicada chorus echoing through the forest. Kirby composes himself, coughs and finds his voice.

It's not clear why Catherine died. What Kirby learns is that, three days before it happened, she had been to Sehulea and attended a clinic. The nurse urged her to stay close by because the baby was due, but someone – it's not clear if it was Catherine or Ronald – insisted they needed to go home to collect a few things, four hours' hard walk away. It's a familiar story. 'Catherine walked back to her village and went into labour on the Saturday. She died on Sunday. She was already at term,' he tells the nurses at Sehulea when he gathers them together for a meeting that night. 'We are professionals. We know a walk like that could bring on the labour. We need to be strong. We need to say to mothers, 'No, you can't go, for yourself and your baby you must stay here. Let the husband go, if he must'.'

In the morning we board the banana boat in the already sweltering dawn. Clara won't be coming – her baby has dropped into position. She will be safe in Sister Dorcas' hands. Kirby puts a cannula into Malika's arm, in case her babies attempt to come out early during the trip and he needs to quickly insert a drip. The motor roars and we power into the blue, heading back to the mainland, carrying Catherine's story, Malika and her mother, and the next generation of Milne Bay women – twin girls – who will be safely delivered in Alotau Hospital a few days later.

Article originally appeared in *The Weekend Australian Magazine*, 6 April 2013. Reproduced with permission from The Copyright Agency. Dr Barry Kirby's work is supported by Send Hope Not Flowers.

For more information about the RANZCOG Media Award of Excellence, visit: www.ranzcog.edu.au/college-announcement/1037-ranzcog-media-award-of-excellence.html .

Research at the forefront

Dr Clare Whitehead, a recent RANZCOG Research Foundation Scholarship recipient, has received widespread recognition for her work on identifying hypoxic fetuses.

Severe preterm fetal growth restriction (FGR) is associated with a five-to-ten-fold increased risk of stillbirth, which may be averted by delivery. However, deciding the optimum time to deliver is a challenge: delivery too early exposes the baby to the risks of iatrogenic prematurity; delivery too late risks death or long-term disability. Current antenatal surveillance strategies in preterm FGR rely on changes in blood flow in the placenta and fetus, and are designed to optimise this timing, but correlate poorly with the degree of fetal hypoxia and acidosis.

An alternative to ultrasound-based biomarkers for fetal wellbeing is the use of blood-based biomarkers to inform the clinician of changes in fetal health. Recently, nucleic acids in the maternal blood have been studied for the diagnosis of aneuploidy but the same technology can be used to inform us of changes in the expression of genes in the placenta in healthy and pathological pregnancies.

Dr Clare Whitehead's research project, 'Measuring Hypoxic-induced mRNA Transcripts in Maternal Blood to Identify the Hypoxic Growth Restricted Fetus', set out to investigate whether hypoxia induced mRNA from the placenta was detectable in the maternal blood and whether this could be used to identify when a fetus is critically hypoxic. Such a test could inform clinicians of the optimum time to deliver the baby: not too early, not too late.

As a RANZCOG Trainee, Clare decided to apply to the RANZCOG Research Foundation since it provides an excellent opportunity to gain a stipend for work she was undertaking as part of her PhD. The Arthur Wilson Scholarship provided essential assistance, extending preliminary studies at a single hospital site. With the funds from the Scholarship, Clare was able to extend recruitment to additional sites to increase the number of cases of fetal growth restriction analysed. In addition, it provided funds for completion of laboratory studies and their analysis.

The study prospectively collected maternal blood from women with preterm growth-restricted fetuses <34 weeks with evidence of abnormal fetal and placental Dopplers. Serial samples were taken from these women at the time of Doppler assessment of fetal wellbeing up until the day of delivery. The team extracted RNA from the maternal blood and compared the expression of hypoxia-induced RNA to the Doppler studies and the pH in the cord blood at delivery.

Using technologies including microarray and PCR, a gene signature (four hypoxia-induced genes) was identified that increased in the maternal blood in a step-wise fashion as the Doppler studies suggested deteriorating fetal condition. It was also found that the expression of this gene signature correlated closely with the degree of fetal hypoxia at delivery as determined by cord pH, performing better than the Doppler studies.

These findings suggest that a maternal blood test for hypoxia-induced RNA may be able to optimise the timing of delivery of severe preterm growth-restricted by more accurately estimating the degree of fetal hypoxia than current methods.

As a result of the funding from the RANZCOG Research Foundation and the promising findings, the team was able to apply for a successful NHMRC grant to fund a large multicentre study called the Fetal Oxygenation (FOX) Study. This study is currently recruiting women with growth-restricted fetuses from tertiary hospitals in Brisbane, Sydney, Melbourne, Hobart and Auckland. The purpose of the FOX study is to determine the accuracy of the test and develop an optimal gene signature score at which to recommend delivery: not too soon, but not too late.

Clare would like to express her gratitude to RANZCOG for the funding for the project, but also to her colleagues, both medical and midwifery, for their support in recruiting women, especially at Mercy Hospital for Women and Monash Medical Centre. In addition, she is very grateful to all the women who have agreed to be part of the study and have serial blood samples taken across their pregnancies, often at difficult times for them.

Research in the news

Dr Whitehead's project, 'Measuring Hypoxic-induced mRNA Transcripts in Maternal Blood to Identify the Hypoxic Growth Restricted Fetus' featured on the front page of the *Age*, as well as articles in the *Herald Sun*, the *Sunday Morning Herald*, *The Australian* and international papers including the *Telegraph* (UK) and *The Economic Times* (India). There was also coverage on the ABC, SBS, Channel 7, Channel 9 and Channel 10 News, and a feature on The Project.

Radio coverage has included the leading interview with Norman Swann on the ABC Health Report, as well as live interviews on ABC Radio National, ABC News Radio, ABC Melbourne/Canberra, ABC The World Today, 2UE and 3AW, with the story also being featured on many other commercial radio stations.

The findings of this research were published in *BMC Medicine* and *PLoS One* with the *BMC Medicine* article becoming one of the most highly accessed articles the journal has published (top five per cent).

News from the Museum

Gráinne Murphy
Museum Curator

Capturing material evidence of contemporary advances and trends in women's health is just as important as collecting artefacts from the past, as the RANZCOG medical collection continues to be discerningly developed.

Recently acquired for the museum collection were Juju brand menstrual cups, more commonly known as moon cups. A menstrual cup is a reusable flexible cup or barrier worn inside the vagina during menstruation to collect menstrual fluid. Unlike tampons and pads, the cup collects menstrual fluid rather than absorbing it.

The earliest reusable rubber menstrual cup was patented in the USA in 1932. In the same decade, the disposable products, sanitary pads and tampons, were developed, mass produced and mass marketed. Lacking in marketing resources and perhaps a victim of women's reluctance to handle their own blood when they could simply and quickly flush used products away, menstrual cups failed to catch on commercially.

The first commercially successful reusable menstrual cup, known as 'the Keeper', came out in 1987 in the USA, and is still on the market. In 2002, a UK manufacturer commercially launched the Mooncup, made of hospital-grade silicone instead of latex. Owing to customer demand, the national chain of pharmacies, Boots, asked to stock the product in 2004. However, the Australian market for this product has been slower to get off the ground. For instance, the Australian-manufactured Juju cup is only available for purchase and home delivery via the internet.

It seems that a growing number of environmentally aware younger women may be driving the growth in use of this product. On average, one woman will use more than 11 000 tampons or pads in their lifetime, generating 125–150kg of waste, which will end up in landfill or in the sea.

RANZCOG Women's Health Award 2013

Julia Serafin
Media and Communications
Senior Co-ordinator

Since the summer issue of *O&G Magazine*, the College presented the RANZCOG Women's Health Award 2013 to the following outstanding university students in obstetrics and gynaecology from medical schools across Australia and New Zealand:

- Genevieve Kan, Department of Obstetrics and Gynaecology, Monash University
- Christina Elizabeth Botfield, University of Newcastle
- Sophie Harmos, School of Medicine, Dunedin Medical School, University of Otago
- Callum Potts and Kelsey Bertrand, University of Queensland

Obituaries

Dr Keith Basil Layton
1925 – 2013

Keith Layton was born in Traralgon, Victoria in 1925. His secondary education was at Wesley College, Melbourne, after which he attended Melbourne University. After graduation, he spent three years at Prince Henry's Hospital, Melbourne.

He then travelled to England in 1951, as a ship's doctor accompanied by Dorothy, his wife. Keith spent three years doing his O and G training in London at the Hammersmith Hospital. He gained his MRCOG in 1954 and his FRCOG in 1974.

He returned from the UK in 1954, and spent two years in a general practice. He then moved to the Royal Women's Hospital, Melbourne, where he worked under Dr JW Johnstone. Later, Dr Johnstone offered Keith the opportunity to practice with him. This happy partnership lasted for many years.

In 1970, Keith became involved with the RCOG and was Secretary, 1971–74, and then Chairman, 1974–1977, of the Victorian State Committee. He was a member of the Australian Council of RCOG for its last two years, and then a Member of the Council of the new RACOG from 1979–81.

Keith had a very busy private O and G practice and was a visiting medical officer at St George's Hospital, Kew, where he made an enormous contribution to the success of the hospital and also as a teacher in the highly respected midwifery school.

On retirement, he pursued his lifelong love of literature, culminating in a bachelor of arts from Deakin University. He would often recite Shakespeare and expect his children to recite passages.

Outside of medicine, Keith had many interests including tennis, golf, growing orchids, sailing and partying. Keith endeared himself to everyone he met. He loved people and his loud laughter echoed around the corridors of hospital wards and homes alike. He was interested in everyone and never talked down to anyone.

Keith passed away on 14 December 2013 after a short illness. He is survived by his devoted wife Dorothy, their four children – Susie, Bill, Peter and David – seven grandchildren and one great-grandchild.

Dr Ian Driscoll
MBBS, FRACP, FRCOG, FRANZCOG
Vic

Dr Ian Ronayne
1920 – 2013

Ian Ronayne, one of the earliest residents at the National Women's Hospital and later one of its visiting obstetricians and gynaecologists, died recently, aged 93.

He was born in Wellington. He concluded his secondary education at Mount Albert Grammar School, where he was a member of the First Cricket XI and the swimming team. He graduated from Otago Medical School in 1947. During the Second World War, he served as a reservist in the Medical School Army Corps, spending a holiday on the Auckland Islands searching for enemy submarines and counting albatrosses. Following house surgeon years in Auckland Hospital, he spent two-and-a-half years as a registrar at the Cornwall (later National Women's) Hospital obstetric and gynaecological unit. When he left to pursue his postgraduate studies in the UK, the senior medical staff gave him an Omega watch.

On arrival in London, in 1953, he contacted the Royal College of Obstetricians and Gynaecologists, seeking assistance in obtaining a training position. To his surprise, that same evening, he was phoned by Mr Joe Wrigley (of forceps fame) offering him an immediate position at St Thomas's Hospital. This included duties at the old General Lying-In Hospital, one of London's oldest maternity units. Later, he moved to St Luke's Hospital in Guildford as a registrar, working with his friend and surgical colleague, Keith Ewen, later to be best man at his wedding. While in Guildford, he met his future wife, Veronica – a ward sister.

Ian passed his MRCOG in 1956, became a FRCOG in 1972, and a Foundation Fellow of the RNZCOG (later RANZCOG) in 1992. He returned urgently to New Zealand, in 1957, to take over the practice of Dr Fred Smale, Auckland's busiest obstetrician at that time. He charged five guineas plus GMS for full obstetric care. He was soon appointed to a visiting obstetrician post at St Helen's Hospital and became heavily involved in midwife training, once claiming 'half the midwives in New Zealand were trained by me'. His contributions were marked by a plaque at the hospital. Later, he was appointed to a visiting position on 'B Team' at the National Women's Hospital, working with Bruce Grieve, Bernie Kyle and Ron Elvidge in the gynaecology team. He had a close working relationship with Pat Dunn at the St Vincent's Home for unmarried mothers whose babies were put up for adoption. They delivered more than 2000 babies. Pat became a Papal Knight, and Ian received a Papal Apostolic Blessing with its 'pledge of heavenly favours'. Ian also worked with Pat Dunn in the diabetic clinic at the National Women's Hospital, co-authoring a 1983 paper 'Fructosamine in Diabetic Pregnancy', in *Lancet*.

Ian was a practical, no-nonsense specialist: countless residents enjoyed his forthright opinions. He was possibly the most conscientious obstetrician and gynaecologist of his era – refusing to take a holiday when any of his obstetric patients was due. He was immensely proud of his association with the Postgraduate Department, then in its heyday of research achievements. He shared a clinic with cytologist Bill McIndoe and, more than anyone, provided friendship and support in the years Bill was battling Dr G H (Herb) Green's 'Unfortunate Experiment' in the treatment of cervical dysplasia.

Ian's move into retirement was gradual and he finally gave up practice in 1990. His diminishing workload gave him more time for leisure activities. Family to one side, his principal interest was golf at the Akarana Golf Club where, at an earlier time, he played off a handicap of eight.

His three children, Richard, Clare and Felicity, were at his bedside when he died.

Prof Ronald Jones CNZM
MBChB FRCS FRCOG FRNZCOG
Auckland