Society for Endocrinology

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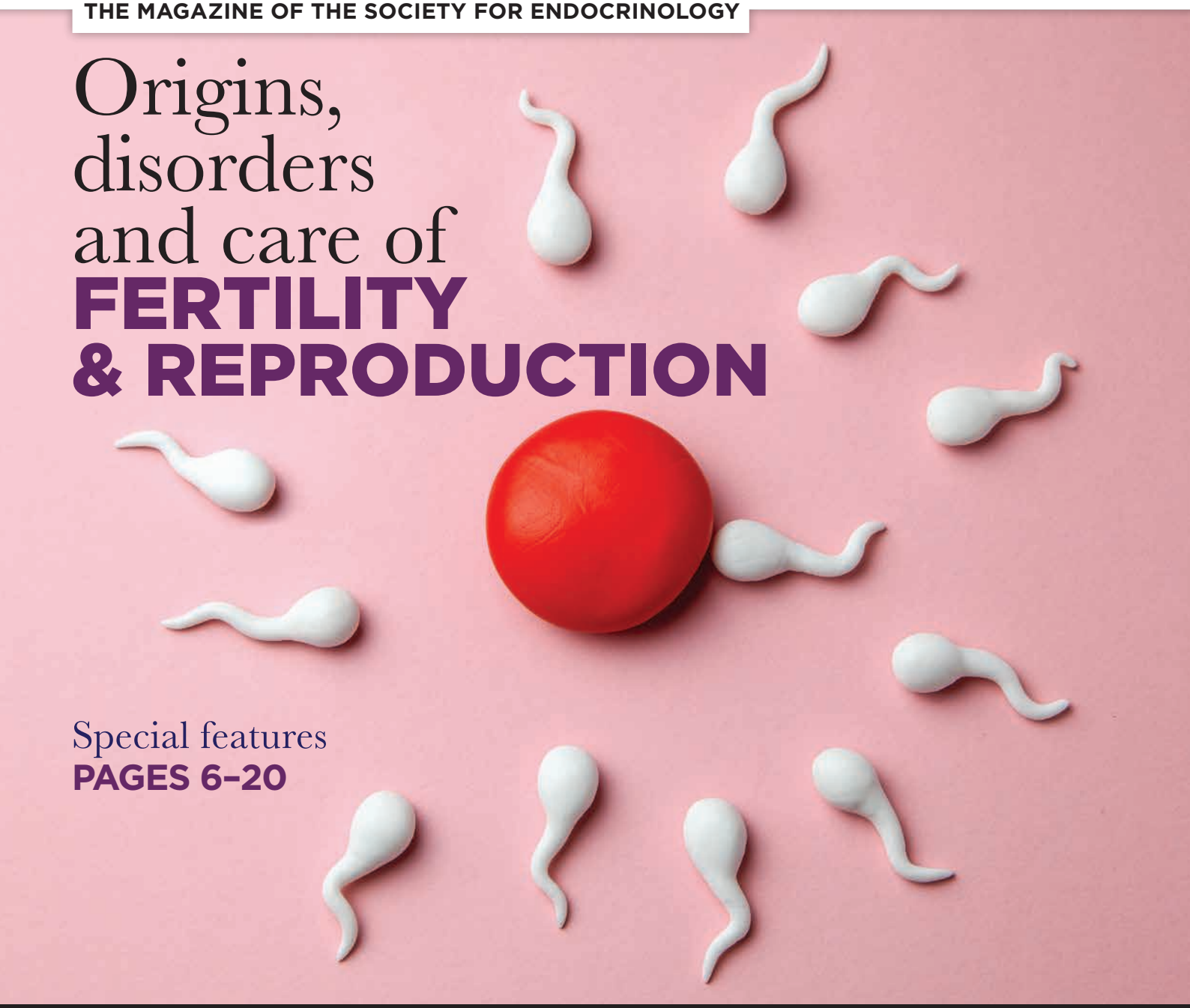
THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

Origins, disorders and care of FERTILITY & REPRODUCTION



Special features
PAGES 6–20

A word from THE EDITOR...

Welcome to the first 2022 edition of *The Endocrinologist*, and my first as Editor! I must say a huge thank you to Helen Simpson, for stewarding the magazine through the 'COVID chronical' years – Helen, you'll be missed. There have been further changes in the editorial team, with Doug Gibson coming to the end of his service – thank you Doug for your input (and laughter!) at our editorial board meetings. We warmly welcome Sophie Clarke, Gareth Nye and Venkatram Subramanian who join Louise Hunter on the editorial board, and are pleased to have Craig Doig as the new Associate Editor. Together, we look forward to bringing you cutting edge and provocative topics in endocrinology over the next eight editions!

With my research interests in reproductive endocrinology, I'm excited to introduce this edition jam-packed with features on the topic. With infertility affecting around one in seven couples, Sarah Martins Da Silva discusses male infertility and the potential of the CatSper ion channel as a novel therapeutic target (p6). Brien Mehmet and Sofia Llahana provide a guide to the clinical management of Klinefelter syndrome (p13), and Caroline Marquis shares a personal account of living with Turner's syndrome (p26). Steve Franks and Colin Duncan provide an update on energy balance and PCOS (p10).

Moving to pregnancy, the role of the placenta in Barker's theory of the developmental origins of disease are described by Gareth Nye (p7) and Phil Lowry and Miles Levy introduce theories and evidence surrounding the origins of morning sickness (p20). From a clinical management perspective, Jackie Maybin provides a guide to specialist menstrual disorders services (p11), Channa Jayasena and Richard Quinton summarise the new clinical guidelines for testosterone replacement therapy in men (p14), and specialist nurse management of microprolactinomas is discussed by Laura Serban (p19). With menopause a pertinent topic gaining increasing media traction and the MHRA launching a public consultation on making 'Gina' vaginal oestradiol tablets available from pharmacies (p27, Sophie Clarke), Annice Mukherjee dispels myths and describes forward-thinking approaches to workplace and clinical management of menopause (p18). Early Career Prize Lecturers, Elisa de Franco and Alessandro Prete, provide interesting summaries of their SfE BES 2021 presentations (p22).

We hope you enjoy the issue.

KIM JONAS

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Become a contributor... Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the SUMMER 2022 issue: **28 March 2022**.

Front cover image ©Shutterstock

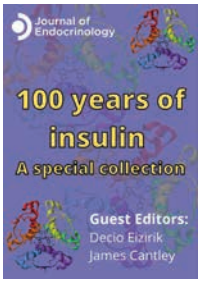
REGISTER FOR ENDOCRINE ACADEMY

Join us in Birmingham on 25–27 April 2022 for our Clinical Update and Endocrine Nurse Update events. Once again taking place face-to-face, these workshops provide essential training on best practice, and feature the latest developments in the field for trainees, consultants and nurses in endocrinology and diabetes.

ARE YOU READY TO BECOME A LEADER?

Apply to join the Society's Leadership and Development Awards Programme (LDAP) to benefit from a wide range of opportunities, all aimed at developing your career and professional profile, to help support you as a future leader in the endocrine field. The 2022 application deadline is **8 April 2022**. Visit **www.endocrinology.org/leadership** for more details.

LDAP training course, June 2021



CELEBRATING 100 YEARS OF INSULIN

Read *Journal of Endocrinology*'s special collection on 100 years of insulin, featuring reviews covering the history, prospects for curing diabetes and future challenges in the field. Guest editors Decio Eizirik and James Cantley introduce the issue and give their perspectives on the topic.

FOND FAREWELL

The Society said a sad goodbye to Zoe Plummer of our Society Engagement Team in February. Zoe joined the Society in August 2017 and has made huge contributions, in particular through her work with the Clinical Committee and in her management of our Research, Audit and Service Improvement projects. Zoe will be missed and we wish her all the best in her new role as Senior Project Manager for the UK Kidney Association.

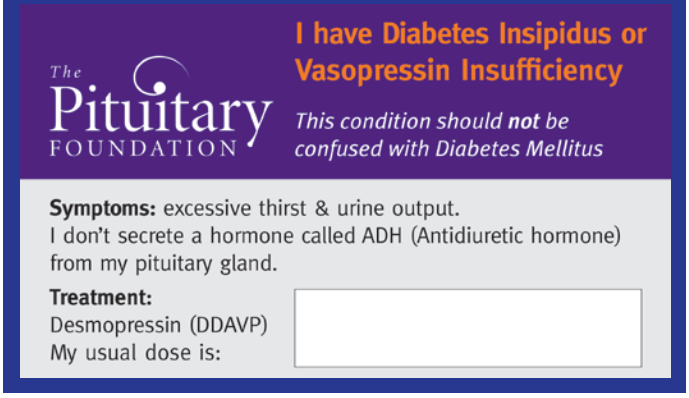
Zoe Plummer

CHAMPION OUR AWARD-WINNING PODCAST

'Hormones: The Inside Story' is the 2021 winner of Best Association Podcast or Audio in the UK Association Awards. The series aims to cut through all the misinformation in the media on hormones and health. It also contributes to the Society's aim of engaging the public with endocrinology and its impact, as well as increasing awareness of our You & Your Hormones website. Help us build on this success by encouraging your family, friends, colleagues, contacts and others to share and listen.

IMPROVING DIABETES INSIPIDUS PATIENT SAFETY

In support of The Pituitary Foundation's safety campaign for people with diabetes insipidus, we have collated resources for medical professionals, including a patient safety card, essential treatment guidance and relevant clinical guidelines. The term 'diabetes insipidus' is very often mistaken for diabetes mellitus, by healthcare professionals as well as the general public. We hope our new web page will be an evolving and convenient source of expert information for medical professionals. Learn more at **www.endocrinology.org/diabetes-insipidus**.



ENGAGE YOUR STUDENTS WITH ENDOCRINOLOGY

Use our Undergraduate Achievement Award to recognise and promote excellence in the study of endocrinology. Your department could receive £300 per year, for 3 years, to reward outstanding undergraduates for their endocrine-related studies. Applications close on **29 April 2022**. Find out more at **www.endocrinology.org/grants-and-awards**.

SOCIETY CALENDAR

24 April 2022
THYROID ULTRASOUND TRAINING COURSE
Birmingham, UK

ENDOCRINE ACADEMY:

25–27 April 2022
CLINICAL UPDATE

25–26 April 2022
ENDOCRINE NURSE UPDATE
Birmingham, UK

14–16 November 2022
SfE BES 2022
Harrogate, UK

www.endocrinology.org/events for full details

SOCIETY-ENDORSED EVENTS

22–23 September 2022
OXFORD ENDOCRINOLOGY MASTERCLASS
Oxford, UK

GRANT AND PRIZE DEADLINES

23 March 2022
PUBLIC ENGAGEMENT GRANT

6 April 2022
PRACTICAL SKILLS GRANT

8 April 2022
LEADERSHIP & DEVELOPMENT AWARDS PROGRAMME

29 April 2022
STUDENT VIDEO AWARD

29 April 2022
UNDERGRADUATE ACHIEVEMENT AWARD

4 May 2022
EARLY CAREER GRANT

4 May 2022
EQUIPMENT GRANT

18 May 2022
ENDOCRINE NURSE GRANT

18 May 2022
MEETING SUPPORT GRANT

www.endocrinology.org/grants for full details of all Society grants and prizes

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the Members' Area on the Society website, **www.endocrinology.org**. *Endocrine Connections*, *Endocrinology, Diabetes & Metabolism Case Reports* and *Endocrine Oncology* are open access and free to all. Publishing in *Endocrine Oncology* is currently free.

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Non-cell autonomous mechanisms and mitochondrial gene dysregulation in PCOS

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder seen in women of reproductive age. Named after the cysts which are often found within the ovaries, it is seen in up to 20% of women in this age range. What is less well understood about the condition is its link with insulin resistance and changes to energy metabolism in skeletal muscle.

Moreno-Asso *et al.* mapped the gene expression of skeletal muscle from women diagnosed with PCOS, and investigated whether cultured muscle cells from this group retain the gene signature of PCOS *in vivo*.

Muscle biopsies showed significant changes in the expression of genes related to mitochondrial function, which were associated with lower protein expression of certain mitochondrial complexes. Interestingly, altered gene expression was not preserved in cultured myotubes, indicating that the changes are due to the muscle's extracellular environment and must, therefore, be linked to endocrine changes in PCOS.

Read the full article in *Journal of Molecular Endocrinology* **68** 63–76

ENDOCRINE-RELATED CANCER

ACT001 reverses drug resistance of prolactinomas

Prolactinomas are a leading type of pituitary adenoma. Dopamine agonists provide the current mainstay of treatment, in the form of cabergoline or bromocriptine. Unfortunately, approximately 20% of patients do not respond well to these treatment options.

A new study from Zhu *et al.* shows that ACT001, a derivative of the promising anti-cancer treatment parthenolide, can reverse the resistance of prolactinoma cells to both cabergoline and bromocriptine. More importantly, this has been shown both in cell line studies and *in vivo* in a mouse model. The proposed method of action includes an increase in reactive oxygen species and inhibition of mTOR to induce cell death in prolactinoma cells through apoptosis.

Parthenolide is a natural product isolated from medicinal herbs, which has already been shown to have a variety of important pharmacological activities, such as anti-cancer roles in breast and prostate cancer. The new structural arrangement improved stability, bioavailability and water solubility to allow crossing of the blood brain barrier, opening up new avenues for treatment options for a wide range of diseases.

Read the full article in *Endocrine-Related Cancer* **29** 33–46

CLINICAL ENDOCRINOLOGY

Managing symptoms of hypogonadism after androgen abuse

Androgen abuse is relatively common amongst young amateur bodybuilders seeking to enhance their performance and physical condition. Prolonged or permanent post-androgen abuse hypogonadism (PPAAH) has been described in some of those who subsequently cease.

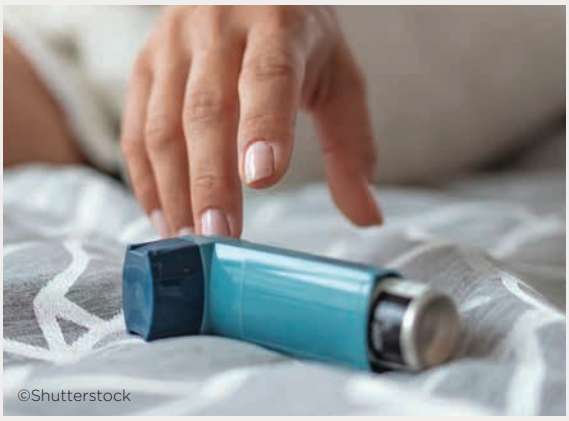
Botman *et al.* describe management of a singular case of an individual in this situation, and use this to illustrate the problems faced by such patients. They highlight difficulties encountered by the normal clinician sourcing investigations for this condition, and discuss the lack of a widely accepted definition of PPAAH, which makes diagnosis more challenging. The case follows the patient through his journey in the healthcare system and charts his diagnosis, investigations and treatment.

However, it is also important for clinicians to note that the patient's account of the issue may not reflect its true extent. There have also been instances of people misappropriating the medical prescription of exogenous androgens to supplement their own misuse. The authors' recommendation, therefore, is to use short duration preparations such as gels when there is a genuine need for replacement; they highlight the reasons for this.

Read the full article in *Clinical Endocrinology* doi:10.1111/cen.14686

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.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Role of the circadian system in night-time asthma

Asthma is often aggravated during the night-time hours. Underlying reasons can be multifactorial, including environmental and behavioural triggers (air temperature, humidity, dust, sleeping position, etc.). However, acquired knowledge of circadian rhythm and its intrinsic role in biological control suggest there are probably mechanisms driving the night-time emergence of symptoms that remain to be identified.

Scheer *et al.* set out to determine how (if at all) the circadian system contributes to nocturnal asthma. Employing protocols to distinguish circadian effects from those identified as environmental or behavioural, they disrupted the circadian cycles in 17 asthmatic individuals. They found that night-time asthma is often unnoticed, with the symptomatic individual sleeping through periodic nocturnal asthma. They also observed bronchodilator use was four times higher during the night-time and in those individuals with the lowest pulmonary function. These subjects exhibited the largest variations in circadian effects on their asthma.

The most significant finding in this study was that the circadian system has a major role in nocturnal asthma, adding further weight to the case for chronotherapy as a key strategy in asthma management.

Read the full article in *Proceedings of the National Academy of Sciences of the USA* **118** e2018486118

Hot Topics is written by Sophie Clarke, Craig Doig, Louise Hunter, Gareth Nye and Venkat Subramanian.

HT

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

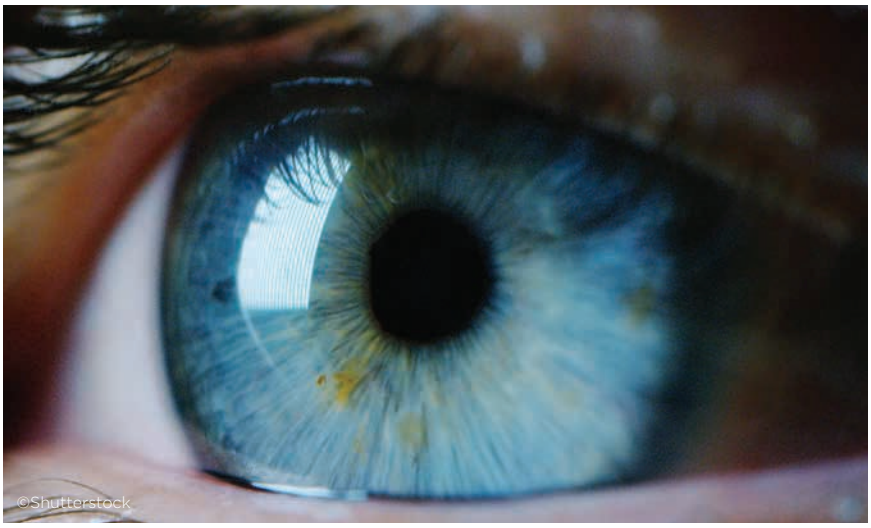
Phaeochromocytoma due to novel SDHD variant, presenting as visual loss

It is not uncommon for endocrinologists to receive referrals from colleagues in ophthalmology. Miller and colleagues report a more unusual instance, however, with a presentation of visual loss ultimately caused by a novel SDHD variant.

In this detailed, illustrated report, they recount the case of a 53-year-old woman who was found to have macular oedema and hypertensive retinopathy. In the hunt for causes of secondary hypertension, plasma metanephrine, normetanephrine and 3-methoxytyramine levels were discovered to be grossly elevated. The clinical team detected and removed a 7.8-cm adrenal phaeochromocytoma, which retained SDHB expression on immunohistochemistry. Subsequent next generation sequencing revealed a novel variant in exon 1 of the *SDHD* gene.

In an interesting discussion, guided by American College of Medical Genetics and Genomics criteria, the authors discuss the likely pathogenicity of this newly discovered variant, and its implications for the woman and her family.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* doi:10.1530/EDM-21-0107



ENDOCRINE CONNECTIONS

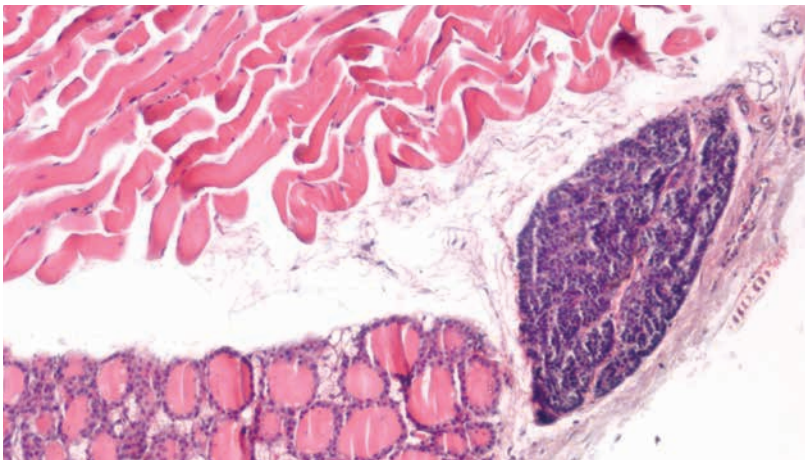


Image kindly provided by Kate Lines, Mark Stevenson and Kreepa Kooblall from the University of Oxford.

Quality of life in hypoparathyroidism and need for PTH analogue

Hypoparathyroidism (hypoPT) causes reduced serum calcium levels that manifest in the individual as severe muscular cramps. In addition, those experiencing hypoPT exhibit a complex mixture of physical and neurocognitive symptoms dramatically reducing health-related quality of life (HRQoL). Supplementation with calcium and vitamin D supplementation is common, as is parathyroid hormone (PTH) analogue treatment. However, the long term success of these approaches upon the measure of HRQoL remains unclear.

Kontogeorgos *et al.* examined medical records from 203 patients between 2007 and 2020, to better understand how QoL is affected by current hypoPT treatment regimens. From these data, they observed that QoL scores were significantly lower in patients with hypoPT compared with those without the condition. Despite this, there was only a moderate increase in co-morbidities and no overall increase in mortality.

This work indicates that both clinicians and patient groups would benefit from greater stratification to identify those (if any) who stand to gain the greatest benefit from PTH analogues.

Read the full article in *Endocrine Connections* **11** e210379

A randomised controlled trial of vitamin D and mortality

The beneficial effects of vitamin D on bone health are well described. However, vitamin D is also known to influence the renin–angiotensin pathway and cell cycling, and is inversely related to cardiovascular disease, cancer and all-cause mortality. Yet, despite these data, there have been no large population-based trials investigating the impact of vitamin D with mortality as the primary outcome.

Neale and colleagues therefore undertook a randomised, double-blinded, placebo-controlled trial of 21,310 Australian participants aged 60–84 years. Participants were randomised to receive either vitamin D3 (60,000IU per month for 5 years), or placebo.

Vitamin D supplementation was not associated with reduced cancer, cardiovascular disease or all-cause mortality. Whilst there appeared to be an increased hazard of all-cause and cancer mortality at 6 years' follow-up, the interaction between study group and time was not significant.

This study is strengthened by high adherence and retention (≥80%) and provides caution to earlier reports that vitamin D supplementation might reduce cancer mortality and all-cause mortality. However, it should be noted that the population studied was likely to be vitamin D-replete and monthly high-dose vitamin D3 supplementation was adopted. Thus, the ability to generalise the findings to non-replete populations, using alternate supplementation regimes, remains to be determined.

Read the full article in *Lancet Diabetes & Endocrinology* **10** 120–128

ION CHANNELS, SPERM AND MALE INFERTILITY

WRITTEN BY SARAH J MARTINS DA SILVA

Infertility is a common health problem, estimated to affect one in seven couples worldwide. Its effects are largely unseen, yet fertility problems have a profound impact on psychological well-being and quality of life. Male infertility accounts for around half of all cases.[1]

Although treatable, endocrine conditions affecting spermatogenesis (for example, hypogonadotrophic hypogonadism) are rare. More commonly, low sperm count and/or reduced sperm motility are apparently unexplained. And, in the absence of any other treatment options, many couples embark on *in vitro* fertilisation (IVF) or intracytoplasmic sperm injection, which are expensive and invasive yet without guarantee of success (25–30% live birth rate per treatment).

There is clearly an unmet need for the development of treatments for male factor infertility[2] but, before we can tackle this global health problem, we first need to better understand how sperm work.

UNDERSTANDING HOW SPERM FUNCTION

The huge spectrum of sperm function required for a sperm to swim, find and fertilise the egg includes progressive motility, capacitation and hyperactivation, chemotactic responses, acrosome reaction, zona binding and oocyte activation.[3] For those outwith the field of andrology, many of these terms will be foreign. Suffice to say, sperm start to swim in response to altered pH on ejaculation, are incapable of fertilising an egg until a complex series of events (termed capacitation) has occurred, and acquire sophisticated (hyperactivated) motility behaviour and the ability to acrosome react in parallel or as part of the capacitation process.

Beyond that, the precise biochemical and molecular mechanisms underlying sperm function are less well understood. Notably, spermatozoa do not transcribe or translate, and therefore rely on post-translational modification for primary signalling mechanisms. For example, cAMP-dependent phosphorylation of flagellar proteins is required for initiation and maintenance of sperm motility. Ion flux and transport (ion channels and ionic gradients) also play an essential part in orchestrating intracellular signalling pathways and cascades, with a trilogy of ion channels (CatSper, KSper and Hv1) fundamental for sperm function.[4]

CatSper CHANNELS

Intracellular calcium (Ca^{2+}) is critical to most, if not all, sperm physiological events, including motility and function *in vivo*, as well as IVF.[5] CatSper (Cation channel of Sperm) ion channels primarily control Ca^{2+} entry into the sperm. Originally identified in mouse sperm, CatSper is expressed exclusively in spermatozoa and is essential for sperm motility and male fertility.[6]

The channel is large and complex and has defied *in vitro* expression to date. There are four alpha subunits (CatSper 1, 2, 3 and 4), which form the channel pore, and at least six auxiliary subunits (CatSper beta, delta, gamma, epsilon, zeta and EFCAB9), as well as a chaperone protein (CatSper tau). All subunits are required in order to produce a functional channel. CatSper channels are weakly voltage-dependent, Ca^{2+}-selective and pH-sensitive, and located in four nanodomains arranged like racing stripes along the length of the flagellum.[7]

Perhaps not surprisingly, given its complex structure, CatSper activation is also complex and polymodal. For example, the application of progesterone to human sperm evokes an immediate Ca^{2+} influx via non-genomic indirect activation of CatSper. (Activation of abhydrolase domain-containing protein 2 results in loss of 2-arachidonoylglycerol CatSper inhibition.) A similar Ca^{2+} influx is seen in response to prostaglandin E1, although CatSper activation is direct.

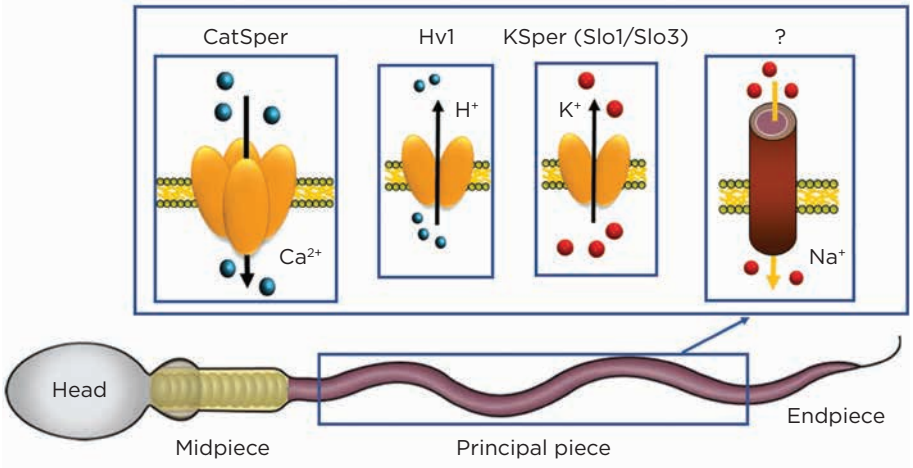
Other physiological stimulants, such as cyclic nucleotides, zona pellucida glycoproteins and bovine serum albumin also stimulate Ca^{2+} entry into sperm via CatSper activation. Notably, CatSper is also activated by structurally diverse endocrine disruptor chemicals and xenobiotics.[8] The issue is that, by mimicking the action of physiological ligands, these chemicals may interfere with the precisely co-ordinated sequence of events underlying fertilisation, resulting in impaired sperm function and male infertility.

> *'There is clearly an unmet need for the development of treatments for male factor infertility but, before we can tackle this global health problem, we first need to better understand how sperm work.'*

Hv1 AND KSper CHANNELS

Hv1 is a voltage-gated channel that mediates the outward flow of protons (H^+) to the extracellular environment. Hv1 is critical for capacitation, hyperactivated motility and acrosome reaction.[4] Hv1 domains are located longitudinally along the sperm flagellum, although they are distributed asymmetrically and therefore regulate rotational movement.[9] Hv1

Figure. Ion channels of the human sperm flagellum. Schematic representation of a human spermatozoon with cellular compartments and distribution of ion channels found along the principal piece: CatSper, calcium channel; Hv1, voltage-gated proton channel; Slo1/Slo3, potassium channels; the identity of a Na^+ channel or transporter is yet to be characterised.



represents an important component in the CatSper activation cascade, but also induces membrane hyperpolarisation by exporting positive charges out of the cell.

Similarly, KSper (Slo3) channels maintain a hyperpolarised cell membrane potential (Vm) and, in doing so, influence the activity of CatSper channels.[4]

ION CHANNEL DYSFUNCTION

Importantly, ion channel dysfunction (ICD) has significant consequences for male fertility. Indeed, approximately 10% of cases affected by low or no fertilisation at IVF can be attributed to (predominantly KSper) ICD.[10]

This raises an exciting possibility for diagnostic or therapeutic intervention. Pharmacological agents to correct ICD could offer huge potential as new treatments for male infertility. Given that they are unique to sperm, direct or indirect CatSper agonists are a particularly attractive prospect, due to negligible off-target effects. Excitingly, high throughput and phenotypic screening drug discovery approaches have recently been developed,[2,11] but the reality is that delivery of new treatments for clinical use is a lengthy, complicated and costly process.

A diagnosis of male infertility can be one of the hardest challenges a man can face. Here's hoping science can make a difference.

SARAH J MARTINS DA SILVA
Senior Lecturer in Reproductive Medicine, School of Medicine, Ninewells Hospital and Medical School, University of Dundee

REFERENCES

1. Agarwal A *et al.* 2015 *Reproductive Biology & Endocrinology* **13** 37.
2. Martins da Silva SJ *et al.* 2017 *Human Reproduction* **32** 974–984.
3. Ritagliati C *et al.* 2018 *Mechanisms of Development* **154** 33–43.
4. Brown SG *et al.* 2019 *Human Reproduction Update* **25** 758–776.
5. Williams HL *et al.* 2015 *Human Reproduction* **30** 2737–2746.
6. Lishko PV & Mannowetz N 2018 *Current Opinion in Physiology* **2** 109–113.
7. Chung JJ *et al.* 2017 *eLife* **6** e23082.
8. Brenker C *et al.* 2018 *Human Reproduction* **33** 1915–1923.
9. Miller MR *et al.* 2018 *Cell Reports* **24** 2606–2613.
10. Brown SG *et al.* 2016 *Human Reproduction* **31** 1147–1157.
11. Gruber FS *et al.* 2020 *eLife* **9** e51739.

THE PLACENTA IN THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

WRITTEN BY GARETH NYE

In issue 142 of *The Endocrinologist* (Winter 2021), Kerri Devine and Rebecca Reynolds discussed how maternal usage of glucocorticoids during pregnancy can influence the baby's ability to regulate glucocorticoids, which may affect their metabolism through life.

It may seem implausible that our lives are so influenced by how our mother's body reacted to stresses, toxins, infections and so on during pregnancy, and how growth and development during our first few years of life could lead to disease in middle age. However, we are now beginning to understand the full extent of David Barker's theory, proposed in 1993, on the developmental origins of health and disease. As we approach its 30th anniversary, it is useful to take stock of what we currently know, so we can build towards the future.[1]

THE PLACENTA: MATERNAL/FETAL INTERFACE

During the nine months of pregnancy, any interaction between mother and baby occurs at the placenta. The placenta is formed from the fertilised egg, along with the growing baby, and is attached to the uterus. It grows with the baby to eventually weigh an average of 650g, and is roughly the size of a normal dinner plate.[2] It is a truly unique organ in the body, taking on several crucial roles to allow the baby to grow successfully, and having both fetal and maternal blood flowing through it at any one time.

This, however, poses a problem. As the placenta itself is half maternal and half paternal in origin, it is essentially foreign graft tissue, and so the placental cells in contact with the maternal blood supply must constantly prevent recognition by maternal immune cells, whilst allowing transport of the required substances. The layer of cells in contact with the maternal circulation are termed the syncytiotrophoblast. This barrier of syncytial epithelium allows for the active and specific transport of substances, keeping fetal and maternal nutrient compositions distinct throughout pregnancy.[3]

UNDERSTANDING PLACENTAL TRANSFER

Our knowledge of placental transfer is not robust at this time. We know gas exchange occurs, although our current understanding of the amount of exchange is limited in human pregnancy, being based on approximations through *ex vivo* work.[4] We have strong evidence of 20 different amino acid transporters along the syncytial membrane, and that fatty acids can cross through, following a multi-stage progression with fatty acid-binding proteins, as well as active synthesis of cholesterol and steroids.[5] Glucose transport proteins have been well categorised within the placenta, and we know that the expression of these proteins does change during pregnancy.[6]

The current mystery is the effect of the external factors that pregnant women constantly face. Any changes in the functioning of the placenta to limit the transfer of the above have the potential to severely limit the growth and development of the fetus. This, in turn, leads to long term changes in metabolism, and the development of diseases in later life, including cardiovascular and metabolic disorders.[7]

THE IMPACT OF EXTERNAL FACTORS

Some external factors are well documented (e.g. poor maternal diet, smoking during pregnancy and maternal stress), but there is a growing base of research which has shown that, during pregnancy, women may be exposed to over 50 different chemicals.[8] Many of these are considered to be endocrine-disrupting chemicals, as exposure to them can alter normal physiological endocrine function, in part due to the high abundance

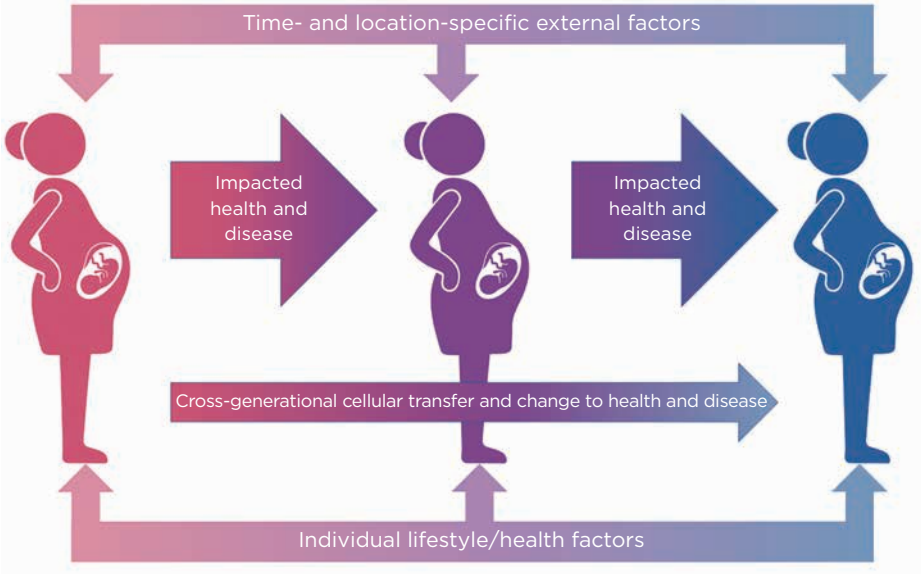


Figure. External factors such as environment, stress and employment, and individual lifestyle factors including diet and medications, can influence the health and development of a growing baby. In turn, these can lead to alterations in health and disease for their entire life. When they themselves become pregnant, the same factors apply to this new growing fetus. However, the influence of the grandmother remains a considerable factor, through direct influence on the mother's development and cross-generational transfer of cellular material. Created with BioRender.com

of steroid hormone receptors present within the placenta. Large scale epidemiological studies have begun to make associations between these chemical exposures and adverse pregnancy outcomes.

A recent study has taken this one step further. Rzhetsky and collaborators have performed large scale statistical tests on country-wide health datasets, to investigate associations between external factors and the sex ratio at birth.[9] Under normal circumstances, the proportion of boys at birth is usually slightly greater than 50%. This study found that the levels of chemicals found in pollution within a given area could potentially control the sex of a baby, although further analysis is required. If these chemicals and signals do have the power to decide fetal sex, there is no end to the possible changes that may occur during fetal growth and development.[9]

'If we influence mums-to-be now, we could begin to alter the frequency of cardiovascular and metabolic disease in the next two generations to come.'

LIMITATIONS ON LAB WORK

Large epidemiological studies like that of Rzhetsky and colleagues are useful for adapting public health messages. However, without 'wet lab' approaches, the findings will always be associations, because our fundamental knowledge of what can and can't cross the placenta is still lacking. This is where our understanding of the developmental origins of health and disease often comes to a halt. The clear ethical and practical issues surrounding the use of human placentas, hampered by a lack of consensus on procedural standardisation in isolating and purifying human placental tissue, have led researchers to routinely use litter-bearing rodents, which in itself presents wide-ranging challenges.

Ex vivo dual perfusion of the human placenta is a widely accepted method of understanding the pharmacological and physiological functions of the placenta, in particular regarding transfer from maternal to fetal circulations. This is achieved whilst maintaining both an approximate *in vivo* environment and an *in vivo* placental structure. Whilst the benefits to research are plain to see, this is a costly method of analysis in terms of both time and money, with a high preparation failure rate and the use of specialised equipment. Currently, only a handful of centres are even set up to do this type of placental work.[4]

Until we can systematically analyse both the transfer of substances across the human placenta and their interaction with maternal and fetal tissues, we may never know directly whether changes levels of hormones, chemicals, inflammatory markers and the like influence the health and disease of the next generation.

AN IMPACT ACROSS MANY GENERATIONS

We may, however, be setting our sights too short with Barker's concept. A recent paper from Karlmark *et al.*[10] has shown the presence of grandmaternal cells within cord blood samples. Due to the bidirectional exchange of cells during pregnancy, pregnant women have acquired maternal cells during their fetal life from their mother, which could transfer grandmaternal cells to their child through the maternal bloodstream during pregnancy. We have already seen transgenerational effects because of environmental exposures as, for example, children have an increased risk of asthma in the first six years of life if their grandmother smoked during early pregnancy, independent of maternal smoking.[11]

Whether this is a passive or active transfer is currently unknown, but it leads those researching the developmental origins of health and disease to begin to look further than the effect on health and disease in the next generation. If we influence mums-to-be now, we could begin to alter the frequency of cardiovascular and metabolic disease in the next two generations to come.

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REFERENCES

1. Barker DJ *et al.* 1993 *Lancet* **341** 938–941.
2. Mayhew T *et al.* 2007 *Placenta* **28** 233–238.
3. Cleal J *et al.* 2011 *Journal of Physiology* **589** 987–997.
4. Nye GA *et al.* 2018 *Journal of Physiology* **596** 5523–5534.
5. Winterhager E & Gellhaus A 2017 *Frontiers in Physiology* doi:10.3389/fphys.2017.00951.
6. Baumann MU *et al.* 2002 *Endocrine* **19** 13–22.
7. Hoffman DJ *et al.* 2021 *Physiological Reviews* **101** 739–795.
8. Gingrich J *et al.* 2020 *Trends in Endocrinology & Metabolism* **31** 508–524.
9. Long Y *et al.* 2021 *PLoS Computational Biology* doi:10.1371/journal.pcbi.1009586.
10. Karlmark KR *et al.* 2021 *EBioMedicine* **74** 103721.
11. Lodge CJ *et al.* 2018 *Clinical & Experimental Allergy* **48** 167–174.

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ENERGY BALANCE, OBESITY AND POLYCYSTIC OVARY SYNDROME

WRITTEN BY STEPHEN FRANKS AND COLIN DUNCAN

Polycystic ovary syndrome (PCOS) is a very common endocrine disorder which causes both reproductive and metabolic dysfunction. The cardinal features are oligo- or anovulation (leading to menstrual irregularity and subfertility) and hyperandrogenism (associated with acne, hirsutism and alopecia). Metabolic dysfunction underlies problems with long term health, including increased prevalence of type 2 diabetes (T2DM), dyslipidaemia, fatty liver and higher risk of cardiovascular disease.

The manifestation of PCOS is typically heterogeneous, but there is strong evidence of a genetic basis for its aetiology. Recent genome-wide association studies (GWAS) have highlighted a shared genetic origin across the spectrum of clinical presentation.[1,2] There is also evidence, principally from animal models of PCOS, that epigenetic programming by exposure to excess androgen during development has a role in its aetiology.[3] But, as with other complex endocrine disorders, such as T2DM, there are important environmental factors, notably diet and lifestyle, that interact with genetic influences and may modify epigenetic effects.

OBESITY AND PCOS

Obesity in women with PCOS is associated with a greater degree of insulin resistance than in obese controls, and increasing body mass index (BMI) has a significant negative impact on reproductive and metabolic function, and long term health. Clinic-based studies typically report that most women with PCOS are obese, but a better indication of the prevalence of overweight and obesity in PCOS comes from population-based studies. Data from studies of the North Finland Birth Cohort (NFBC 1966) confirm a higher prevalence of obesity amongst women with symptoms of PCOS than in the reference population (26 vs 8% at age 31, increasing to 43 vs 22% at age 44).[4] A similar trend, over 10 years, was seen in the Australian Longitudinal Study of Women's Health.[5,6]

So, why the higher prevalence of obesity in PCOS? Does PCOS predispose to obesity or does obesity expose underlying PCOS? Both are probably involved, but there does appear to be a predisposition to obesity in women with PCOS. In the 2018 GWAS meta-analysis of women of European descent (the international PCOS genetic consortium), Mendelian randomisation analyses indicate that variants in genes associated with BMI play a causal role in PCOS.[1] Low birth weight is a risk factor for later development of PCOS and, in the NFBC, adiposity rebound in childhood (a predictor of later obesity) was earlier in the PCOS cohort than in the reference population.[7]

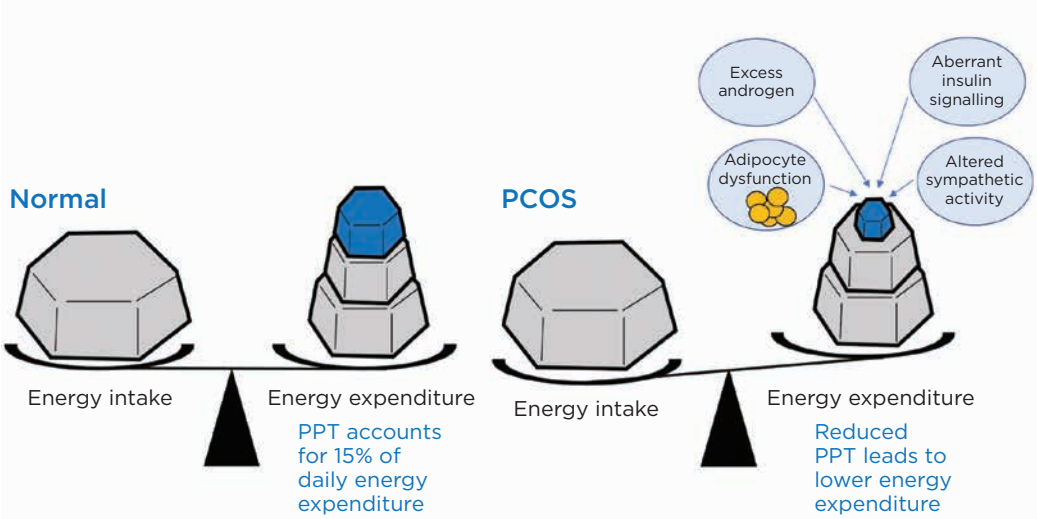
ENERGY BALANCE AND PCOS

What do we know about energy balance in women with PCOS? There is no consensus about whether appetite and food intake are altered in PCOS. Eating disorders appear be more common in PCOS, but these are probably secondary to concerns about weight gain and the now well-described negative effect of PCOS on mental health. So, is energy expenditure altered in women with PCOS?

An important element of energy expenditure is postprandial thermogenesis (PPT) which accounts for about 15% of daily energy expenditure. We measured energy expenditure by indirect calorimetry in women with PCOS and control subjects.[8] As reported in other studies,[9] resting energy expenditure was similar but, for equal degrees of obesity (but higher abdominal fat), women with PCOS were more insulin-resistant and had lower energy expenditure after a test meal than (individually matched) controls. Insulin resistance and PPT were negatively correlated in PCOS but not in controls. It was estimated that, for the same calorie intake, women with PCOS would add 1.9kg more of fat over the course of a year, compared with those without PCOS. It is tempting to speculate that there is an evolutionary advantage in having reduced PPT. At times of food *excess*, reduced PPT in PCOS contributes to obesity, infertility and increased risk of diabetes. But, at times of food *shortage*, women without PCOS are more vulnerable to reduced fertility due to negative energy balance, whereas reduced PPT in PCOS protects energy expenditure and maintains fertility.

We considered the possible mechanisms underlying reduced PPT in PCOS, and first investigated whether it was driven by exposure to excess androgen during development. We studied a clinically realistic animal model of PCOS, the prenatally androgenised sheep, and found that the androgenised animals had a remarkably similar reduction in PPT to that seen in women with PCOS.[10] There were associated changes in structure and function of adipose tissue, including reduced sympathetic drive and lower capacity for thermogenesis. Significantly, there was reduced central sympathetic nervous system activity, which was associated with decreased insulin signalling in the brain.

Figure. Post-prandial energy expenditure (thermogenesis; PPT) is reduced in women with PCOS and contributes to obesity. The probable mechanism(s) of reduced PPT involve(s) an interaction of several factors including excess androgen action, adipocyte dysfunction, aberrant insulin signalling (including in the brain) and altered sympathetic nervous system activity, both in fat and centrally.



MODIFYING ENERGY BALANCE IN WOMEN WITH PCOS

Of course, reducing calorie intake is a time-honoured method of improving energy balance and losing weight, but calorie-restricted diets are rarely sustainable. Can we instead or (more likely) in addition increase energy expenditure? Clearly increasing daily exercise has an important place in lifestyle modification, but is there a way of increasing PPT which, as suggested by the studies detailed above, would be particularly helpful in women with PCOS? Working on the premiss that insulin signalling in the brain is a key element in mediating diet-induced energy expenditure, the androgenised sheep were given intranasal insulin which significantly enhanced PPT. Are these remarkable findings translatable to the clinical realm? Clearly there is much more to be learned about energy balance in PCOS, but the results of these studies in the sheep with 'PCOS' have pointed the way to preliminary clinical studies.

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REFERENCES

1. Day F *et al.* 2018 *PLoS Genetics* **14** e1007813.
2. Dapas M & Dunaif A 2020 *Current Opinion in Endocrine & Metabolic Research* **12** 26–32.
3. Abbott DH *et al.* 2002 *Journal of Endocrinology* **174** 1–5.
4. Ollila MM *et al.* 2016 *Journal of Clinical Endocrinology & Metabolism* **101** 739–747.
5. Teede H *et al.* 2013 *Obesity* **21** 1526–1532.
6. Awoke MA *et al.* 2021 *Human Reproduction* **37** 129–141.
7. Koivuaho E *et al.* 2019 *International Journal of Obesity* **43** 1370–1379.
8. Robinson S *et al.* 1992 *Clinical Endocrinology* **36** 537–543.
9. Roumaldi D *et al.* 2019 *Journal of Endocrinological Investigation* **42** 1089–1097.
10. Siemienowicz K *et al.* 2020 *iScience* **23** 101164.

THE SPECIALIST MENSTRUAL DISORDERS SERVICE

PLAYING A KEY ROLE IN ENDOMETRIAL HEALTH

WRITTEN BY JACQUELINE A MAYBIN

It is estimated that one in three women will experience abnormal uterine bleeding (AUB) at some point in their reproductive lives. Heavy menstrual bleeding is an unrecognised cause of iron deficiency anaemia, may require blood transfusion, and has a significant negative impact on emotional, social and material quality of life.[1,2] Yet menstruation is taboo, meaning it is rarely discussed, under-researched and often suboptimally managed. A principal role of a specialist menstrual disorders service is to address the health inequalities that are all too often experienced by those who menstruate.

WHAT CONSTITUTES 'TYPICAL' AND 'PROBLEMATIC' MENSTRUATION?

Due to the embarrassment and shame that surrounds menstruation, many people do not know what typical menstrual bleeding comprises. This societal problem was previously compounded by a lack of standardised terminology in menstrual research and clinical practice.

The lack of terminology was addressed by the International Federation of Gynecology and Obstetrics (FIGO) in 2011 (with updates in 2018).[3] They recommended assessing menstruation by four main parameters: (i) volume, (ii) duration, (iii) frequency and (iv) regularity, and reviewed the available evidence to define typical and abnormal menstrual bleeding (see Table). The FIGO AUB System 1 provides researchers and clinicians with a set of standardised parameters and simplified terminology (e.g. heavy, prolonged, frequent or irregular menstrual bleeding) to enable global scientific collaboration in menstrual research and to drive clinical excellence.

CURRENT TOOLS TO TREAT AUB

There are a range of medical and surgical treatment options available for those experiencing AUB. Selecting appropriate treatments can present challenges for the patient and physician, and requires consideration of the underlying diagnosis, co-morbidities, user preferences and desire for fertility.

The majority of medical treatments are hormonal, acting to override or alter physiological ovarian hormone production. The levonorgestrel-releasing intrauterine system is recommended by NICE for the treatment of heavy menstrual bleeding[1] and can be very effective, resulting in amenorrhoea or significant reductions in menstrual blood loss. However,

Table. FIGO AUB System 1.[3]

	Typical	Abnormal uterine bleeding
Volume of menstrual flow	Normal (patient-determined)	Light/heavy (patient-determined)
Duration *(number of days of menstruation)*	≤8 days	>8 days (prolonged)
Frequency *(number of days from first day of one menses to first day of next)*	24–38 days	<24 days (frequent) >38 days (infrequent)
Regularity *(shortest to longest cycle variation)*	≤7–9 days (regular)	≥8–10 days (irregular)

some women will experience intolerable side effects such as irregular, frequent menstrual bleeding or mood changes. Occasionally, the insertion process may be unacceptably painful or can result in uterine perforation, infection or spontaneous expulsion.

Non-hormonal options are limited to non-steroidal anti-inflammatories or the anti-fibrinolytic medication tranexamic acid. These oral medications can be helpful, but are often not effective enough for those with very heavy menstruation.

The most common surgical interventions for abnormal uterine bleeding include endometrial ablation (removal of the womb lining) and hysterectomy (removal of the womb). Hysterectomy can guarantee amenorrhoea but introduces surgical risks of severe blood loss, infection and organ damage.

IDENTIFYING THE CAUSE OF THE PROBLEM

AUB is a symptom and not a diagnosis. Yet, those experiencing menstrual disturbance are often treated without appropriate efforts to identify the underlying cause. The FIGO AUB System 2 provides a practical framework to aid clinicians in establishing a diagnosis.[3]

The underlying causes of AUB are divided into structural causes (those detectable on examination/imaging) and non-structural causes (normal uterine anatomy).

Structural causes include:

- endometrial **P**olyps
- **A**denomyosis (endometrial-like tissue within the myometrial layer of the uterus)
- **L**eiomyoma (fibroids) and
- **M**alignancy (e.g. endometrial).

They are denoted by the acronym PALM.

Non-structural causes (acronym COEIN) include:

- **C**oagulation disorders
- **O**vulatory dysfunction (including perimenopausal bleeding and polycystic ovary syndrome)
- **E**ndometrial causes
- **I**atrogenic causes and
- those **N**ot-otherwise classified (e.g. arteriovenous malformations, caesarean scar defects).

'Abnormal uterine bleeding is a symptom and not a diagnosis. Yet, those experiencing menstrual disturbance are often treated without appropriate efforts to identify the underlying cause.'

APPROPRIATE USE OF CURRENT TOOLS

After detailed history taking and clinical examination, a provisional diagnosis (e.g. AUB-A/E, that is adenomyosis and/or endometrial in origin) should be recorded and further refined by appropriate investigations.

The diagnosis (or diagnoses) should then inform discussions about clinical management. For example, current hormonal treatments are more likely to be effective in those with ovulatory dysfunction than in the patient with a large submucosal leiomyoma (fibroid). Specific, personalised treatments are only possible after accurate diagnosis, e.g. hysteroscopic removal of endometrial polyps (AUB-P) or haematology input and DDAVP treatment (AUB-C).

An accurate diagnosis, good clinical judgement and shared decision making will result in more acceptable, effective treatment of the symptom of AUB.

ADDING TO THE TOOLKIT FOR TREATING AUB

Despite the range of medical and surgical treatment available, many experiencing menstrual disorders are unsatisfied with current options. There is a clear unmet clinical need for better non-hormonal treatments for AUB. The electric lightbulb did not come from the continuous improvement of candles, and AUB presents an opportunity to think outside the box when identifying novel therapeutic targets.

For example, AUB-E is a diagnosis of exclusion, and the exact endometrial aberrations resulting in increased menstrual blood loss remain undefined. Recent research has identified a transient but intense hypoxia in the endometrium during menstruation.[4,5] This hypoxia drives repair of the denuded menstrual endometrium to stop menstrual bleeding.[4] Those with AUB-E appear to lack this localised tissue hypoxia and have prolonged menstrual bleeding.

Medications are available that mimic the hypoxic response in tissues and these represent an attractive potential therapeutic option to restore endometrial physiology. These treatments would only be required during menstruation and the endometrium is amenable to local delivery methods, creating exciting opportunities for new therapeutic strategies.

ADDRESSING INEQUALITIES BY IMPROVING CLINICAL CARE

AUB can impact education, work, family, finances and mental and physical health. Addressing the problems experienced by those with menstrual disorders will require a truly transdisciplinary approach.[6] The role of the specialist menstrual disorders service is to use the currently available tools to their best effect, personalising treatments to restore quality of life. In addition, it is essential to embed menstrual research into clinical practice to develop new and improved options for those facing these debilitating symptoms. Only then can the inequalities experienced by those with AUB begin to be reduced.

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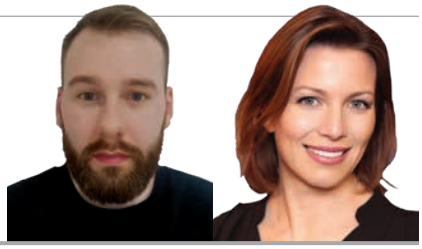
REFERENCES

1. NICE 2018 *Heavy Menstrual Bleeding: Assessment and Management* NG88 www.nice.org.uk/guidance/ng88.
2. RCOG 2014 *National Heavy Menstrual Bleeding Audit Final Report* www.rcog.org.uk/globalassets/documents/guidelines/research--audit/national_hmb_audit_final_report_july_2014.pdf.
3. Munro MG *et al.* 2018 *International Journal of Gynecology & Obstetrics* doi:10.1002/ijgo.12666.
4. Maybin JA *et al.* 2018 *Nature Communications* **9** 295.
5. Cousins FL *et al.* 2016 *BMC Research Notes* **9** 30.
6. Critchley HOD *et al.* 2020 *American Journal of Obstetrics & Gynecology* **223** 624–664.

UNDERSTANDING KLINEFELTER SYNDROME

AN OVERVIEW AND NURSING CONSIDERATIONS

WRITTEN BY BRIEN MEHMET AND SOFIA LLAHANA



Klinefelter syndrome (KS) is a common aneuploidy in men, clinically characterised by small testes, gonadal failure (hypergonadotrophic hypogonadism), disrupted spermatogenesis (infertility), gynaecomastia and eunuchoid proportions (arm span exceeds height by ≥7cm).[1,2] It affects 1 in 600 men, but 50–75% of men with KS go undiagnosed in their lifetime.[1,3] Almost 90% of men with KS have an XXY karyotype, and the remaining 10% have mosaicism (46,XY/47,XXY), higher grade aneuploidy (48,XXXY/49,XXXXY), or structurally abnormal X chromosomes.[1]

The extent of mosaicism in KS causes an array of cognitive, psychosocial and physical symptoms which can affect men with varied degrees of severity. These include hypogonadism, gynaecomastia, tall stature, small phallus, reduced level of intelligence, depression, autism traits, schizotypal traits and social anxiety, which lead to impaired quality of life.[1,4] Milder phenotype and lack of distinct dysmorphic features present a real challenge for early diagnosis.[2]

MANAGING KLINEFELTER SYNDROME

KS is characterised by primary testicular failure resulting in hypergonadotrophic hypogonadism with elevated luteinising hormone and follicle-stimulating hormone levels, and low testosterone. Testosterone replacement therapy is recommended for patients with KS once serum gonadotrophins begin to rise in early puberty, or when serum testosterone levels become hypogonadal.[2,4,5] Infertility in men with KS ensues due to the progressive gonadal failure, where normal testicular architecture alters, causing tubular atrophy, sclerosis or maturation arrest, and ultimately degenerates to fibrosis and hyalinised tissue.

Advances in surgical techniques, in particular microsurgical testicular sperm extraction (micro-TESE), provides patients with KS with the possibility of fathering a child (Figure). A meta-analysis of 37 trials (n=1,248; mean age 30.9±5.6 years), showed that the surgical sperm retrieval rate per TESE cycle was achieved in almost half of the men with KS (44%; 95% CI 39–48%),[7] although evidence on take-home baby rate after micro-TESE and female assisted reproductive treatment is still very limited.

Increasingly, the onset of puberty has been recognised as the critical time to address the fertility potential of men with KS, and early sperm retrieval and semen or testicular tissue cryopreservation has been recommended by several investigators, although there is still no robust evidence to support this.[8] However, there is considerable controversy regarding this approach, given the ethical concerns surrounding non-essential invasive procedures in minors, as well as potential implications and confounding issues related to the adolescents' and young adults' comprehension and maturity to weigh risk–benefit.[9] This needs to be considered on a case-by-case basis, and the patient with KS and their parent(s) should be adequately consulted and supported to make an informed decision.

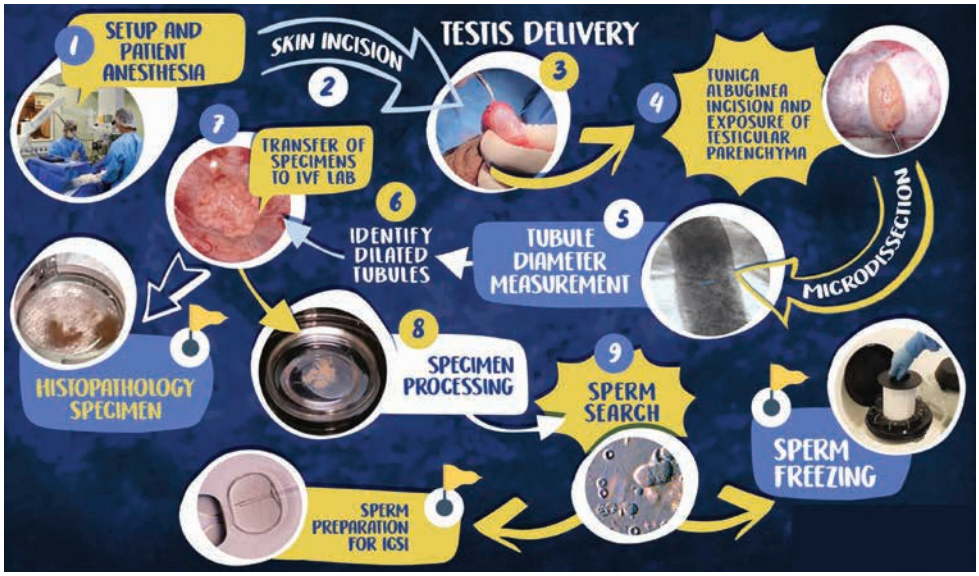
For many adult patients, presentation with infertility while trying for a family leads to diagnosis of KS. A detailed semen analysis determines whether sperm collection may be feasible if healthy spermatozoa are present in the ejaculate. For patients with azoospermia, a pre-existing protocol for the management of this condition can be followed.[10] This includes stopping testosterone replacement therapy, starting oral clomiphene citrate, and monitoring total testosterone and oestrogen levels throughout, followed by micro-TESE. Sperm can then be used for 'synchronous sperm retrieval', i.e. immediate use in combination with oocyte retrieval and/or cryopreserved for future use by the partner in her assisted fertility cycles with intracytoplasmic sperm injection. The former has higher success rates for positive pregnancy. However, the couple need to be consulted on the risk of not finding viable sperm during TESE, as oocyte retrieval can be an invasive and expensive procedure for the female partner.

THE NURSES' ROLE IN SUPPORT

Effective management of patients with KS undergoing fertility treatment requires a multidisciplinary approach, including endocrinology, andrology, genetic counselling, psychology and nursing. Infertility can put couples under significant psychological, physical and financial stress, and the endocrine nurse plays a vital role in supporting patients with their treatment management and suggesting psychological referral as appropriate. Adopting a Nursing Process framework, the endocrine nurse provides a systematic approach to decision making and care planning, comprised of five stages: assessment, diagnosis, planning, implementation and evaluation.[2] The patient and his partner should be actively involved in the decision-making process and consulted throughout the duration of the fertility treatment.

Assessment starts with a holistic evaluation of clinical, physiological and psychological needs, in order to highlight any current areas of negative impact. A medical history should also be taken from the patient's partner, to identify any potential fertility issues and concerns. The endocrine nurse will

The micro-TESE process. ©2021, Achermann APP *et al.*, under exclusive licence to Springer Nature B.V.



'Effective management of patients with Klinefelter syndrome undergoing fertility treatment requires a multidisciplinary approach, including endocrinology, andrology, genetic counselling, psychology and nursing.'

support the couple to prepare for a potentially lengthy and stressful process, advise them accordingly and/or make appropriate referrals for counselling.

Once all assessments are completed, the treatment plan should be discussed and agreed with the multidisciplinary team. The endocrine nurse plays a crucial role in providing the patient with the relevant information about the fertility treatment changes and the TESE surgical procedure, including a detailed explanation of the success rates, based on available research and statistics from their local centre.

For successful implementation of the agreed care plan, the endocrine nurse needs to ensure that the patient understands the information provided regarding fertility treatment, and provides him with the opportunity to ask questions. Evaluation will be completed at designated time points, such as clinic appointments to monitor treatment progress and the patient's overall physical and psychological well-being. The partner should also be involved in the follow up consultations and supported for assisted fertility treatment planning, when micro-TESE is successful in retrieving healthy sperm.

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REFERENCES

1. Gravholt CH *et al.* 2018 *Endocrine Reviews* **39** 389–423.
2. Dwyer AA & Quinton R 2019 In *Advanced Practice in Endocrinology Nursing*, Eds Llahana S *et al.*, pp 853–870. Cham, Switzerland: Springer International Publishing.
3. Bojesen A *et al.* 2003 *Journal of Clinical Endocrinology & Metabolism* **88** 622–626.
4. Jayasena CN *et al.* 2022 *Clinical Endocrinology* **96** 200–219.
5. Llahana S 2019 In *Advanced Practice in Endocrinology Nursing*, Eds Llahana S *et al.*, pp 885–902. Cham, Switzerland: Springer International Publishing.
6. Achermann APP *et al.* 2021 *International Urology and Nephrology* **53** 2193–2210.
7. Corona G *et al.* 2017 *Human Reproduction Update* **23** 265–275.
8. Mehta A & Paduch DA 2012 *Fertility & Sterility* **98** 274–283.
9. Dwyer AA *et al.* 2019 In *Advanced Practice in Endocrinology Nursing*, Eds Llahana S *et al.*, pp 903–923. Cham, Switzerland: Springer International Publishing.
10. Kailash Y *et al.* 2021 *Frontiers in Reproductive Health* doi:10.3389/frph.2021.636629.

MALE HYPOGONADISM AND TESTOSTERONE REPLACEMENT

WRITTEN BY CHANNA N JAYASENA AND RICHARD QUINTON

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism have recently been published in *Clinical Endocrinology*.[1] Here, guideline working group members Channa N Jayasena and Richard Quinton discuss some of the topical issues that they addressed in developing the guidelines.

Many of us find male hypogonadism (MH) a difficult condition to diagnose and manage. Unfortunate trends in over-diagnosis and over-prescribing, which originated in North America, but which resonate worldwide, have put clinicians 'on guard' about the safety of testosterone treatment. The lack of unified clinical and biochemical thresholds for treatment, and the considerable heterogeneity among existing (largely monospecialty) guidelines has created huge variation in how men presenting with possible MH are managed.

For this reason, the Clinical Committee of the Society for Endocrinology commissioned us to develop new guidance for the UK, which we felt was best achieved through a multidisciplinary approach, comprising expertise from endocrinology (medical and nursing), primary care, clinical biochemistry, urology and reproductive medicine practices, and a patient expert. Using a narrative approach, we aimed to address head-on those particular issues that clinicians feel most uncomfortable about with regard to MH management, aiming to offer pragmatic advice based on consensus opinion. We also aspired to create something that clinicians might actually enjoy reading. Here is a selection of some key issues upon which we have provided guidance.

NON-GONADAL ILLNESS

Not all cases of MH are equal. It is easy to diagnose primary hypogonadism (low testosterone level and raised gonadotrophins), but hypogonadotrophic or central MH may be difficult to distinguish from non-gonadal illness (NGI), and thus careful clinical correlation is required.

The big problem in treating NGI with testosterone is that there is poor evidence for its efficacy to relieve symptoms. This makes sense when considering that symptoms such as low libido and tiredness will be caused by many (non-testosterone-related) reasons, due to systemic ill-health in NGI. Thus, solving a patient's low testosterone will neither magically address these symptoms, nor make them healthier overall.

So, it should not surprise us that, following an initial appearance of benefit, the effects of testosterone treatment in NGI might be disappointing for both patients and clinicians in the long term.

Obesity is a great example of NGI. Weight loss is a highly effective way of increasing testosterone levels in men with obesity, just like testosterone treatment. However, weight loss substantially reduces cardio-metabolic risk (*unlike* testosterone treatment, which is probably neutral; see below). For this reason, lifestyle intervention and addressing other root causes of NGI should be the first-line treatment for hypogonadal symptoms, over testosterone treatment, as these have the best chance of alleviating symptoms and improving overall health.

DIAGNOSING MH

We all get preoccupied with the testosterone threshold for 'how low levels need to be for testosterone treatment', but spotting the clinical features of MH is equally important. The most specific features of MH are sexual (low libido, erectile dysfunction, loss of morning erections), non-sexual (low bone density, vasomotor flushing, normocytic anaemia and gynaecomastia) and testicular (cryptorchidism, infertility). By contrast, altered mood, sleep or concentration, are much less specific to MH, and correspondingly less likely to improve with testosterone treatment.

Many criteria have been proposed for the diagnosis of MH, as discussed in two recent reviews comparing current guidelines.

In 9,000 healthy young men without obesity from Europe and North America, 95% had serum testosterone levels between 9.2 and 31.8nmol/l. Several double-blinded randomised controlled trials have shown that testosterone treatment improves sexual symptoms in men with serum testosterone <8nmol/l unrelated to NGI; so, there is little doubt of treatment effectiveness for these men. However, there are hardly any data demonstrating that testosterone treatment improves features of MH in men when the serum total testosterone is >12nmol/l. Clinicians would also benefit from better standardisation of local testosterone assays and assay-specific reference ranges across the UK.

FREE TESTOSTERONE

When sex hormone-binding globulin (SHBG) is abnormal, total testosterone measurement may not accurately assess the true biological effects of testosterone, or 'androgenicity'. In particular, men with obesity may have slightly low total testosterone levels, but with very low SHBG levels due to hyperinsulinaemia, androgenicity is usually preserved.

Free testosterone is notoriously difficult to measure; calculated free testosterone is an accepted estimate, which has been shown in the European Male Ageing Study (EMAS) to correlate with sexual symptoms associated with MH. Unfortunately, substantial assay variation affects the key components needed to calculate free testosterone (total testosterone and *especially* SHBG), and the mass action equation itself is not fully perfected. It is therefore a sobering reality that the accuracy and clinical utility of free testosterone quantification in optimising the diagnosis of MH will remain limited until these issues have been fully addressed.

CARDIOVASCULAR SAFETY

It seems a paradox that MH is associated with increased cardiovascular risk, yet testosterone treatment has been mired in controversy regarding the risk of provoking cardiovascular events cited by the US Food and Drug Administration, although not by the European Medicines Agency or the UK Medicines and Healthcare Products Regulatory Agency.

Although testosterone treatment increases the risk of erythrocytosis, the available randomised controlled trials and observational data have failed to reveal any consistent association (positive or negative) between testosterone treatment and cardiovascular or cerebrovascular events. This year, the National Institute for Health Research testosterone safety and efficacy consortium study will report results from the most robust analysis of testosterone safety to date. Meanwhile, clinicians are advised to consider cardiovascular risk in men before initiating testosterone treatment. In men with high cardiovascular risk, we recommend counselling them that the cardiovascular safety of testosterone therapy remains uncertain.

PROSTATE SAFETY

We enlisted a prostate onco-urologist to review this contentious issue. It is broadly accepted that testosterone treatment *does not* increase the risk of developing new prostate cancer. But we also know that there is a physiological restoration of prostate size after starting testosterone treatment for MH which may unmask *incidental* problems. We strongly advise that you ask men with MH about new urinary symptoms within the first few months following testosterone treatment initiation and refer for urological assessment appropriately.

Theoretically, prostate screening might exclude a pre-existing tumour during testosterone treatment, but endocrinologists have little experience recognising prostate cancer during digital rectal examination (DRE), which therefore risks harm. In contrast, increased age, black ethnicity and family history of prostate cancer unquestionably increase the risk of prostate cancer, which have triggered some countries to roll out national screening for high risk individuals. However, testosterone therapy does not have sufficient evidence of prostate cancer risk to recommend mandatory screening.

AGE AND DISABILITY

With the overwhelming majority of males retaining Leydig cell sensitivity to luteinising hormone stimulation into old age, we can envisage no compelling circumstances wherein testosterone treatment should be withheld from patients with MH on the basis of chronological age per se. Indeed, treatment would be anticipated to improve clinical parameters that are even more important to older men, such as anaemia, frailty, sarcopenia and osteopenia. Similarly, we cannot envisage compelling circumstances wherein testosterone treatment should be withheld from patients with MH who have physical or mental disabilities.

We hope this guidance provides a sensible and rational framework for diagnosing and managing MH, which chimes with the views of members of the Society for Endocrinology and helps us all to treat men effectively.

If you found this information interesting, please do read the full version published in *Clinical Endocrinology*.[1] Finally, we wish to acknowledge the useful input we received from members of the Society's Clinical Committee and the Irish Endocrine Society.

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Royal Victoria Infirmary,
Newcastle-upon-Tyne

REFERENCE

1. Jayasena CN *et al.* 2022 *Clinical Endocrinology* **96** 200–219.

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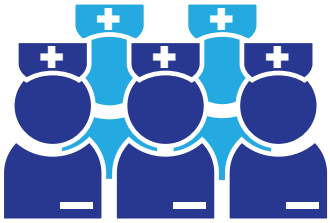

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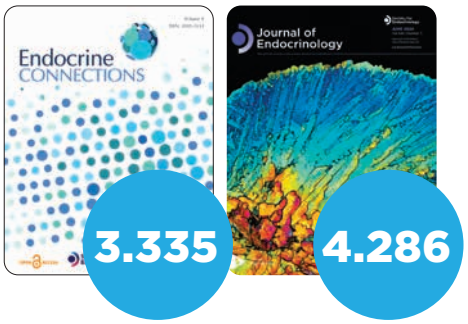

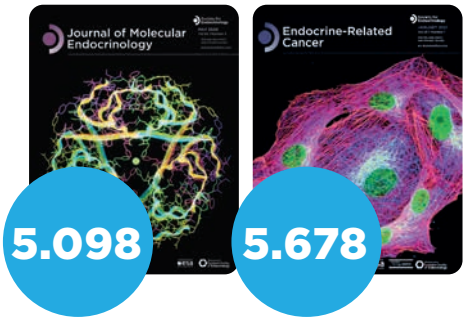

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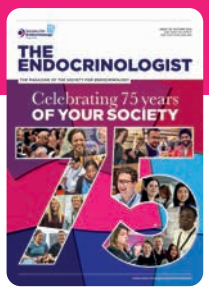

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MENOPAUSE: SPEAKING AN UNSPOKEN TRUTH

WRITTEN BY ANNICE MUKHERJEE

Menopause, like puberty and childbirth, is a physiological stage of reproductive health. However, negative stereotypes, lack of positive representation and confusion about where to access support make this a complex issue for women today, especially within the workplace.

We know that approximately three out of four women experience menopausal symptoms, and more openness is needed. For approximately 25% of women, symptoms will be bothersome enough to impact their daily life.[1]

BREAKING THE TABOO

Media interest in menopause has sky-rocketed in recent years. Davina McCall's 2021 Channel 4 television documentary 'Sex, Myths and the Menopause' raised awareness on a broad scale about issues surrounding menopause. Today, many women seek health information from media and social media platforms, and menopause is a growing commercial industry. Increasing awareness regarding menopause-associated health concerns and high adoption of women's health apps indicate that women are increasingly a commercial target for the 'menopause industry'.

There has also been considerable recent political interest. A parliamentary Private Members' bill reading in October 2021 resulted in Government action to cut the cost of repeat hormone replacement therapy (HRT) prescriptions and a new Menopause Taskforce to improve support for women experiencing menopause symptoms, with implications in the workplace.

MENOPAUSE IN THE WORKPLACE

Women over 50 are the fastest-growing employee demographic in the UK workforce, with over 3.5 million such women in employment.[2] They offer a wealth of experience and skills.

However, 60% of 45–55-year-old women who are experiencing menopause symptoms say it impacts negatively upon them at work.[3] So, it is unsurprising that menopause is becoming an increasingly important concern in UK workplaces. It deserves an open conversation, but menopause remains taboo at work. As such, menopause today is a personal journey and societal concern.

Over the last six years, the publication of several national guidelines concerning menopause in the workplace has aimed to redress the balance. Guidance has been provided by the Faculty of Occupational Medicine, the conciliation service ACAS, UNISON and the Chartered Institute of Personnel and Development, among others.

Menopause symptoms can be diverse, but usually settle over time. Support in the workplace aims to optimise productivity, facilitate retention and career progression for women in midlife, and help achieve gender balance in leadership roles.

In July 2021, a study highlighted the lack of gender parity amongst leadership roles in medicine.[4] The British Medical Association (BMA) circulated a menopause survey to its members in 2019. It found that the majority of respondents in this demographic were not receiving any support from their employer. The results highlighted the need for cultural change in workplaces and made recommendations to facilitate flexible working, workplace adjustments and well-being support to help break the taboo.[5]

With increased awareness, some companies are starting to take action to support employees suffering from menopausal symptoms and to create menopause-friendly working environments.

Big brands such as Vodafone, the UK broadcaster Channel 4, HSBC and the car sales website Auto Trader have adopted menopause at work policies, including paid leave and menopause training. Such policies are currently considered good practice but are not mandated. Training for managers, fostering a culture of openness, identifying menopause-related difficulties early and referring for occupational health support where disruptive symptoms persist are strategies recommended to reduce any negative impact of menopause on workforce logistics going forward.

MANAGING MENOPAUSAL SYMPTOMS

The use of HRT during menopause has an established role in managing symptoms. Research into the risk–benefit ratio for HRT during the last two decades shows that risks are linked to age, co-morbidities, duration of treatment, type, dose and route of delivery. Reduced risks are associated with micronised progesterone and dydrogesterone for endometrial protection in women with an intact uterus, compared with other progestogens, and a favourable risk profile is observed with the use of transdermal oestrogen alone in hysterectomised women. Risk stratification can minimise previously documented cardiovascular, thromboembolic and breast cancer risks, and identify those unsuitable for hormone therapy.

For those unable to use hormone therapy due to risk factors or co-morbidities, lifestyle strategies and several natural and non-hormone pharmacological therapies are available that women often find helpful. A novel neurokinin-3 receptor (NK3R) antagonist is in the pipeline, which significantly reduces menopausal flushing and other symptoms, with a good safety profile. It does not affect serum oestrogen levels and therefore may be suitable for women who are intolerant of or cannot use HRT safely. Pioneering work by Whaljit Dhillo and colleagues at Imperial College London resulted in the seminal paper on NK3R antagonists in 2017.[6] Since then, several research groups have reproduced these results. Japanese-owned Astellas Pharma may be first to the mass market with Fesolinetant, which is expected to be licensed in 2022/2023.[7]

For all women, lifestyle approaches and an individualised, tailored approach to pharmacological intervention are critical for successful menopause health outcomes and workplace productivity.[8]

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Annice Mukherjee is author of The Complete Guide to the Menopause.[8]

REFERENCES

1. British Menopause Society 2021 www.thebms.org.uk/2021/08/the-british-menopause-society-response-to-the-department-of-health-and-social-cares-call-for-evidence-to-help-inform-the-development-of-the-governments-womens-health-strateg.
2. Royal College of Obstetricians & Gynaecologists 2019 *Better for Women* www.rcog.org.uk/globalassets/documents/news/campaigns-and-opinions/better-for-women/better-for-women-full-report.pdf.
3. NHS Employers 2021 *Menopause and the Workplace* www.nhsemployers.org/articles/menopause-and-workplace.
4. Salem V *et al.* 2021 *Lancet Diabetes & Endocrinology* **9** 556–559.
5. BMA 2020 *Challenging the Culture on Menopause for Working Doctors* www.bma.org.uk/media/2913/bma-challenging-the-culture-on-menopause-for-working-doctors-report-aug-2020.pdf
6. Prague JK *et al.* 2017 *Lancet* **389** 1809–1820.
7. Astellas Pharma 2021 *News Release* https://newsroom.astellas.us/2021-09-22-Astellas-to-Present-Fezolinetant-12-Week-Findings-from-Phase-3-SKYLIGHT-2-TM-Trial-in-Oral-Session-at-The-North-American-Menopause-Society-2021-Annual-Meeting.
8. Mukherjee A 2021 *The Complete Guide to the Menopause* London: Vermilion.

SPECIALIST NURSES IN MICROPROLACTINOMA MANAGEMENT

WRITTEN BY LAURA SERBAN

It is anticipated that 1 in 500 women of reproductive age will have a prolactinoma. Elevated prolactin levels inhibit the release of luteinising hormone and follicle-stimulating hormone. The degree of menstrual disturbance corresponds to the degree of hyperprolactinaemia. Even in the presence of regular cycles, hyperprolactinaemia is thought to make conditions less favourable for embryo implantation.

MEDICAL MANAGEMENT

Dopaminergic agonists (DA) are the primary therapy for patients with prolactinomas. Medical therapy is remarkably effective in restoring gonadal function and fertility. Cabergoline is widely recognised to be superior to bromocriptine, both in terms of tolerability and efficacy.

DA should be continued in women seeking pregnancy. Observed rates of spontaneous miscarriage, preterm delivery and neonatal malformation are comparable in women taking DA to those in the general population. Current guidelines recommend the use of cabergoline at the lowest possible effective dose until a pregnancy is confirmed.

Common side-effects, such as nausea, postural hypotension and nasal stuffiness, can often be mitigated by gradual dose titration. However, there remains a significant group of patients in whom DA intolerance and/or resistance necessitate alternative treatment strategies.

Neuropsychiatric side-effects remain particularly challenging. The prevalence of impulse-control disorders in patients treated with DA has historically been underestimated, and is now recognised to be up to 1 in 6 patients.

'Specialist nurses are often best placed to recognise the failure of medical treatment in a timely manner. There is also a key role to be played in counselling patients regarding alternative management options and advocating for the consideration of surgery, as and when appropriate.'

ALTERNATIVE TREATMENT STRATEGIES

Hormone replacement therapy can be used to ameliorate hypogonadism. However, it does not restore fertility.

Surgical intervention offers an alternative management option. Selective adenomectomy has been demonstrated to be both safe and effective in several neurosurgical cohorts. Importantly for this group of patients, anterior pituitary function is almost always preserved (100% of patients were eupituitary at three months in a recent series).

THE ROLE OF THE SPECIALIST NURSE

As a titrated therapy, management with DA requires regular blood testing and subsequent dose adjustment. This can be overseen by a specialist nurse with knowledge of this area of practice.

Additionally, patients starting on DA need clear counselling about the potential side-effects at the point of initiation. They also require a clear mechanism or 'point of contact' for reporting and discussing potential concerns once on treatment.

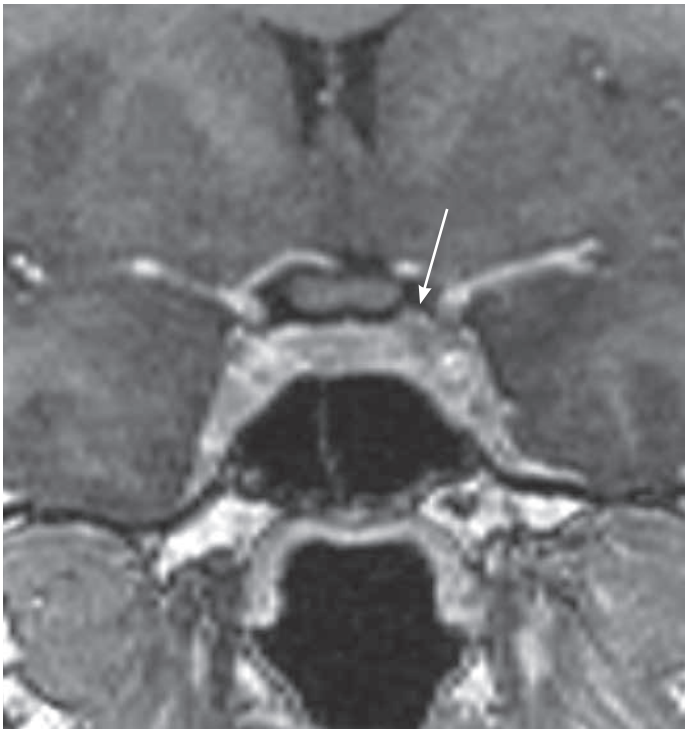

Figure. MRI with arrow showing left-sided microprolactinoma, which was removed at trans-sphenoidal surgery with positive histology and subsequent remission. ©Mark Gurnell, Addenbrooke's Hospital

Specialist nurses are often best placed to recognise the failure of medical treatment for a prolactinoma in a timely manner. There is also a key role to be played in terms of counselling patients regarding alternative management options and advocating for the consideration of surgery, as and when appropriate.

AN ILLUSTRATIVE CASE

A woman in her late 30s presents with oligomenorrhoea and difficulty in conceiving. Hyperprolactinaemia is identified and non-tumoural causes are excluded. Pituitary magnetic resonance imaging (MRI) confirms a sub-centimetre adenoma. Cabergoline is initiated at 250µg twice a week; however, dizziness and nasal stuffiness are intolerable at higher doses. Bromocriptine and quinagolide produce a similar profile of adverse effects. Exploratory trans-sphenoidal surgery is discussed as a potential alternative. Selective adenomectomy is subsequently undertaken, with post-operative normalisation of prolactin levels.

LAURA SERBAN
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MORNING SICKNESS, FIRE SMOKE AND PLACENTAL IMPLANTATION

WRITTEN BY PHIL LOWRY AND MILES LEVY

Human beings are the only animal species that develop morning sickness (emesis) during early pregnancy. Even higher apes have not been observed to suffer from this debilitating condition. Yet, 80% of pregnant women do, even to the extent where it can be life-threatening in some cases, due to severe dehydration which affects mother and baby (hyperemesis gravidarum). It has long been felt that morning sickness is somehow a sign of a healthy pregnancy, and it is possible that this has some scientific merit.[1]

High blood concentrations of pregnancy hormones, such as human chorionic gonadotrophin and oestrogen, or low sugar, have been proposed as candidates contributing to morning sickness – but no experimental evidence has been reported regarding the precise neurological mechanism of nausea and vomiting, despite its high prevalence.

Another feature of pregnancy in humans is hyper-salivation (ptyalism), but this is also observed in other pregnant animals. Again, pregnancy hormones have been proposed as the cause, but none have been identified.

A ROLE FOR TACHYKININS?

The neuropeptide substance P (SP) has long been recognised as the principal agonist stimulating the neurokinin 1 receptor (NK1R), which is found to be involved in both emesis and salivation. However, there is no evidence for its secretion from, or its gene expression in, the placenta.

SP belongs to the family of neuropeptides called the tachykinins, which includes neurokinin A (formed from an alternate splice of the SP precursor gene), neurokinin B (NKB) and endokinin.[2]

NKB has been found to be expressed and secreted by the placenta. It can be detected in the circulation during pregnancy and is the principal agonist of the NK3R. It has been proposed that the resulting vasoconstriction of the portal and mesenteric blood vessels diverts more blood to benefit the uterine/placental interexchange, but high concentrations of NKB result in hypertension and pre-eclampsia.[3]

'No experimental evidence has been reported regarding the precise neurological mechanism of nausea and vomiting, despite its high prevalence.'

Endokinin is a potent neuropeptide agonist at the NK1R and is expressed in several peripheral tissues, including the placenta and lungs. It has been suggested that its secretion from the placenta in early pregnancy is the cause of morning sickness.[2] Its blood concentration also increases after tobacco smoke inhalation into the lungs,[4] and could thus be the cause of the nausea experienced by smokers.

It has been proposed that the endokinin gradient across the placental/uterine boundary is important for the development of the spiral arteries which are important in efficient placental/uterine transfer of nutrients and gases. In women who smoke, this endokinin gradient is disrupted by the lung-derived endokinin concentrations increasing on the uterine side, thus affecting normal directional development of the spiral arteries, which results in poor placental implantation.[5]

AN EVOLUTIONARY PURPOSE?

Mankind started taking advantage of fire over a million years ago, initially in cooking meat, but then in helping to keep warm in enclosed spaces, such as caves, when moving north into colder climates. It is in this latter situation where the inhalation of smoke from the fires would have led to nausea, as it is detrimental to health, and particularly to placental implantation, resulting in poor pregnancy outcomes.

A simple evolutional trait that would have reduced this effect would have been an increase in the sensitivity/density of the nausea NK1Rs to endokinin, so that pregnant women in particular would tend to seek a less smoky atmosphere and therefore improved pregnancy outcomes. But this would have also resulted in the same receptors responding more to placental endokinin and therefore morning sickness.

'It is just possible that morning sickness in an evolutionary adaptation to warn pregnant women in the first trimester that they should dwell in a safe environment for the early development of their offspring.'

Once mankind started to have chimneys in dwellings, this evolutionary pressure may have receded, therefore explaining why 20% of women still don't suffer from morning sickness during early pregnancy. Smoking tobacco during pregnancy should still be discouraged, however, as it will lead to endokinin being released from the lungs during smoke inhalation, and is probably the reason for the resulting poor placental implantation.

In conclusion, it is just possible that morning sickness is an evolutionary adaptation to warn pregnant women in the first trimester that they should dwell in a safe environment for the early development of their offspring. It therefore is a protective and helpful symptom, and a sign of a healthy feto-placental unit.

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REFERENCES

1. Hinkle *et al.* 2016 *JAMA Internal Medicine* **176** 1621–1627.
2. Page *et al.* 2000 *Nature* **405** 797–800.
3. Page *et al.* 2003 *Proceedings of the National Academy of Sciences of the USA* **100** 6245–6250.
4. Vaiyapuri 2017 *Endocrine Abstracts* **50** P270.
5. Lowry & Woods 2018 *Journal of Molecular Endocrinology* **60** R23–R30.

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EARLY CAREER SCIENTIST: STUDYING RARE DISEASES TO UNCOVER THE MECHANISMS REGULATING HUMAN PANCREATIC DEVELOPMENT

WRITTEN BY ELISA DE FRANCO

Understanding the mechanisms which regulate the formation of the human pancreas *in utero* has important implications for diagnostics, research and therapies.

Knowing which cellular pathways orchestrate pancreatic development can highlight genes which, when affected by DNA mutations, cause monogenic forms of diabetes (such as MODY (maturity-onset diabetes of the young) or neonatal diabetes[1]). Recent studies have shown the importance of genes involved in pancreatic development which increase the risk of type 2 diabetes,[2] emphasising the value of an improved understanding in gaining insights into the pathogenesis of this disease. Finally, by accurately mapping the *in vivo* processes leading to development of the pancreas, we could inform current efforts to improve protocols to differentiate β cells *in vitro*, providing a better cellular model to study diabetes and potentially accelerating the introduction of cell-based therapies in this disease.[3]

LIMITATIONS OF RODENT MODELS

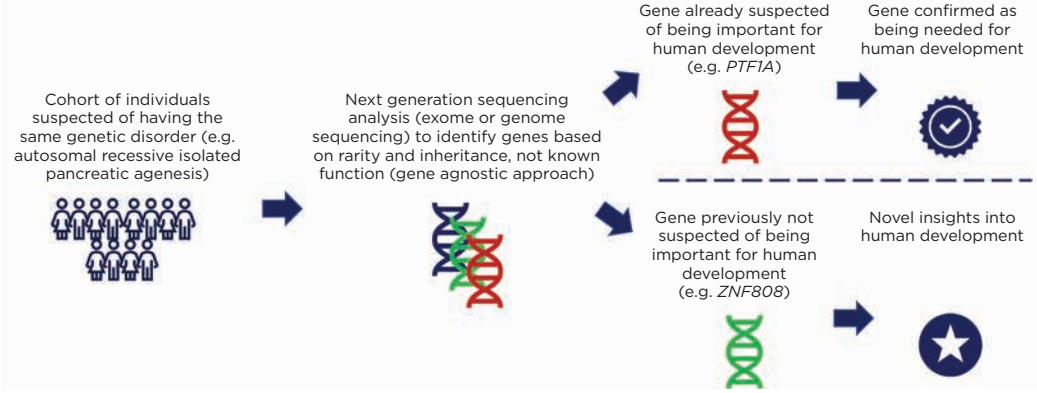
Traditionally, insights into human development have been extrapolated from studies in mouse models. These have been essential to highlight some of the master regulators of pancreatic development. However, there are many differences between the human and rodent pancreases. For example, (a) the structure of the islets of Langerhans is remarkably different (both in terms of cell composition and organisation), (b) mice have two genes encoding insulin whilst humans have one, and (c) heterozygous mutations in genes such as *GATA6* result in pancreatic agenesis in humans but no phenotype in mice.[4,5] These differences suggest that we can't exclusively rely on animal models to understand human pancreas development.

STUDIES OF PANCREATIC AGENESIS

We aimed to discover novel regulators of human pancreatic development by studying the genetics of individuals with a rare genetic form of diabetes, called pancreatic agenesis. These individuals are born with a very small (or absent) pancreas, and develop diabetes in the first few weeks of life. They also have exocrine pancreatic insufficiency, which could affect their growth. Pancreatic agenesis is mostly caused by a single, rare, genetic mutation disrupting a gene essential for pancreatic development.[6]

We used whole exome sequencing (a technique which allowed us to sequence the protein-coding portion of the patients' genomes) in two unrelated individuals diagnosed with pancreatic agenesis at 5 days. Both were born to parents who were related to one another. Our genomic analysis found that both individuals had homozygous variants resulting in loss of function of a gene called *ZNF808*.[7] This gene had never been associated with human disease before. Analysis of the *ZNF808* gene in 232 additional individuals with diabetes diagnosed in the first 6 months of life found homozygous mutations in 11 cases. All the individuals with *ZNF808* mutations had diabetes diagnosed in the neonatal period and a very low birth weight, consistent with absent insulin secretion *in utero*. Five individuals were confirmed to have pancreatic agenesis; the remaining cases are being followed up. None of them had additional clinical features affecting other tissues.[7]

Figure. Genetic studies in individuals with rare diseases allows the identification of key regulators of human development.



UNDERSTANDING THE ROLE OF ZNF808

The protein coded for by *ZNF808* belongs to the family of KRAB zinc finger transcription factors. This is an evolutionarily dynamic family of genes, binding and repressing transposable elements.[8] Tracing the evolution of *ZNF808* through species found that the corresponding protein is present only in higher primates and is absent in other primates and rodents.[8] To the best of our knowledge, this is the first example of a primate-specific gene which causes a congenital developmental disorder in humans.[7]

We sought to investigate the role of ZNF808 during human pancreatic development using *in vitro*-differentiated stem cells. We used CRISPR-Cas9 to introduce a homozygous deletion of *ZNF808* in human embryonic stem cells, and then differentiated them to pancreatic progenitors. ChIP-seq analysis showed that ZNF808 actively represses transposable elements during these early differentiation stages and, upon ZNF808 loss, many of these transposable element-derived regions become aberrantly activated.

Transcriptomic analysis showed that the biggest differences in terms of differentially expressed genes were observed at the primitive gut tube and posterior foregut stages. Among the genes which were overexpressed, there was an enrichment of liver genes with an enrichment of pancreas-related genes among the downregulated ones.[7] These results led us to formulate the hypothesis that ZNF808 may have a role as 'gatekeeper' of cell fate early during pancreatic differentiation and be essential for liver versus pancreas fate decision. Under this model, absence of ZNF808 would result in cell fate diversion from pancreas to liver lineages, leading to pancreatic agenesis in individuals with *ZNF808* loss of function mutations. Additional experiments are currently in progress to validate this hypothesis.

IN CONCLUSION

Our work highlights the power of using genomic studies in individuals with rare conditions to gain novel insights into human development. This study identified the first example of a primate-specific gene where loss of function mutations cause a human congenital developmental disorder. Furthermore, we have discovered a novel regulator of human pancreas development, providing a new avenue towards further understanding of how to replicate this process *in vitro*.

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REFERENCES

1. Hattersley AT & Patel KA 2017 *Diabetologia* **60** 769–777.
2. Geusz RJ *et al.* 2021 *eLife* **10** e59067.
3. Balboa D *et al.* 2019 *Diabetologia* **62** 1329–1336.
4. Allen HL *et al.* 2011 *Nature Genetics* **44** 20–22.
5. Watt AJ *et al.* 2007 *BMC Developmental Biology* **7** 37.
6. De Franco E *et al.* 2019 *American Journal of Human Genetics* **104** 985–989.
7. De Franco E *et al.* 2021 *medRxiv* doi: 10.1101/2021.08.23.21262262.
8. Imbeault M *et al.* 2017 *Nature* **543** 550–554.

EARLY CAREER CLINICIAN: MILD AUTONOMOUS CORTISOL SECRETION: AN UNDERESTIMATED CARDIOMETABOLIC DISEASE ICEBERG

WRITTEN BY ALESSANDRO PRETE AND WIEBKE ARLT

Up to 5% of adults and 10% of over 70-year-olds harbour an adrenal tumour. The vast majority of these tumours arise from the adrenal cortex, are benign, and do not cause specific clinical symptoms. Therefore, adrenal tumours are mostly discovered incidentally when carrying out a scan of the abdomen for unrelated reasons, prompting the use of the term 'adrenal incidentaloma'.

Once an adrenal tumour is diagnosed, two crucial questions need to be answered to guide management:

1. Is the tumour malignant?

Answering this question usually requires taking a detailed medical history (any previous history of extra-adrenal cancer?) and assessment of the imaging characteristics of the tumour, namely the size and the unenhanced computed tomography (CT) attenuation value of the tumour area.

2. Is the tumour hormonally active?

This second question relies on physical examination and several hormonal tests to rule out excess production of cortisol, aldosterone, androgen precursors and catecholamines, all of which are produced by the adrenal glands. Cortisol excess is assessed by the 1mg dexamethasone overnight suppression test (1mg-DST).

MILD AUTONOMOUS CORTISOL SECRETION

About 50% of benign adrenal tumours demonstrate evidence of hormone excess.

Clinically overt cortisol excess, also known as Cushing's syndrome, is rare and typically presents with distinct clinical signs such as proximal myopathy and purple striae, but also with less specific metabolically adverse consequences, including type 2 diabetes, hypertension and dyslipidaemia.

Mild autonomous cortisol secretion (MACS) is far more common than Cushing's syndrome. It is associated with up to one third of benign adrenal tumours, according to previous small-scale studies. However, patients usually show no characteristic clinical signs of Cushing's syndrome. MACS is defined by failure to suppress serum cortisol sufficiently after overnight administration of 1mg dexamethasone in the 1mg-DST.

Several smaller-scale studies have suggested that MACS is potentially associated with frailty and an increased risk of mortality and cardiometabolic morbidities, including metabolic syndrome, cardiovascular events, atrial fibrillation and osteoporosis. Due to the high prevalence and potential clinical consequences of MACS, the joint guideline by the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ENSAT) recommends that all patients with adrenal tumours should undergo a 1mg-DST.

THE EURINE-ACT STUDY

In 2011, the University of Birmingham started a large, prospective, multi-centre study on patients with newly diagnosed adrenal tumours: the

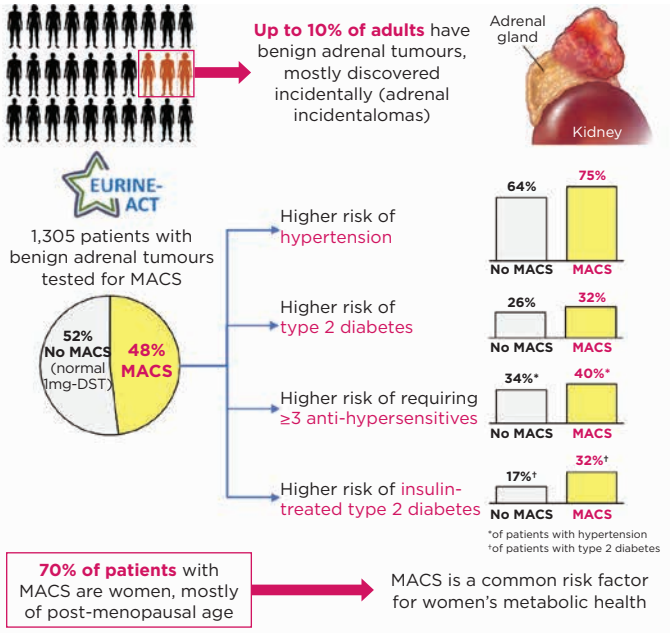


Figure. All patients with newly diagnosed adrenal tumours should undergo a 1mg-DST to screen for MACS. In the EURINE-ACT Study, 1,305 patients with benign adrenal tumours (incidentally discovered in 1,240) underwent a 1mg-DST. 48% of patients with adrenal incidentalomas had abnormal 1mg-DST results. Patients with MACS were more likely to be post-menopausal women and carried a higher cardiometabolic risk than those with normal 1mg-DST results.

Evaluation of Urine Steroid Metabolomics in the Differential Diagnosis of Adrenocortical Tumours (EURINE-ACT) Study. Over the course of 5 years, more than 2,000 participants were enrolled from 13 European and 1 American specialist ENSAT centres. This study was primarily designed to prospectively validate urine steroid metabolomics (USM), the combination of mass spectrometry-based steroid metabolome profiling and machine learning-based steroid data analysis. The EURINE-ACT Study results demonstrated that USM has superior specificity to imaging, and that the combination of unenhanced CT attenuation and USM provides the most sensitive and specific diagnostic information for detecting adrenocortical carcinoma.

However, more than 1,300 of the EURINE-ACT Study's participants were diagnosed with benign adrenal adenomas and were tested for MACS with the 1mg-DST. This yielded the largest prospective cohort of this kind collected to date, and provided us with an excellent opportunity to investigate the impact of MACS on metabolic health in a very large, prospectively collected cohort. All patients underwent a detailed clinical assessment of their cardiometabolic risk and provided a 24-hour urine collection. The urine samples were analysed by multi-steroid profiling using tandem mass spectrometry to provide a detailed overview of adrenal steroid production and metabolism.

MACS, HYPERTENSION AND TYPE 2 DIABETES

It surprised us just how common MACS was: it was diagnosed in almost half the patients harbouring a benign adrenal incidentaloma. Notably, 70% of patients with MACS were women, and most of them were of postmenopausal age (over 50 years old).

Compared with those without MACS, we observed that patients with MACS were more likely to be diagnosed with hypertension and to require three or more anti-hypertensives to achieve adequate blood pressure control. When we looked at patients with a diagnosis of type 2 diabetes, those with MACS were twice as likely to be insulin-dependent, indicating that other medications have not helped in managing their blood sugar levels.

Examination of the steroids in the urine of patients with MACS, in comparison with those in subjects with normal 1mg-DST results, showed an increase in the excretion of cortisol and related metabolites. Conversely, the excretion of androgen metabolites was reduced in patients with MACS. Adrenal androgen production is stimulated by adrenocorticotrophin (ACTH); therefore, this observation is possibly linked to the negative feedback exerted by the cortisol excess on the pituitary, leading to reduced secretion of ACTH.

MACS: A VASTLY UNDERESTIMATED PROBLEM

Only a minority of patients with adrenal incidentalomas are referred to an endocrinologist and undergo optimal work-up to exclude MACS. Just one in six patients underwent a 1mg-DST in a recently published population-based study. If left undiagnosed, patients with MACS are at risk of developing adverse cardiometabolic consequences and presenting with poorly controlled hypertension and type 2 diabetes.

Based on our findings and the high prevalence of adrenal tumours, we estimate that up to 1.3 million adults in the UK could have MACS. Considering that around two out of three of these patients are women, MACS is potentially a key contributor to women's metabolic health, particularly after menopause.

THE NEXT STEPS

Our study is the largest ever to establish conclusively the extent of the risk and severity of hypertension and type 2 diabetes in patients with MACS. We advocate that all patients with an adrenal incidentaloma are tested for MACS and, if MACS is confirmed, are regularly tested for type 2 diabetes and high blood pressure.

Going forward, our research will focus on three main areas. First, we want to investigate how MACS is linked to this increased risk by investigating how cortisol excess affects human metabolism. Secondly, we are working on a test that can be used at an early stage to identify which patients with MACS carry a higher risk of developing adverse cardiometabolic consequences. Thirdly, we are testing new treatment strategies to mitigate this risk in affected individuals.

ALESSANDRO PRETE
Diabetes UK Sir George Alberti Research Fellow, Institute of Metabolism and Systems Research, University of Birmingham

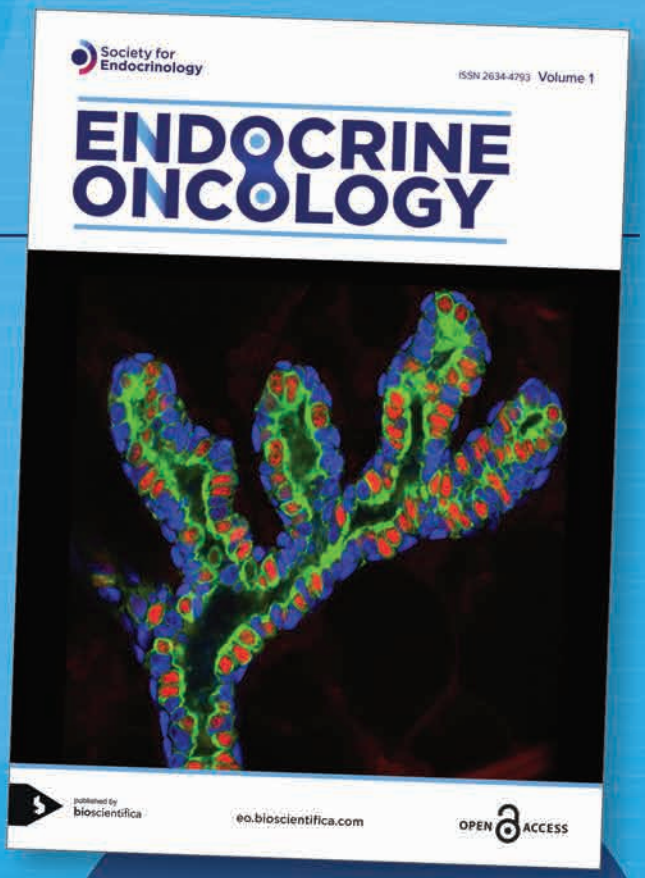
WIEBKE ARLT
William Withering Chair of Medicine, and Director, Institute of Metabolism and Systems Research, University of Birmingham

FURTHER READING

1. Prete A *et al.* 2022 *Annals of Internal Medicine* doi: 10.7326/M21–1737.
2. Bancos I *et al.* 2020 *Lancet Diabetes & Endocrinology* **8** 773–781.
3. Elhassan YS *et al.* 2019 *Annals of Internal Medicine* **171** 107–116.
4. Kjellbom A *et al.* 2021 *Annals of Internal Medicine* **174** 1041–1049.
5. Ebbehoj A *et al.* 2020 *Lancet Diabetes & Endocrinology* **8** 894–902.
6. Bancos I & Prete A 2021 *Journal of Clinical Endocrinology & Metabolism* **106** 3331–3353.
7. Fassnacht M *et al.* 2016 *European Journal of Endocrinology* **175** G1–G34.

Society for Endocrinology

Publish in our early career special collection



Endocrine Oncology **and the Society for Endocrinology are delighted to announce that a new special collection, showcasing the latest work from early career researchers and clinicians in the field of hormones and cancer (and related topics), is now open for submissions.**

Find out more at eo.bioscientifica.com/page/sfe-early-career-collection

Proposal deadline for original research and review suggestions: August 2022.

Endocrine Oncology **is an open access, peer-reviewed journal publishing basic, translational and clinical research and reviews across the field of endocrine cancers.**

All Article Processing Charge fees are currently waived, so publishing your work in the collection is free!

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MY TURNER SYNDROME FERTILITY STORY

Caroline Marquis describes her personal experience of living with Turner syndrome as a patient.

HOW DID YOU DISCOVER THAT YOU HAD TURNER SYNDROME?

My story is unusual in that doctors always knew there was something wrong with me but, despite numerous hospital admissions, a diagnosis of Turner syndrome was not made until I was 24 and pregnant with my first child.

I was born in 1957. For my generation, diagnosis of Turner syndrome typically followed referral to a consultant for lack of pubertal development. However, I had spontaneous puberty and started a regular menstrual cycle at the age of 15.

DID YOU SUSPECT YOU MIGHT HAVE FERTILITY PROBLEMS?

At the age of 21, when I got engaged, my mother took me aside and told me that the doctors did not envisage me having normal puberty, etc., and perhaps I might not be able to have children. I then arranged an appointment with my GP, at which I said I wished to know if I could have children. The GP said that I had developed more than they had expected and that only a gynaecologist could give me an answer. I was referred to a gynaecologist at Aberdeen Royal Infirmary. After tests and examinations, I was told they could not say for definite, but I had two functioning ovaries and a womb (which I was told was of a slightly abnormal shape). They said to go ahead and try for a family. There was still no Turner syndrome diagnosis.

DID YOU RECEIVE SPECIAL CARE DURING YOUR PREGNANCY?

Fast forward three years and, after being married for nine months, I became pregnant after only two months of us trying to start a family. I was immediately referred by my GP to Aberdeen Maternity Hospital, due to my short stature of 4′5″(135cm), so that my pregnancy could be monitored by a consultant gynaecologist and obstetrician. This turned out to be the same consultant that I had previously seen when I was 21.

HOW DID YOUR PREGNANCY PROCEED?

My pregnancy continued smoothly, although regular scans to monitor the baby's growth showed I had placenta praevia and my baby would definitely be delivered by caesarean section. The placenta praevia also meant that my consultant wanted to admit me into hospital at 37 weeks of gestation, a week before my elective caesarean section at 38 weeks. This was due to the risk of early labour and the 66-mile journey I would have to get to hospital.

WHAT LED TO THE DIAGNOSIS OF TURNER SYNDROME?

During my pregnancy, my consultant asked whether I would mind seeing a colleague of his, who was interested in people of short stature, such as myself. Whilst I agreed and was subsequently seen by his colleague, because of the excitement of preparing for our new arrival, I never gave it a lot of thought. On the arranged date in November 1981, I gave birth to a bouncing baby boy who weighed in at 7lb 10ozs. It was 3 days after my son's birth that I was to learn from my gynaecologist and his colleague (whom I discovered was a genetic consultant) that I had Turner syndrome, and that was the reason for my short stature.

WHAT IMPLICATIONS DID THE DIAGNOSIS HAVE FOR YOU?

The consultants told me I was extremely fortunate to be fertile, and that, if I wanted more children, I shouldn't wait, as they didn't know how long I would be fertile for. They also recommended that I had an amniocentesis test due to my higher risk of having a child with a chromosome abnormality.

At the end of 1982, we decided we would like to have another child. After months of trying, despite my regular menstrual cycle, nothing happened. My gynaecologist arranged for bloods at a specific point in my cycle, to check my ovulation. Those tests came back fine and, shortly afterwards, I fell pregnant with our second child.

HOW WAS YOUR NEXT PREGNANCY?

I was monitored closely from 12 weeks of gestation. At 18 weeks, I had the recommended amniocentesis, and 4 weeks after that we learned that no abnormalities had been found and that our baby was fine. Shortly after this, I suffered a threatened abortion, so was put on bedrest for a few weeks. We also learned we were having another boy.

As with my first pregnancy, I had regular scans. At 36 weeks it was decided that I would deliver by caesarean section again, as my baby was going to be too big for me to deliver him naturally. Our second son weighed in at 8lbs.

WHAT FOLLOW-UP CARE DID YOU AND YOUR SONS RECEIVE?

Both babies had chromosome analysis at birth. The gynaecologist and geneticist continued to take an interest in me and our sons. As the consultants had expected, I had premature menopause, starting when I was 29 years old. Results of sample analyses from my ovaries, taken at the time of my caesarean sections, showed that my ova count was that of a woman 10 years older than my chronological age. I appreciate how fortunate I was to be able to conceive two children naturally, given that my karyotype is 45X,O.

CAROLINE MARQUIS

with thanks to the Turner Syndrome Support Society (UK)

The Turner Syndrome Support Society (UK) is a national support group for individuals with Turner syndrome and their families. It offers accurate information and support. It works closely with the almost 30 clinics for adults with Turner syndrome that are currently running throughout the UK, and is a Society for Endocrinology-approved patient support group. Find out more at **www.tss.org.uk**.

OTC HRT THE FUTURE?

WRITTEN BY SOPHIE CLARKE

At the beginning of February, the Medicines and Healthcare products Regulatory Agency UK launched a public consultation regarding the reclassification of vaginal oestradiol (Gina 10 µg tablets) to make it available from pharmacies[1]. This announcement was published widely across news outlets in the UK with some reporting that 'hormone replacement therapy could be available over the counter'[2].

Hormone replacement therapy (HRT) involves the administration of hormones after the menopause, and aims to both relieve symptoms and protect against side effects of hypo-oestrogenism, including increased cardiovascular events and reduced bone mineral density. HRT typically includes the replacement of oestrogen either in isolation (for women without a uterus) or in combination with progesterone and, for some individuals, testosterone supplementation.

Estimates suggest that 85% of women experience at least one menopausal symptom during their lifetime[3]. Whilst vasomotor symptoms are the most widely reported, genitourinary syndrome of menopause, characterised by vaginal dryness, dyspareunia and recurrent urinary tract infections has been recently been observed in 37% of women aged 40–55 years in a cross-sectional study in Italy [4].

'The potential availability of vaginal oestradiol reflects an increasing awareness of the prevalence of menopausal symptoms and the desire to improve access to treatment.'

Although in the UK the average age of onset of menopause is 51 years, premature ovarian insufficiency (POI, loss of ovarian function <40 years of age) affects approximately 1% of the female population. Additionally, it should be noted that the menopause may occur due to either loss of intrinsic ovarian function or as a result of medical treatments (including surgical removal of the ovaries, bilateral oophorectomy, or chemotherapeutic agents).

The menopause has recently risen in public awareness following a series of high-profile campaigns and programmes. In a survey of 846 women aged 40–65 conducted by Ipsos MORI in 2020, 47% had experienced 3 or more symptoms whilst at work, and half of these women felt that this had negatively impacted their work[5]. Additionally an earlier survey undertaken by Ipsos MORI on behalf of the British Menopause Society (BMS) in 2016 revealed that one in two women had not consulted a healthcare professional for their menopausal symptoms, despite 42% saying that they were worse than expected[6]. It therefore is unsurprising that some have welcomed this news regarding the potential availability of a form of HRT from pharmacists for symptomatic relief.

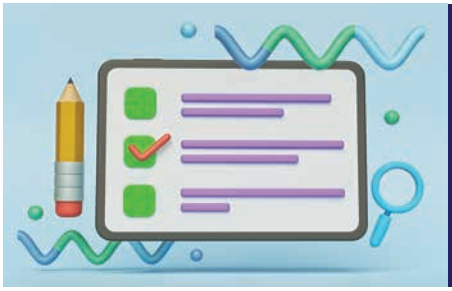
Vaginal oestradiol is typically administered once daily for two weeks on initiation, and then twice weekly thereafter and can provide important relief from genitourinary symptoms. However low-dose vaginal oestradiol has minimal systemic absorption and as such it is not an effective treatment for symptoms including hot flushes, reduced libido and cognitive function. For these, other preparations of HRT, including either oestrogen alone (in women without a uterus) or in combination with progesterone are required, the selection of which requires a careful appraisal of individual patient characteristics and discussion with the patient to determine the most appropriate mode of delivery.

In summary, the potential availability of vaginal oestradiol reflects an increasing awareness of the prevalence of menopausal symptoms and the desire to improve access to treatment. However, for those patients experiencing more widespread symptoms, a consultation between the patient and clinician remains important in evaluating both the symptoms being experienced and the most suitable form of HRT to provide relief.

SOPHIE CLARKE
Consultant Endocrinologist, University College London Hospital

REFERENCES

1. Medicines and Healthcare products Regulatory Authority. 2022 Open consultation: Proposal to make Gina 10 microgram vaginal tablets (Estradiol) available from pharmacies. https://www.gov.uk/government/consultations/consultation-on-proposal-to-make-gina-10-microgram-vaginal-tablets-estradiol-available-from-pharmacies/proposal-to-make-gina-10-microgram-vaginal-tablets-estradiol-available-from-pharmacies. Accessed February 16, 2022.
2. Sky News. 2 Feb 2022 Menopause: Hormone replacement therapy could become available over the counter. Available at: https://news.sky.com.
3. Woods NF and Mitchell ES. 2005 Symptoms during the perimenopause: Prevalence, severity, trajectory, and significance in women's lives. *The American Journal of Medicine* **118**(12 SUPPL. 2) 14–24.
4. Cagnacci A at al. 2019 Vaginal atrophy across the menopausal age: results from the ANGEL study. *Climacteric* **22** 85–89.
5. Ipsos MORI 2020. Menopause in the workplace. *Ipsos MORI.* doi:10.12968/denn.2021.17.12.586.
6. BMS 2016 Are women suffering in silence ? New survey puts spotlight on significant impact of menopause despite recent guideline. *British Menopause Society.* Available at: https://thebms.org.uk/wp-content/uploads/2016/05/FINAL_BMS-2016-Annual-Conference_Press-Release_060516.pdf [Accessed 23 February 2022]



Celebrating and rewarding EXCELLENCE IN ENDOCRINOLOGY

MEET OUR 2022 MEDALLISTS AND AWARDEES

Join us in congratulating the Society for Endocrinology's 2022 Medallists and Awardees! These world-leading endocrinologists have made significant contributions to advancing research, knowledge and clinical practice in our field.

Our Medallists will present plenary lectures at the Society for Endocrinology BES conference on 14–16 November 2022 in Harrogate.

DALE MEDAL

Professor Mark McCarthy
San Francisco, CA, USA

"I am honoured to be the recipient of the 2022 Dale Medal. Over the past three decades, my research has focused on using human genetics to decipher the processes that are driving common endocrine and metabolic diseases, such as diabetes and obesity. I am thrilled to have the opportunity to describe some of this work at the meeting in Harrogate later this year.

EUROPEAN MEDAL

Professor Geert Carmeliet
Leuven, Belgium

"I am very honoured and grateful to receive this Society Medal, I have always highly valued and enjoyed interactions with other researchers in the field of endocrinology, and especially in the domain of skeletal biology and related disorders.

INTERNATIONAL MEDAL

Professor Peter Croucher
Sydney, Australia

"It is a great honour and a wonderful surprise to be awarded the International Medal. Although an individual award, this really recognises the work of the many amazing colleagues and collaborators whom I've have had the pleasure and privilege of working with over many years.

JUBILEE MEDAL

Professor Adrian Clark
London, UK

"I am immensely honoured to receive the 2022 Jubilee Medal. The Society has been part of my life in endocrinology since my days as a clinical fellow, and has provided a rich and supportive environment in which to develop my research and interests in scholarly publishing.

NIKKI KIEFFER MEDAL

Dr Sofia Llahana
London, UK

"I am truly honoured and delighted to be the winner of the 2022 Nikki Kieffer Medal and would like to thank the Society for its continuous support to develop and raise the profile of endocrine nursing. It is the greatest of honours to be accepting this Medal, as Nikki was my mentor and dear friend and, without her pioneering work, endocrine nurses would not now be celebrating such great achievements.

SOCIETY MEDAL

Dr Giles Yeo
Cambridge, UK

"It is a great honour to be recognised by the Society for Endocrinology, an organisation I've been a part of for my entire career. I am forever grateful to my colleagues, past and present, without whom this would not have been possible.

STARLING MEDAL

Dr Cynthia Andoniadou
London, UK

"I am deeply honoured to receive this Medal, and extremely grateful to the Society for promoting scientific advances in endocrinology and supporting our community at every career stage. I am indebted to my team and collaborators for their stellar work and support over the years, which led to this recognition.

TRANSATLANTIC MEDAL

Professor Philipp E Scherer
Dallas, TX, USA

"Born and raised in Europe, but with most of my professional life spent in the USA, this award carries a very special meaning to me. The Transatlantic Medal reflects and stands for the close cultural and scientific ties that I, and many colleagues in my generation, have between the two continents.

Our Teaching Achievement and Outstanding Clinical Practitioner Awards recognise excellence in teaching and in delivering patient care.

TEACHING ACHIEVEMENT AWARD

Dr Punith Kempegowda
Birmingham, UK

"I am humbled by this Award and dedicate it to the eternally energetic group of medical students and junior doctors in the SIMBA and CoMICs team, who have helped us break several glass ceilings in teaching, learning, teamwork and leadership over the last couple of years. As a junior doctor in training, an international medical graduate and a person of a coloured background, I'm hoping this national recognition will encourage more early career physicians and researchers from diverse backgrounds to pursue their passion and achieve similar accolades.

OUTSTANDING CLINICAL PRACTITIONER AWARDS

Professor Karim Meeran
London, UK

"I'm both proud and delighted to have received such a high honour from the Society. The Society has been very supportive in so many ways, and I'm particularly grateful for its support in achieving a reduction in the price of hydrocortisone. I am proud to have been associated with the availability of 2.5mg and 5mg tablets, enabling patients to accurately dose themselves without having to cut tablets in half. These little things that the Society does for patients is one of the reasons that I am so happy to receive this Award.

Professor William Drake
London, UK

"At SfE BES 2022, I will be presenting some clinical material that 'goes somewhere': into a piece of research; into a collective departmental effort to provide high quality care for patients; or simply to illustrate a point of clinical philosophy. In doing so, I hope to be true to the spirit of this Award, which I am thrilled and honoured to receive.

Visit www.endocrinology.org/grants-and-awards for more information

Governance review **UPDATE**

As you may be aware, the Society instigated a full review of its governance processes and structure in 2020. Headed by Professor Karen Chapman, this member-led project surveyed the membership, as well as undertaking a number of interviews with those involved in the Society's governance.

Following the conclusion of the review in summer 2021, the findings, now known as 'The Chapman Report' were published and a consultation period was held. Council then met in September to debate and agree which recommendations should be taken forward at this time.

The main recommendations that are being implemented are as described below.

- It is vital that the Society represents all its different types of members, encouraging under-represented groups to get involved in its governance. Equality, diversity and inclusion (EDI) considerations are of great importance to the future of the Society, and a new member-led working group will be set up to consider the points raised and recommendations made in the governance review. We are currently recruiting a member of Council to chair this group, before an open call is made for volunteers from across the Society membership.
- To address the need for more inclusive election processes, to foster better member engagement and diversity with the governance at all levels, the Society will move from a nomination- to an application-based model, with member voting. The Society will increase the transparency around all the processes involved in governance, including clear job descriptions and desirable skills for each position. We are currently agreeing the timings for these elections and will publish the details in the next issue of *The Endocrinologist*.
- This transparency will also be extended to the processes for medals, prizes and grants.
- To raise the importance of education and training, and supporting future generations within the Society, members from across all the Committees will meet to review past results and set the strategy, looking forwards.

The complete Chapman Report is being finalised and is due to be shared with the full membership in early 2022.

Endocrine Specialist Networks **A YEAR OF PROGRESS**

A year ago (in *The Endocrinologist* issue 139), John Wass wrote an article introducing the concept of the Endocrine Specialist Networks (ESNs). He commented, "The purpose of these networks would be to ensure the provision of experience in some of these rarer forms of endocrinology, within each locality." Twelve months and at least one major COVID wave later, we thought it was a good time to provide colleagues with an update on progress in setting up the networks.

BONE AND CALCIUM ESN

In the bone and calcium ESN, we have advertised for membership, reviewed applications (which were rigorously scored against pre-agreed criteria) and announced the results of this initial application process. We are pleased to report that there were 11 applications in spring/summer 2021, of which nine were successful. Two meetings of the nine centres have been held so far and an initial work plan agreed.

Probably one of the most important goals at this stage is to raise awareness of these nine centres amongst colleagues in other hospitals, so that there will be a low and comfortable threshold for picking up the phone or emailing for advice. Hopefully, communication will be further improved as regional multidisciplinary teams are established, audits and research projects get underway, and other initiatives, such as training meetings, begin.

ANDROLOGY ESN

The andrology ESN was created to gather endocrinologists, urologists and reproductive medicine gynaecologists with an interest in male reproductive health. It brings together expertise from England, Scotland, Wales and Ireland, to provide referral hubs for 'tricky problems'.

For instance, gonadotrophins, such as human chorionic gonadotrophin, can restore sperm in the ejaculate of men with hypogonadotrophic hypogonadism. However, their prohibitive costs put them out of the reach of most hospitals. The andrology ESN is applying to NHS England to fund this important therapy centrally, so that men could receive treatment within its hubs. This will take time, but a national co-operative has a greater chance of winning than a lone, ivory tower.

Emerging therapies such as microdissection testicular sperm extraction (micro-TESE) offer the possibility of fatherhood for a minority of men with Klinefelter syndrome. However, few UK centres offer micro-TESE, and the potential reward of fatherhood needs to be weighed against the potential devastation of unsuccessful treatment. The andrology ESN will give all endocrinologists (and their patients) access to current advice and state-of-the-art treatments, regardless of their postcode.

GENDER HEALTHCARE ESN

The gender healthcare ESN has held its inaugural meeting. The aim of the group is to improve the sharing of knowledge and create a network of endocrinologists with an interest in gender medicine, to help support our colleagues in the field.

Given that gender medicine is an important endocrine topic, we have approached the Specialty Advisory Committee of the Royal College of Physicians to ensure that this area can be included in the core endocrine curriculum soon. We have also recognised that there is a significant expansion of gender healthcare medicine, with new gender clinics being set up throughout the UK which will need endocrine support. The gender healthcare ESN is also keen to improve the research base that underpins medicine in this area.

LOOKING FORWARD

An interesting, emerging theme is that all three ESNs are evolving with a degree of cross-disciplinarity. For example, the bone and calcium ESN has some rheumatology membership, while similarly in the andrology and gender healthcare ESNs there is involvement from urologists and other specialists. This seems like a positive development and one that bodes well for the future.

While there is clearly a long way to go in terms of getting the ESNs fully up to speed, maximising awareness of them and achieving delivery of improved care for patients with complex endocrine conditions, hopefully this is a reasonable start, and things will go from strength to strength.

JEREMY TURNER
NEIL GITTOES
CHANNA JAYASENA
LEIGHTON SEAL
JOHN WASS

KEITH EDWIN KIRKHAM OBE


History of Modern Biomedicine Research Group

Keith Kirkham was born in 1929 in Lytham St Annes, the first child of Thomas and Clara Kirkham, who were bakers and confectioners. He attended Kirkham Grammar School, representing the school at both cricket and rugby, and was Head Boy in his final year.

He supported Preston North End and did not consider any other footballer fit to lace Tom Finney's boots. However, having followed Willie Shankly's career journey from Preston to Liverpool, he transferred his allegiance to Liverpool FC.

In 1949, he went to study Zoology at Birmingham University. It was here he met his future wife Mollie, whom he married in 1953. He left Birmingham to study at Fitzwilliam College, University of Cambridge, initially for a Diploma in Agricultural Sciences.

After completing his National Service in Oswestry. He returned to Cambridge for his PhD, on 'The gonadotrophic potency of avian pituitary glands', which he completed in 1958.

In 1960, he took a research position at the MRC's Clinical Endocrinology Research Unit in Edinburgh. His extensive research into thyroid hormones included early investigations into long-acting thyroid stimulator (LATS), and the evaluation of radioimmunoassay methodology. He made numerous contributions to the literature.

It was during his time in Edinburgh that he served as Secretary of the Society for Endocrinology.

Keith enjoyed many activities outside work while living near Edinburgh, including singing in the church choir with Mollie, and landscaping and designing the family garden from scratch. He took up fishing as a new hobby, encouraged by his work colleagues Raymond Bain and Jimmy Lowe, who often accompanied him to the many fishing reservoirs on the outskirts of Edinburgh and to St Mary's Loch in the Borders. He was also elected as an Independent District Councillor for Balerno, where he lived, and served the community with great humour and diligence.

After the closure of the Clinical Endocrinology Research Unit in Edinburgh in 1973, Keith became Assistant Director of the Clinical Research Centre that had recently opened on the Northwick Park Hospital campus in Harrow. He was awarded an OBE in the Queen's Birthday Honours in 1987.

As he approached retirement, the MRC asked him instead to stay on and oversee the Clinical Research Centre's closure at the end of 1994. He was therefore the Centre's last Director. It was to his great credit that every researcher and member of staff was found an alternative position prior to its closure.

His life was full of activities after retirement. Many visitors were welcomed at the family home. There were frequent holidays both in the UK and abroad, and many trips to the Theatre Royal in Windsor, to Twickenham and other venues for rugby matches, and to the family boat on the River Thames for holidays and weekends. In particular, he derived great pleasure from time spent with his family.

'His extensive research into thyroid hormones included early investigations into long-acting thyroid stimulator (LATS), and the evaluation of radioimmunoassay methodology.'

He was appointed as a Governor of Harrow College of Further Education, now the University of Westminster. He took his duties very seriously and served for many years. He received an Honorary Doctorate in 1999 in recognition of his efforts.

Keith celebrated 60 years of marriage to Mollie in 2013. The care he provided and the love he showed for her as her vascular dementia evolved was inspiring. She sadly died in 2019, and he missed her dreadfully after having being married for nearly 66 years.

Keith was immensely proud that his last public outing was to his grandson Harry's Commissioning Parade at Sandhurst in November 2019. Since then, his chronic renal failure deteriorated, and he required almost daily peritoneal dialysis. He was also discovered to have clear cell renal carcinoma. As his health failed, he was cared for magnificently at home by Margaret, a retired District Nurse who had initially been a visiting carer for Mollie. He died peacefully at home, leaving two sons, Jonathan and Christopher, two daughters-in-law Susie and Liz, and four grandchildren James, Sarah, Harry and Molly.

He had a long and very happy marriage, and a great life, well-lived. He was a shining example to all, as was confirmed by the many humbling messages received from family, friends and eminent colleagues. He was a remarkable man from humble beginnings, whose intelligence, humour, hard work and ambition enabled him to lead the life he wanted, and whose example and support encouraged all.

JONATHAN KIRKHAM