TWENTY-FIVE YEARS AGO: THEN AND NOW

Progestogens: the good, the bad and the ugly

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Background

Whereas progesterone was originally recognised for its role in protecting gestation early in the first trimester, its applications have been largely for non-obstetric indications. As the use of ethinylestradiol was not limited by patents and the subsequent development of oestrogen-related compounds therefore not commercially interesting, hormonal contraceptive research focused on progesterone-related compounds that led to the arbitrary 28-day cycle of '21 days on, 7 days off' for oral contraception. Apparently, Gregory Pincus 'decided women would prefer it that way'¹ as withdrawal bleeding mimics menses and does not alter the overt features of a normal menstrual cycle. With major first-pass hepatic metabolism of oral progesterone leading to its poor bioavailability, the search for synthetic progestogens initially emphasised molecules that are active when taken orally: early interest focused on estranes, such as norethisterone, whereas subsequent emphasis switched to gonanes such as levonorgestrel, desogestrel and gestodene.

The early scenario

Injectable depot-medroxyprogesterone acetate (DMPA) was initially recognised as a valuable female-controlled method but, regrettably, partly due to its association with breast tumours in beagle dogs, this method later faced much opposition which resulted in a 'Ban the Jab' campaign. This misinformation of the public, through sensational reporting in the lay media, led the *British Journal of Family Planning* to publish 'reasoned statements' for readers to be well informed by watching 'the emergence of a solid and reliable body of data'.² A progesterone-releasing intrauterine contraceptive device was found to improve menorrhagia and dysmenorrhoea. Its association with an apparent increased risk of ectopic pregnancy was unfortunate, especially as comparative studies using life-table analyses were bereft of strong epidemiological evidence to exclude causality, despite the lack of biological plausibility.³ Progestogen-only pills (POPs) had the major disadvantage of poor cycle control with irregular bleeding. Overall, progestogens were not showing promise for contraception.

Conversely, progestogens were being used for various other reasons, examples being the treatment of menorrhagia, endometriosis and premenstrual syndrome besides the postponement of menstruation for events such as school examinations and holidays. By inhibiting ovulation, which also provided contraceptive cover, the 19-norsteroid lynestrenol was especially effective in suppressing menstruation. It was found to be useful for 'mentally handicapped women', especially those with cerebral palsy or multiple handicaps, who are unable to deal with their menstruation.⁴ With 'powerful steroids' in oral contraceptives, some practitioners favoured extensive screening and investigations before prescribing for adolescents. However, arbitrary restriction of fertility control provision was criticised at an international symposium by a 'fiery red-headed' female Canadian professor who made 'women's lib comments' arguing the case that reproductive health services should be more easily

available.⁵ The value of progestogens for postcoital contraception was still not widely appreciated despite numerous presentations⁵ by Albert Yuzpe. A handbook, which was widely distributed by all health authorities, instead recommended 'ethinylestradiol, 5 milligrams in divided doses, taken for 5 days started within 72 hours'.⁶ The diabetogenic effect of combined oral contraceptives (COCs) was linked to the structural characteristics of progestogens: estrane and gonane progestogens were associated with insulin resistance whereas pregnane progestogens increased serum triglyceride. It was suggested that adverse metabolic effects of oral contraceptives could be reduced by modifications 'with respect to the type and concentration of the progestogen component'.⁷

The quest for designer progestogens

The search for better progestogens has been at the vanguard of hormonal contraceptive development. Whilst aiming for a panacea, we should recognise that only a placebo can be inert and any active drug may have side effects. Over the last 25 years, a cornucopia of novel progestogens has been used in diverse formulations for contraception. The 19-nortestosterone derivatives have a higher progestogenic-to-androgenic selectivity, desogestrel and gestodene exemplifying chemical characteristics and metabolic profiles that looked promising for major improvements in the active ingredients of COCs. As a pregnane with substantial anti-androgenic properties, cyproterone acetate is valuable in dermatology practice for treating androgen-related conditions such as acne, hirsutism and seborrhoea. Drospirenone, a derivative of 17 α -spironolactone, is an androstane with anti-androgenic properties. Its antimineralocorticoid properties were perceived as being useful for avoiding fluid retention.

Clinical expectations of oral contraceptives containing desogestrel, gestodene and cyproterone acetate were overshadowed by the controversy over an association with an apparent small risk of venous thromboembolism. Recent postmarketing surveillance studies have shown no significant differences between COCs with levonorgestrel, drospirenone and other formulations as far as cardiovascular events such as venous thromboembolism, myocardial infarction and stroke.^{8,9}

Meanwhile, there is a resurgence of interest in POPs, with a formulation of desogestrel which suppresses ovulation being licensed with a 12-hour 'missed pill' rule.¹⁰ Nestorone, a 19-norprogesterone derivative, is a very potent progestogen which is inactive orally. Its administration, through sustained-release delivery systems, seems promising for various applications including postpartum contraception as its excretion in breast milk does not lead to its transfer into the neonatal circulation.

Beyond daily pills and 3-monthly injections

Recent contraceptive methods rely largely upon innovative formulations of progestogens and associated delivery systems. Combined oestrogen and progestogen preparations can now also be administered through the 3-week vaginal ring and weekly transdermal patch, both

methods avoiding first-pass hepatic metabolism. The value and safety of 3-monthly intramuscular DMPA have been ascertained¹¹ and an injectable monthly contraceptive with combined oestrogen and progestogen is also available. Recently, a male long-acting delivery system consisting of intramuscular DMPA and testosterone implant has been found to have a high contraceptive efficacy, which is even superior to the male condom.¹² Besides providing excellent contraception, the levonorgestrel-releasing intrauterine system is licensed for treating menorrhagia and has great potential for hormone replacement therapy. Progestogen-releasing subdermal implants have a very high use-effectiveness, whereas a single dose of levonorgestrel given within 5 days of unprotected intercourse constitutes a recognised regimen for emergency contraception.

COCs continue to be used off-label for modifying the length of the menstrual cycle including continuous use of more than one cycle of 21 pills: bicycling for two cycles and tricycling for three cycles. The latest regimen consists of an annual pattern with four seasonal withdrawal bleeds through 91-day cycles: four continuous packs, each of 21 pills of COCs, for 84 days are followed by an interval of seven pill-free days.

Implications for current practice

Newer products should be given a chance to prove themselves, as any risk of belying expectations from their biochemical and pharmacological profiles can be identified through clinical trials and postmarketing surveillance. Individuals seem to be more interested in the positive aspects of health and the avoidance of side effects, such as acne, bloating and perceived weight gain, as compared to concerns regarding an apparent small increase of mortality risk from thromboembolism and cancer. Therefore, it seems reasonable to seek products that address morbidity issues pertaining to contraceptive methods.^{13,14} Hormonal replacement therapy for the prevention of postmenopausal coronary heart disease was popular until recently when it was associated with the opposite effect: the metabolic effects of the progestogen component being incriminated, there is current interest in regimens using newer progestogens administered through alternative delivery systems.

Whereas the ramifications of new products and procedures are not always clear, clinicians have a duty to apply sound research findings in their professional practice even in defiance of official guidelines, promulgations from drug regulatory authorities and product labelling from manufacturers. In selecting products for primary care and

public health programmes, cost considerations should permeate a culture of maximising benefits at the community level whilst recognising the need for certain products to be available beyond the primary care level for medical conditions, such as menorrhagia, that interface with contraception.

The search for new compounds and subsequent development of related formulations are expected to enable individuals to exert the right to choose the most appropriate product to meet their needs. With advances in molecular biology, progestogens have recently been defined in terms of their affinity for binding with progesterone receptors. Applications of selective progesterone receptor modulators could drastically alter the future use of contraceptive products containing progestogens whose original recognised role in protecting gestation has resurfaced lately, albeit beyond the first trimester, for the prevention of preterm labour.¹⁵

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BOOK REVIEW

Exploring Human Sexuality. Making Healthy Decisions (2nd edn). R McNulty, M Burnett. Boston, MA: Pearson Education, 2004. ISBN: 0 205 38059 X. Price: £36.99. Pages: 136 (hardback)

The two authors have an extensive background in clinical psychology. The book speaks to an American audience and the authors state in the preface that they aim to 'arm students with information that will help them to make healthy decisions about their sexuality'. They do not define their target student population. However, the book covers a breadth of information for qualified professionals coming from all medical, nursing and paramedical backgrounds and indeed would interest the student and layperson.

The text is wide ranging and is divided into five key sections covering the following topics:

introduction to sexuality and sexual health, the biological basis of sexuality, the social context of sexuality, reproduction and sexual development, and issues and challenges in sexuality.

Each key section comprises several chapters and each chapter begins with a provocative quotation from individuals offering a perspective on sexuality or from a popular sexuality text such as 'Mars and Venus in the bedroom'. The text is readable and thought provoking but is disjointed by various directions to the reader. Featured subsections in each chapter are 'Did you know?', 'Looking at, thinking about', 'Close up on culture' and 'Health matters'. The text is also peppered with a range of definitions despite an extensive glossary and directs the reader to websites for further exploration of a topic. These textual interruptions give a discontinuity to the text, which may irritate some readers.

The sections on the physiological and biological issues of reproductive health, contraception, sexually transmitted infections, pregnancy and abortion are accurate and offer a comprehensive, up-to-date, broad ranging

review for specialist and primary health care providers.

The strength of the book is in its holistic approach to relationships, psychosexual problems, sexuality, gender and cultural issues. It challenges the readers to review their own attitudes and experience and offers excellent insight into the human and sexual being. Issues affecting lesbian, gay, bisexual, transgender and ethnic minority groups resonate from the text although there is less that is pertinent to those with learning and physical disability.

This is not an experts' book but it contains a great deal of useful information absent from the conventional gynaecology and reproductive health care texts and challenges professionals from a variety of disciplines to explore the human aspects of sexuality. This would be a good reference book for a general practice or sexual health service library.

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