“Understanding combined oral contraception”

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“Through out the history of medicine, thousands of drugs have been developed, but only one has been influential enough to earn the title of simply, the pill[1]”

Practical tips and lessons for clinical practice:

The development of the pill is the single most significant scientific advance of the 20th century

Clinicians prescribing the pill should be familiar with the UK medical eligibility criteria (UKMEC 2009, FSRH)

The combined oral contraceptive contains oestrogen and progestin

Most pills contain ethinyl oestradiol

Progestins are classified as 1st, 2nd, 3rd and 4th generation

Variation in the chemical structure of progestins defines their effect on the various hormone receptors

Jane presents to her GP with a request to "go on the pill".

She is 28 years old and has never been pregnant.

She is overweight – her current BMI is 29.

She has infrequent, but increasingly heavy periods. She and her long-term partner recently split up, and she has lost 4 stones in weight. This has coincided with more regular periods.

She has noticed that she has had to pluck her upper lip more frequently over the past few years.

She has met someone that she really likes and does not want to become pregnant at the moment. She does not want a long acting reversible contraceptive method.

She is not keen to use a progestogen only pill as she had problems with unscheduled bleeding when she used this in the past.

Is Jane eligible to use the combined pill?
The UKMEC 2009, is an assessment tool designed to facilitate safe prescribing of contraception[2].
Following an assessment using the UKMEC, Jane is found to have no contraindications to the use of combined hormonal contraception.

So, which combined pill would be most suitable for her?

A discussion follows regarding the potential benefits of the different sex steroid hormones included in the available combined oral contraceptives in the UK in 2014.

A scenario such as this is not uncommon. Understanding the chemical structure of exogenous sex steroid hormones in the combined oral contraceptive is essential, as this may provide some indication of the combination with the greatest potential benefit for the patient.

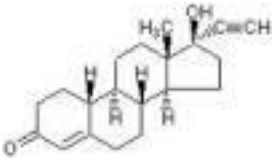
<u>Back to basics – what influences a clinical decision?</u>
All combined oral contraceptives contain an oestrogen and a progestin. Both naturally occurring progesterone and synthetically produced progestins come under the "progestogen umbrella" – hormones with a pro-gestational activity.
All sex steroid hormones are derived from cholesterol and both oestrogens and progestogens share a structural similarity.

Oestrogens are characterised by a C18 carbon skeleton.
Currently available pills contain one of the following oestrogens:
Ethinyl oestradiol
Oestradiol valerate
Oestradiol

Most “pills” contain ethinyl oestradiol, but more recently two preparations containing “natural” oestrogens have become available. These “natural” oestrogens are bio-identical to the naturally occurring hormone. Consequently they have less of a metabolic impact and theoretically a reduced thromboembolic risk associated with their use.

Progestogens are characterised by a C21 carbon skeleton.
It is accepted practice globally to describe progestins according to “generation”. This terminology reflects their biochemical characteristics. However, this should be regarded as a guideline as not all progestins fit neatly into this classification. The information below attempts to explain the classification of the different progestins in current use.
It is important to remember that all sex steroid hormones share a basic “chicken wire” structure, with side chain variations resulting in individual characteristics. It is possible for the different progestins to “morph” between structural forms, hence sharing specific features of the different sex steroids. This includes androgens, oestrogens, progestogens and also mineralocorticoid and glucocorticoids.

First generation progestins:
Norethisterone is a first generation progestin, still used frequently today for contraception and to manage gynaecological problems.



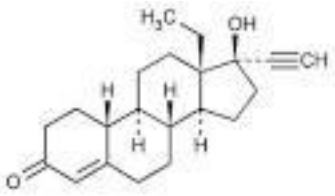
Norethisterone

Naturally occurring progesterone interacts with the progesterone receptor in a “key in a lock” fashion . Synthetic progestins interact in a “less perfect fit” fashion. They also interact with other hormone receptors, either blocking or stimulating these receptors.
These include all other steroid receptors, namely oestrogen, androgen, mineralocorticoid and glucocorticoid.

Norethisterone stimulates the oestrogen receptor, giving it some degree of oestrogenic effect. Consequently, Norethisterone should not be the first choice progestin for women with risk factors for oestrogen therapy. Taking Norethisterone, in a dose of 5 mg three times daily, is commonly prescribed to delay menstruation in women going on holiday. This might increase the risk of venous thromboembolism(VTE)[3].

Second generation progestins:

Norgestrel was developed as a more potent progestin; it is 20 to 30 times more potent, weight for weight, than Norethisterone. Hence, lower doses can be used, to achieve the desired effect, thus minimising potential side effects.
Initially a mixture of *d* and *l* isomers were used. However, as only the *levo* form is orally active, using this alone enabled the amount of hormone required to be reduced by 50%, potentially further reducing side effects.



Levonorgestrel

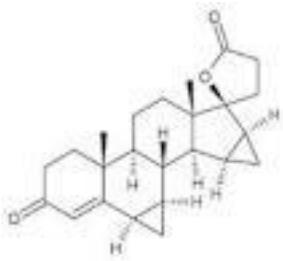
Third generation progestins:

These include, Desogestrel, Gestodene and Norgestimate.
These progestins have minimal androgenic activity, with a more favourable effect on lipid profile and are twice as potent as Levonorgestrel. They provide high efficacy with less side effects, but have been tainted by the VTE controversy of 1995[4].

Fourth generation progestins:

This group are in a class of their own, being derived from 17 alpha spironolactone and sharing a diuretic effect with spironolactone. This helps to reduce the fluid retaining effect of oestrogen when used in a combined oral

contraceptive . The pharmacological action of drospirenone is similar to progesterone and there is no androgenic activity associated with this synthetic hormone. Drospirenone blocks the androgen receptor – ie. it is anti androgenic and in addition it has anti-mineralcorticoid effects as described above. This reduces the risk of common side effects associated with fluid retention, namely breast tenderness, headaches and weight gain. Its anti-androgenic properties reduce sebaceous secretions, which can improve acne.



Drospirenone

Cyproterone Acetate (CPA):

This synthetic steroid hormone stimulates the progesterone receptor and also blocks the androgen receptor. CPA is the most potent anti-androgenic progestin available. In the UK, a combination of 35 micrograms of ethinyl oestradiol and 2 mg of cyproterone acetate is licensed as a treatment for acne, but not as a method of contraception. However, this combination is an effective contraceptive. Despite this, some clinicians allegedly are prescribing this preparation in combination with a traditional COC, which significantly increases the dose of oestrogen and hence the risk of VTE, and should not be done.
Women with Polycystic ovarian syndrome (PCOS) have symptoms associated with excess androgenic activity. Therefore, cyproterone acetate has potential therapeutic benefits. However, as many of these women are overweight use of a combined oral contraceptive could be associated with a higher risk of VTE.

Rather than focusing on a differential risk of VTE with different generation progestins, clinicians should focus their attention on the individual woman's risk factors for VTE –think dangerous women rather than dangerous pills!

Table 1. Biologic activity of progesterone and progestins used in combined oral contraceptives

	Progestogenic	Oestrogenic	Androgenic	Glucocorticoid
Progesterone	+	-	-	-
Levonorgestrel	++	-	+	(+)
Desogestrel	+	-	+	+
Norgestimate	++	-	+	-
Gestodene	++	-	+	-
Drospirenone	+	-	-	-
Dienogest	+++	-	-	-
Norethisterone	+++	+	+	-
Cyproterone acetate	+	-	-	+++

	Antigonadotrophic	Antioestrogenic	Antiandrogenic	Antimineralcorticoid
Progesterone	+	+	+	+
Levonorgestrel	+	+	-	-
Desogestrel	+	+	-	-
Norgestimate	+	+	-	-
Gestodene	+	+	-	(+)

Drospirenone	+	+	+	++
Dienogest	+	(+)	+	-
Norethisterone	+	+	-	-
Cyproterone acetate	+	+	+++	-

Which pill would you prescribe for Jane to provide additional non-contraceptive benefits?

These might include:

- A reduction in bleeding – both intensity and duration of bleeding.
    - All COCs result in an average reduction in bleeding of approximately 40 %.
    - Qlaira®, which contains oestradiol valerate and dienogest, in a variable dosing regimen, has a license to treat heavy menstrual bleeding in women who require contraception and results in an 88% reduction in median menstrual blood loss[5].
- A reduction in the symptoms of excess androgens eg facial hair and spots. This will depend upon the generation of progestin prescribed.

There are other potential benefits associated with taking the combined oral contraceptive pill.
These include a reduction in gynaecological cancers (ovary and endometrium), reduction in the risk of bowel cancer, control of the symptoms of both endometriosis and pre-menstrual syndrome.

Based on the information given above, the logical choice of progestin is the one with the greatest ability to block the androgen receptor.

As all COCs reduce bleeding significantly, the combination of ethinyl oestradiol and cyproterone acetate offers the best solution to Jane's symptoms.

This case discussion illustrates how an understanding of steroid biochemistry facilitates logical and informed prescribing.

1. Liao PV, Dollin J. Can Fam Physician. 2012;58:757-60
2. UKMEC 2009, Faculty of Sexual and Reproductive Healthcare website
3. Mansour, D. Safer prescribing of therapeutic norethisterone for women at risk of venous thromboembolism. *J Fam Plann Reprod Health Care.* 2012:38:148-9.
4. Committee on Safety of Medicines. Combined oral contraceptives and thromboembolism. London: CSM 1995
5. Fraser IS, Parke S, Mellinger U, Machlitt A, Serrani M, Jensen J. Effective treatment of heavy and/or prolonged menstrual bleeding without organic cause: pooled analysis of two multinational, randomised, double-blind, placebo-controlled trials of oestradiol valerate and dienogest. *Eur J Contracept Reprod Health Care.* 2011;16:258-269.