QUALITY USE OF MEDICINES: THE YOUNG 'PILL' USER WITH POOR CYCLE CONTROL

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This review – the last in the present "Quality Use of Medicine" series - will again seek to demonstrate the applicability of the P-drug process in making a rational medicines choice in a typical family practice case. The patient in this instance is a woman in her early twenties, seeking contraceptive advice. Although she has been using a combined oral contraceptive (for argument's sake, Mercilon®) for six months, she now indicates that she "would like to try something new". She mentions that she has read that monthly bleeding can be avoided by extending the traditional 21-day pill-taking interval and would like to know more about this. A friend has recommended a new pill called "Yasmin", because she has heard it can help a woman lose weight. After careful probing she reveals that the actual reason for her visit is that she has experienced frequent breakthrough bleeding, which she describes as making her feel as though she is "bleeding more often than not". This has led to dissatisfaction with her contraceptive and her search for a method which will help her escape the nuisance of poor cycle control. First, though, a quick aside – strictly speaking what she is swallowing is a tablet (made by compressing granules), not a pill (rolled and then cut), but the literature on the "Pill" generally refers to "pill-taking", so that convention will be retained.
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Therapeutic objective - efficacy

The therapeutic objective is to safely prevent an unintended pregnancy. Only female sterilization has a lower failure rate than the combined pill, provided this is under conditions of "perfect use". When typical use is measured rather than ideal or perfect use, however, the efficacy of the Pill (and any method requiring consistent use) falls, especially during the first year. Failure rates for the combined pill during the first year of use have been reported to rise from 0.1% under ideal conditions to 7.5% under typical use.[1]

This decrease in efficacy has been attributed to inconsistent pill taking. In a nationwide US survey of 943 women, who completed questionnaires two months after initiating or resuming oral contraceptive use, 47% of users reported having missed one or more pills per cycle, and 22% missed two or more.[2] In this study, women reporting breakthrough bleeding were 1.6-1.7 times as likely to miss two or more pills per cycle as those not reporting these side effects. The authors recommended that providers take the opportunity of follow-up contact resulting from poor cycle control to evaluate consistency of pill taking, since this may indicate heightened chances of adherence difficulties. Other patient characteristics that were found to affect consistency of use were lack of an established pill-taking routine and failure to read and understand the written information accompanying the Pill.

Counselling

The first intervention needed for the patient in question is therefore an assessment of adherence: if she is missing pills regularly she can be counselled that this practice both increases the risk of contraceptive failure and compromises cycle control, and may be the cause of her irregular bleeding problems. She can be helped to establish a regular pill-taking routine, e.g. by suggesting she link pill taking to an already established habit such as brushing her teeth or a morning cup of tea. She should be urged to carefully read the literature accompanying the pill package and her understanding of this material should be checked. In particular, attention should be paid to the patient's understanding of the risk of extending the pill-free interval. The patient should know what to do if pills are missed, including using a backup method when indicated. The suggested strategy is shown in Box 1 – this can also be used as an *aide memoire.*[3] If these strategies do not improve pill taking the patient could be advised to consider a method that relies less on user memory, such as an intrauterine device or one of the progesterone only methods, but only where routes other than the oral are used. These include the depot injections (medroxyprogesterone or norethisterone) and levonorgestrel-releasing intrauterine systems.

Extended contraceptive regimens - suitability

However, the key problem appears to

cycle control, not adherence *per se*. Another option might therefore be to consider an extended oral contraceptive regimen. For any monophasic pill, the standard 21 days of active pill taking may be extended to six weeks by skipping the hormone-free weeklong break. A common extended regimen is the trimonthly approach, where women take active pills for 84 days or 4 pill packs followed by a hormone-free week. A 91-pill pack in this form has recently been approved by the US Food and Drug Administration and will be launched soon in that market, even though questions have been raised about long-term effects.[4] Women may also continuously use active pills with no hormone-free break, or the length of the break may be shortened, commonly to 6 days. Decreasing the frequency and length of pill-free intervals in a patient who regularly misses pills should offer greater protection against pregnancy as hormone levels remain consistent for longer, decreasing the likelihood of ovulation.[5] All of these options are associated however with irregular bleeding.

Contraceptive failure may also be caused by the discontinuation of a method and failure to replace this with an alternative, or by changing the combined pill for a less effective or less consistently followed method. Irregular bleeding is an adverse event commonly associated with oral contraceptive use, especially during the first 2-3 cycles. Poor cycle control is the side effect most associated with increased discontinuation rates. Women who discontinue contraceptive use due to such 'nuisance side effects' usually do so without informing their clinician and often without use of a backup method.[6] The large US survey previously mentioned also found that where patients were counselled to anticipate bleeding irregularities, the importance of these were lessened and pill acceptability improved.[2] Therefore, if the patient is experiencing problems with cycle control despite good adherence, and she is finding this adverse effect intolerable, then a new method which offers better cycle control needs to be sought. However, Guillebaud cautions that important alternative causes of bleeding must first be excluded, such as cervical pathology.[3]

The extended regimen oral contraceptive methods or non-oral progesterone-only methods might be an option as they decrease the volume and duration of withdrawal bleeds overall, but the bleeding pattern is irregular and unexpected. This effect lessens over time and the bleeding pattern may change to one of amenorrhoea.[5] This pattern will need to be discussed with the patient to determine whether intermenstrual bleeding is acceptable to her. If not a pill with a different oestrogen/progestogen mix, which provides better cycle control needs to be considered.

Different combined oral contraceptives – efficacy and safety

The patient in question has been taking a pill containing a very low oestrogen dose (20 μg). A potential disadvantage of lowering the oestrogen dose is loss of menstrual cycle control.[7] Due to the risk of discontinuation of the oral contraceptive if breakthrough bleeding occurs, an Australian review recommends that preparations providing good cycle control are preferred when initiating contraceptive use in young women.[8] A better option might have been a pill containing 30μg of ethinyloestradiol – e.g. Marvelon® 30μg oestrogen together with same type and strength of progestogen as Mercilon®, the pill the patient has been using).

The pill currently being used contains a newer "third-generation" progestogen, desogestrel. As a switch is being considered it would also be a good time to check whether the patient has been informed that pills containing this progestogen (and also other third generation progestogens such as gestodene and norgestimate) carry an additional risk of causing thromboembolic disease, compared with older progestogens. Care must be taken to keep this information in perspective. A statement issued about this risk in 1995, by the Committee on Safety of Medicines (CSM) in the UK, provoked a panic reaction that resulted in an increase in the abortion rate. This could be directly attributed to patients abandoning their third generation progesterone-containing methods, without starting a reliable alternative. A press release from the UK Department of Health compared the risk to that occurring in pregnancy.[9] About 60 cases of venous thromboembolism (VTE) occur per 100 000 pregnancies. The spontaneous incidence in healthy non-pregnant women is about 5 cases per 100 000 women per year. The incidence in users of older progestogen-containing pills is about 15 cases per 100 000 women per year of use. The incidence in users of third generation pills is somewhat higher, at about 25 cases per 100 000 women per year of use, but still lower than that seen in pregnancy. The risk of VTE increases with age and is likely to increase with other known risk factors, such as obesity. The press release advises that women must be fully informed of these very small risks and provided they find this acceptable, may, together with their doctors, choose to use this method, depending on their medical history.

Thus, if the patient is comfortable with this small extra risk, the desogestrel component may be continued, or changed to gestodene. Although large-scale comparative trials are needed to confirm this finding, evidence suggests that cycle control with gestodene is better than for monophasic preparations containing desogestrel, norgestimate or levonorgestrel,[10] as well as for levonorgestrel-or norethisterone-containing triphasics. Combinations of gestodene and 30μg oestrogen could be considered, such as Femodene® or Minulette®. Lower oestrogen dose/gestodene preparations are best kept for after cycle-control is achieved, when a patient is better able to cope. If the lower risk second generation progestogens are preferred, one of the levonorgestrel- or norethisterone-based triphasic pills could be considered, such as Triphasil®,Trinovum® or Logynon®), as these tend to give a better bleeding pattern for a given (low) dose of hormones.

The cost implications of the various options outlined are shown in Table 1, based on retail prices to the client, with VAT.

Table 1: Costs of contraceptive options

Options for the inconsistent pill taker (if counselling fails)	Cost per unit	Cost per year of use
Extended regimen: 6 week e.g. Mercilon® (for other pill options, cost per year = cost per unit x 15)	R98.31	R1474.65
Extended regimen trimonthly: e.g. Mercilon® (for other pill options, cost per year = cost per unit x 16)	R98.31	R1572.96
Depot Provera® injection	R40.31	R161.40
Nur-Isterate® injection	R83.73	R502.38
Mirena® intrauterine device (if used for 5 years; cost per year increases if use is stopped sooner)	R2181.90	R436.38
Options for the consistent pill taker		
Mercilon®	R98.31	R1179.72
Marvelon®	R85.69	R1028.28
Femodene®	R90.24	R1082.88
Minulette® (lower dose options, such as Melodene®, Minesse® and Mirelle® can be considered after cycle control is achieved. All are more than 10% more expensive than Femodene® or Minulette®)	R90.03	R1080.36
Logynon®	R77.41	R928.92
Triphasil®	R70.38	R844.56
Trinovum®	R75.46	R905.52

Patient autonomy – choosing the "new"

The importance of patient autonomy is stressed repeatedly in contraception literature. The South African policy framework for the provision and use of contraception states that "the need for service providers to be sensitive and responsive to clients' needs, and to respect the right of each client to make an informed choice of contraceptive method" is "central to the concept of high-quality care".[11] A clinical practice guideline relating to informed choice is provided: "all women, men and young people should be provided with the contraceptive method that they request, subject to meeting the relevant medical eligibility criteria and without the influence of service provider biases". The WHO has developed a classification system of contra-indications or "medical eligibility criteria" in order to standardise contraceptive provision and to remove unnecessary restrictions on the use of various methods. This user–friendly system can be accessed at http://jhuccp.org/pr/j44/j44who.shtml.

Returning to the case in question - reducing bleeds may well be only one of a number of considerations that will be weighed by the patient in making her contraceptive choice. A second consideration is also apparent from the patient's interest in her friend's choice of pill: the issue of weight loss. The prescriber can support the patient's decision-making strategy by "providing accurate and impartial information, offering practical solutions to practical difficulties and providing access to a full range of methods".[12] However, here she might be at risk of being influenced by advertising, which promotes the "new" as the "best".

A Cochrane Review of the effects of combination contraceptives on weight was updated in January 2003.[13] No association between combination contraceptives and weight gain could be found, based on three available placebo-controlled randomized trials. Most comparisons of different combination contraceptives showed no substantial difference in weight or discontinuation due to weight gain (where discontinuation was studied). The authors conclude that, while the available evidence is insufficient to determine the effect of combination contraceptives on weight, no large effect is evident.

Yasmin®, the friend's recommendation, has been available in South Africa since early 2003. It is a combined oral contraceptive containing 30µg ethinyloestradiol and drospirenone, which is derived from spironolactone and has pharmacological properties similar to progesterone. It has similar contraceptive efficacy and cycle control to the other combined pills.[14,15] Concerns have

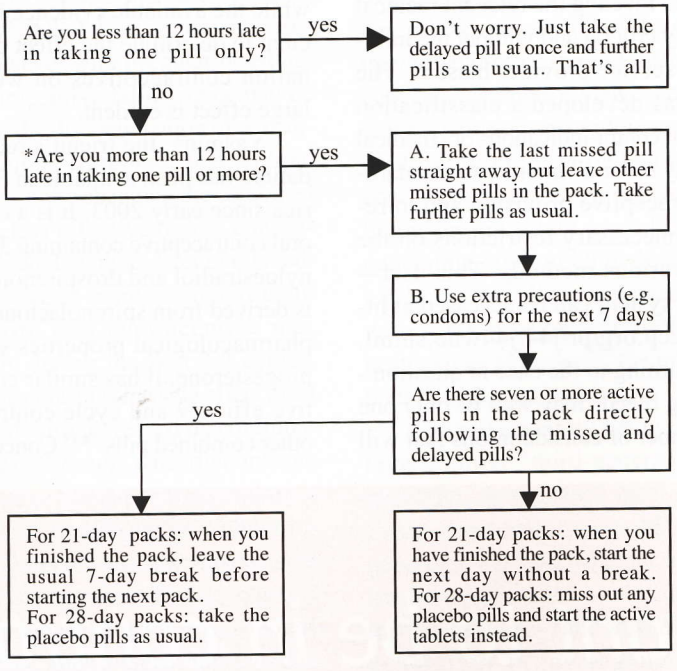
been raised over the safety profile of this drug as there is a lack of epidemiological data on the risk of thrombosis and further studies are needed to establish whether it is as safe as other contraceptive pills. The Netherlands Pharmacovigilance Centre has received 5 reports of thromboembolism as a suspected adverse drug reaction to Yasmin®, and Dutch general practitioners have been advised by their College not to prescribe the product.[16,17] The Yasmin® website refers to it as "The contraceptive pill with a package of reasons to feel good". The "lifestyle" advantages claimed include a lack of influence on weight gain, beneficial effects on the skin, positive effects on premenstrual symptoms and feelings of well-being.[18] As has been stated, there is a lack of evidence that the pill has much effect on weight. In two studies comparing Yasmin® with a desogestrel-containing contraceptive (Marvelon®), more weight loss was reported with Yasmin®, one study reported a significant difference but no actual figures were presented,[14] and the other reported an average weight difference of 0.27kg.[15] In both studies women measured their own weight and knew which preparation they were taking so bias cannot be excluded. A third study comparing drospirenone and doses of ethinyloestradiol ranging from 15-30 µg with a levonorgestrel-containing pill containing ethinyloestradiol 30µg(Microgynon30®) also showed a significant but small weight difference – a loss of 0.78kg versus a gain of 0.68kg.[19] This study was also open-label and consisted of only 80 participants who weighed themselves. As a clinically important effect on weight has not been demonstrated and, given the conclusions of the Cochrane Review that there is insufficient evidence to link weight gain to combination contraceptives, the patient should be informed of the lack of evidence to support her friend's claims for Yasmin®.

It might be worth warning the patient that competition in the oral contraceptive market is causing manufacturers to make claims of additional benefits for their products and to market these.[20] Even the perception of weight gain can deter the initiation of combined contraception or can lead to contraceptive discontinuation, as was seen in a US study where women who discontinued oral contraceptive use were more likely to report weight gain than those who continued the method despite a lack of statistically significant difference in weight gain between the two groups.[21] Thus the concern about weight gain limits the use of a highly effective method of contraception. Unfounded myths of an association between weight gain and hormonal contraceptive methods should be dispelled.

Box 1

Guillebaud's 7-day rule and advice for missed pills

1. Seven consecutive pills are enough to 'put the ovaries to sleep'. The remaining pills are taken to keep them in a dormant state.
2. Seven pills can be omitted without ovulation, which is done when there is a pill-free week.
3. More than seven pills missed in total risks ovulation.



*NB If two or more pills are missed and if they were all from the first seven active tablets after the pill-free or placebo tablet interval and if you have had unprotected intercourse since the end of your last pack, you need emergency contraception (e.g. two tablets of Norlevo® (Levonorgestrel 0.75mg) - one to be taken immediately and one after twelve hours), then you should return immediately to taking your pill, and use a condom for the next 7 days as an extra precaution.

Reference: Guillebaud J: Contraception: your questions answered. 3rd Edition. London: Churchill Livingstone Press; 2000.

Conclusion

The final choice of contraceptive in this case therefore depends on a complex interplay of technical issues and the exercise of patient autonomy, but must be freed from commercial considerations. Simple solutions are rarely sufficient. Finally, the prescriber needs to make the patient aware that all of these options do not protect against infectious diseases, including HIV. It is imperative that all healthcare providers assist clients in assessing their risk for HIV/STI and promote dual protection strategies i.e. a strategy preventing both unwanted

pregnancy and STI/HIV. Options include the use of condoms alone or together with a hormonal contraceptive method, mutual monogamy of uninfected partners together with the use of a contraceptive method or abstinence.

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