Should combined oral contraception with absent or shortened pill-free intervals (PFIs) – 365/365 & 84/4 regimens – already seen as *good options*, now become the NORM?

COMBINED ORAL CONTRACEPTIVES (COCs)

Is the traditional COC taken 21/7 outdated! [1]

The COC was devised in the 1950s by John Rock with Gregory Pincus and other pioneers. It was a unique contraceptive. Yet John Rock, the team's OBGYN, gave the world's women the first-ever ovarian suppressant along with a unique instruction, for a contraceptive, namely: ***please don't use it* - at all**, for a whole week, 13 times a year! Thereby regularly un-suppressing the suppressed ovary. That decision, based arbitrarily on the calendar and not on science (ie biochemical and ultrasound studies of the unsuppressed ovary, data which did emerge but 20 years later), permits - unsurprisingly - varying degrees of return of follicular activity during the pill-free interval (PFI).

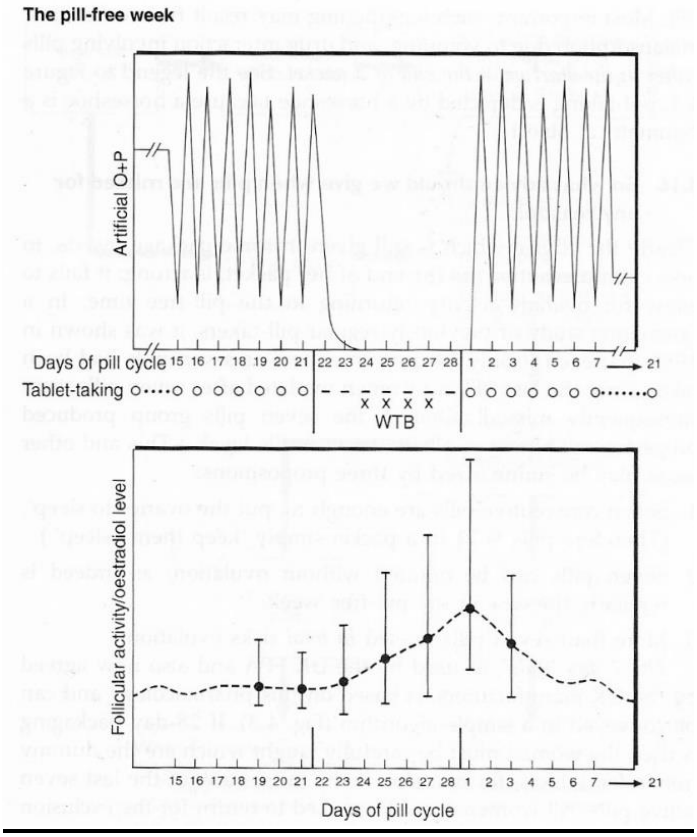

Figure 1. The estradiol data with standard deviation bars in lower part of Figure are from Gillmer *et al*, 1980.[2]

EFFICACY AND THE PILL-FREE INTERVAL (PFI)

The top half of the Figure above[2] is a stylised depiction of the daily variation in blood levels of ethinylestradiol and the progestogen after taking COC tablets, and their reduction towards zero during the first days of the pill-free interval (PFI). The bottom half is based on real data from the Margaret Pyke Centre (MPC) in 1978.[1,2] It shows rising levels of estradiol of ovarian origin in the PFI, but the line can equally represent the increasing diameter of the largest ovarian follicle during any 7 days without pill-taking, as shown in numerous later ultrasound studies.[3-7] In Figure 1 wide standard deviations are shown[2], meaning that in an important small subgroup the estradiol levels are higher than in the majority - indeed, as high as has been observed well into the follicular phase of spontaneous menstrual cycles. This implies the presence of a maturing pre-ovulatory follicle, as was confirmed at the Margaret Pyke Centre using ultrasound.[4] In most women (over 75%), all with no lengthening of the PFI beyond 7 days, there was continuing quiescence of the ovaries. However apparently pre-ovulatory follicles of diameter 10 mm or more were present on the seventh pill-free day in 23% of 120 pill-takers; in three women the follicle was 16–19 mm in diameter, i.e. potentially on the point of ovulation.[4] Such follicles grow by c 2-3 mm per day. Thus they can readily reach sizes (mean 21 mm but minimum 16 mm) leading with the LH surge to fertile ovulation, if the PFI is ever lengthened by 'late restarting' of the next pack, as it commonly is. However if the PFI begins by being shorter, ovulation must be less likely when tablets are missed after it. See Figure 2.[7]

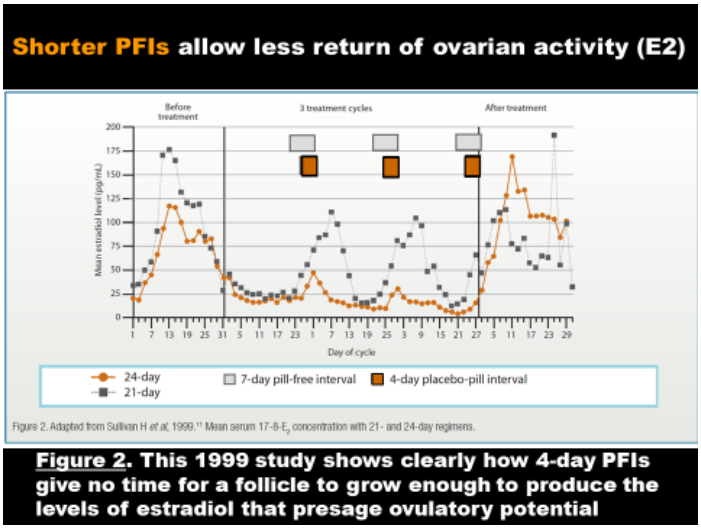

Figure 2. This 1999 study shows clearly how 4-day PFIs give no time for a follicle to grow enough to produce the levels of estradiol that presage ovulatory potential

That point was confirmed by Klipping et al (2008), see Figure 3.[8] In this randomised controlled trial (RCT), two groups were followed taking 20 µg ethinylestradiol EE/ 3 mg drospirenone for 3 cycles, with either 4- or 7-day PFIs. These were increased in Cycle 3 to 7 or 10 days, respectively

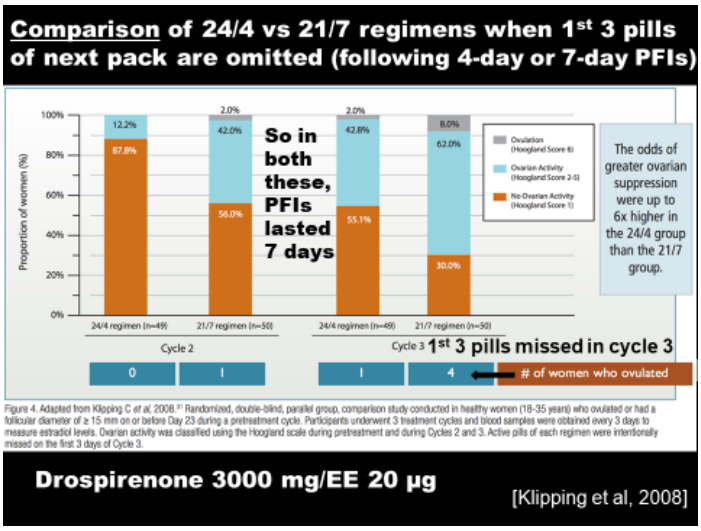

Figure 3

Ultrasound scanning and ovarian hormone data showed 70% ovarian activity and 8% ovulation if the 7-day PFI was extended to 10 days. Of even greater interest, however, actual ovulation occurred in no less than 2 out of a total of 99

volunteers with a *normal* 7 day gap, ie with no 'missed' pills! These numbers come from combining the two middle bars in the Figure. The left of these is a control cycle 21/7 (N=50), the other a test cycle 24/4 (N=49) where the PFI was 'extended' to the normal 7 days. There was one ovulation in each group (2 %).[8]

We believe the too-long PFI of the traditional 21/7 COC, as demonstrated in Figures 1-3, is the primary explanation for its horrendous failure rate, namely up to 9% in the first year for typical ('ordinary') users.[9] It also explains the 3 per 1000 failure rate among perfect-users, which without any PFIs would surely approach to zero. Moreover in any ovulating case, after either a 7-day or lengthened PFI, the hoped-for adjunctive contraceptive (sperm-block) effect of the progestogen component of COCs on the cervical mucus must tend to be at its lowest ebb, it being at least a week since that was last ingested. Thirdly, it can be argued that intercourse is very likely just then, given that couples tend to abstain during withdrawal bleeding earlier in the PFI.

In this manner, from the off c 60 years ago, the 21/7 COC was for some women on the edge of failure, 13 times a year: moreover at a common time for tablet omissions, when users fail to take the first pill(s) of the next pack. We contend that pill-teaching for 21/7 regimens should routinely stress "*never be a late restarter*[1]", ideally backed by electronic reminders. Here, however, we argue for substituting improved regimens that do not intermittently cease to provide full ovulation suppression.

The above model, that with 21/7 pills follicular activity and associated risk of pill-failure are related primarily to the duration of the PFI, is supported by the 2013 systematic review by Zapata et al. The studies reviewed indicate that missing up to four consecutive pills on days *not* adjacent to the pill-free interval results in little follicular activity and low risk of ovulation.[10] Smith *et al*[5] (1986) showed that ovarian estradiol levels are routinely suppressed once 7 COC tablets have been taken. Yet in their Group 1 subjects, who discontinued for 7 days after taking 7 daily tablets, one woman out of 12 did show luteinisation, with a rise in plasma levels of progesterone to 6.8 nmol/l. This would equate to only risking ovulation in mid-packet by omission of 7 tablets. However in a study in which just one pill was omitted to create an 8-day pill free interval, ovulation occurred in one of 9 cycles;[11] also in 5 of 69 cycles where 2 tablets were missed to give a 9-day PFI[12].

All hormonal and ultrasound studies of this phenomenon have been small. The potential therefore for not recruiting members of the above-mentioned small subgroup of most 'vulnerable' subjects explains why so few ovulations have been documented, even in studies with deliberate pill-omissions that lengthen the PFI.[10] The established method-failure rate of 3 women in 1000 per year[9] indicates that ovulation can certainly occur even without such lengthening, during 'perfect use'. Due to its rarity plus the obvious need to trust users' reporting (re correct pill-taking and dates of sexual activity), there appear to be no *published* reports of conceptions that finally prove the only explanation that fits with all the above data: namely, that fertile ovulation can (only) occur at or after the 7-days of non-taking of the COC.

However, it is far from unknown for experienced clinicians in SRH to report that they have encountered one or more well-attested cases of true 21/7 pill failure: pregnant COC-takers who are adamant in their claim, which is believed, of *correct and consistent* pill-taking. For this to be true, the previous cycle's tablets must have been taken correctly, with no omissions or hint of any absorption problem in the week before the PFI, after which the next pack was started with no delay and no omissions. In one such case reported to us, subsequent pregnancy imaging by ultrasound was congruent with her assertion that intercourse in the relevant weeks had been on one occasion only, which was - as would be predicted – Day 7 of her PFI (after which the first tablet of the next pack was taken on time).

The rarity of true method-failures of the 21/7 COC means they are in themselves of little public health importance. That is not the case for a much larger group of "typical" COC-takers, The *timing* of failures, combined with the complete absence of substantiated ovulations (leave alone conceptions) with omitted tablets on days *not* adjacent to the PFI,[10] reinforces the argument here for a new norm to eliminate or at least shorten the pill-free interval. This would greatly ***increase the margin of error when 'late in restarting' – which is as common as the women are unconcerned, typically,*** *being falsely reassured by their recent bleed and not even recognising the first tablets in the pack as 'missed pills'!*

The evidence-base that the 7-day PFI is contraceptively insecure – particularly in respect of margin for error, at possibly the commonest time of error – is now indisputable, and the manufacturers are well aware of these data. Indeed most recently marketed COC products are either packaged for extended or tricycle use (see below) - *or,* since 2000, use placebos to give PFIs of 4 days or less (ie in 24/4 packs).

Unfortunately, however, there has been insufficient pressure on the Pharma companies from prescribers, or unwantedly-pregnant users, to change their Pill-packaging appropriately for the *existing* established products. In our view ALL brands should be re-packaged, with marketing authorization (which given the evidence ought to be 'pushing at an open door' at the Regulatory authorities) for regimens with PFIs that are absent altogether - or last no more than 4 days (using 4 placebos) if scheduled at all, and that only at a woman's specific request.

What are current COC options that avoid the 'embedded' contraceptive failure-risk of the marketed 21/7 products?

Option 1. 'Tailored' 365/365 pill-taking[1,13,14,15]
Surprisingly, preliminary data suggest that bleeding patterns in continuous users are best with very low-dose (≤20 µg) pills. Edelman et al in an RCT of LNG versus NET formulations found that sustained use of a pill equivalent to UK's Loestrin 20 was the best of those tested for producing oligo-amenorrhoea.[15] How to 'tailor' pill-taking, the management of unacceptable bleeding[14,16] if it occurs, is described below.

Option 2. Tricycling[1,17] is another extended-use option with the same potential to minimise user failures, and indeed most of the above advantages of 365/365 regimens. The principle, that bleeds on the COC pill can readily and safely be reduced to four per year was established 40 years ago![17] At the time (and often since) this was seen only as an option for those who do not wish to have frequent scheduled bleeds, but it obviously also enhances efficacy. We advise

84/4, for women who would like to have a regular 'period', quarterly, taking 4 packets of a chosen COC in a row, *with for added contraceptive safety PFIs of 4 days*[1] – not the 7-day ones of the US-marketed products such as Seasonale®.

Established or Highly Probable 'Pros' of Pill-taking 365/365 with ≤20-μg COC** (NB: most below apply also to Tricycling 84/4)

□ *Greater margin for human error.* ALL users can miss up to 7 tablets with negligible conception risk. By contrast, in 21/7 pill-taking, for the established subgroup whose ovaries escape COC-suppression fastest and if omissions lengthen the 13 annual 'contraceptively risky' pill-free intervals (PFIs): only c 1-2 tablets. Hence:

□ *Greater efficacy in typical use* despite low doses (significantly so in one study, an RCT with COC pills, albeit taken vaginally[18]).

□ ***MUCH** less confusing 'rules' if pills are missed*: indeed, in nearly all cases, 'just restart your tablets, no added precautions'.

□ Far less need after missed COCs for emergency contraception (EC) and for the added complexity on return to COC-taking if ulipristal acetate EC is used

□ Vaginal bleeding (whether scheduled or unscheduled) having no known health benefits,[14] many (not all) women appreciate regimens with *fewer total days of bleeding* per year, though with the downside of unpredictability. This is a menstrual protection advantage[13] compared with the 21/7 regimen with its 'inevitable' 13 scheduled bleeds each of say 3-4 days duration. Hence:

□ *More days likely to be available for sex*, and potentially:

□ *Higher haemoglobin levels.*

□ *Reduced cyclical symptoms* for many, with *less:* –

- *headaches and migraine attacks,*[14] which so commonly occur in the pill-free interval
- *menstrual pain,*[14] a problem for some in their pill-withdrawal bleeds.
- *premenstrual syndrome-like symptoms*, which are often replicated on COCs when given 21/7
- *epilepsy seizures* (frequency can be reduced by steadier hormone levels) and:

□ Expected improvement in, or at least maintenance of, *known non-contraceptive benefits of COCs* [epidemiological confirmation required]: namely the reduced risk of cancers of colon and rectum, ovary and endometrium (re the latter, endometrial assessments by ultrasound and biopsy in several studies were uniformly reassuring[14]). Probably also:

□ *Improved symptoms of endometriosis* (probable here because of fewer bleeding days, into any ectopic endometrium).

□ *Maintained reversibility:* in one study, there was 99% return to cycling by 3 months.[19]

**NB In the "tailored pill" variant of continuous regimens[13] – see text – the woman is advised that in the event of unacceptably long bleeding/spotting, a 4- day break from pill-taking will usually produce a better bleeding pattern thereafter.

Are there added risks from continuous use? More RCTs and observational studies are clearly needed to establish fully the risks and benefits, as compared with the 21/7 regimen. However, in our view the risks should not differ significantly and **after further studies might even prove to be less, *given that:***

<> there is no evidence that either the PFIs, as representing 'breaks' from the drug, or the hormone withdrawal bleeds themselves, have any important health advantages, also

<> 365 days of 20 *μg* EE pills supply *less* dose [7300 μg] of EE than the 8190 μg/year of 21/7 regimens with 30 μg pills.[13] (Note however that if 30 μg pills are used, the 365/365 scheme lacks that plus point [10,950 μg EE/year]).

<> Moreover, to date, compared with 21/7 use endometrial[14], reversibility[19] and metabolic data[20] are all reassuring**.**

Should we not cater for those who retain a preference for monthly bleeds?

Certainly, though we believe this is a preference that will become uncommon, with the expected change of mindset, among providers as well as users, that will come with full acceptance that such bleeds have no benefits. Such women still do not need to risk having 7-day PFIs: a large US cohort study showed, for COCs using drospirenone and norethisterone, significantly lower failure rates for the marketed 24/4 regimens, *in typical users*, than for otherwise identical versions taken 21/7[21]. The odds ratio for not conceiving was even better for teenagers having the shorter PFI than for adults (0.5 versus 0.7).

When there is not a marketed 24/4 version of the chosen COC, we have described a user-friendly 21/4 regimen.[1] This uses an electronic application (mypillapp) for smartphones, available from www.mypillapp.com**,** which permits setting those numbers 21 and 4 - so the pill-taker is reminded on each day of pill-taking and non-taking, respectively.

Options 1 and 2 are solidly evidence-based and available now. Every new user needs warning that unscheduled bleeds and spotting may occur - esp. in early weeks. (In Miller's study[13] 88% of continuing users had oligo-amenorrhoea during cycles 10-12, with maybe some added spotting)**.** She should be advised *in advance* of her option to take a 4 day break in pill-taking[14,16] for any kind of to-her unacceptable bleeding – without extra precautions if there have been at least 7 days of good pill-taking prior to the break. After this (seemingly) 'pharmacological curettage', with resumed continuous pill-taking acceptable oligo-amenorrhoea usually follows. Option 1 with the advance advice just described (though it can also be helpful for those who choose to tricycle) is now known as **the 'tailored' pill**, an empowering choice for women.[16]

These alternative regimens are fully supported by WHO and the UK's Faculty of Sexual and Reproductive Health (FSRH).[22] Yet it is important to recognise that they are both, so far, **unlicensed uses** – although both are in reality but extensions of "running on packets" which is already licensed short term in certain circumstances for nearly all COCs. Until marketing authorisation is obtained, each service will need to follow precisely the requirements for unlicensed use, as clearly described by the GMC.[23] Until 'official' printed leaflets are available, these must include *crucially*, desk-top publishing a short dedicated local patient information sheet which explains all, including the important

differences from the manufacturer's leaflet, always ensuring:

<> a clear perception that though this is an ***unlicensed use of a licensed product*** it has a very strong evidence base, and is "a small change to make the COC 'contraceptively safer'"

<> full understanding and 'ownership' of the regimen.

CONCLUSIONS:

1 Extended use options 1 and 2 above have been offered by us and other providers for many years, as *good options where there are medical or personal-choice indications.* What this paper proposes is that they should now be recommended by the FSRH and the Family Planning Association (FPA) and all other relevant bodies as *the NORM, the methods of first choice, on efficacy grounds.* Since it has been clear for decades that typical (*ordinary*) pill-users do frequently omit one or more tablets[1]**,** *it is time to improve the margin for error when they do so before and above all after the PFI.*
We appreciate that this will require a significant change of mindsets worldwide, among pill-takers, pill-providers, medicines regulators and manufacturers.

2 **An exceedingly poor option,** surely, is to continue for another 60+ years with outdated 21/7 regimens, so tolerating:

<> *avoidably-high failure rates* through method-failure or, far more often, through *reduced margin of error in the common event of missing 1-2 pills* due to 'late restarting' after cessation of ovarian suppression for a week whereas in continuous use efficacy is maintained despite omission of up to 7 tablets *at any time.* Since it is quite common to forget a pill, ordinary women find the pill lets them down about 10 times more often than if "over 99% effective" was true, in the real world.

<> *avoidable induced abortions.* BPAS reported that, in a total of 60,592 abortions performed in 2016, 8799 or 28% of the 31000 contraception-failure cases conceived *while using a COC.*[24] Other abortion providers have reported, similarly, a higher proportion of clients claiming "COC-failure" than expected from the routine assurance that it is "over 99% effective", based, unrealistically, on PFIs that are not sometimes inadvertently lengthened.

<> *completely unnecessary 'periods' for millions of women* who have been kept in the dark that menstrual bleeding (whether as menses or as scheduled pill-withdrawal bleeds) - and the nuisance and expense of any form of menstrual protection – is, in reality, optional.

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