EXHIBIT 1016

The forgotten pill—and the paramount importance of the pill-free week

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Summary

It is now well established that in many women on current low dose pills there is a variable degree of restoration of endogenous ovarian function during the pill-free interval, as shown by rising levels of gonadotrophins plus oestradiol and also by serial ultrasound scanning of the ovaries. It follows that breakthrough ovulation is most likely to occur at the end of any lengthened pill-free interval, the lengthening being caused by omitted pills either just prior to the seven day break or immediately following it.

Following discussions between the Medical Advisory Bodies of the Family Planning Association and the National Association of Family Planning Doctors new advice has been agreed and pilot testing proved satisfactory. Simplified wording to be used in leaflets remains to be finalised, but the content is as follows.

> *If you forget a pill*
> *Take it as soon as you remember, and the next one at your normal time. If you are 12 or more hours late with any pill, especially the first in the packet, the pill may not work. As soon as you remember, continue normal pill taking. However, you will not be protected for the next seven days and must either not have sex or use another method such as the sheath. If these seven days run beyond the end of the packet, start the next packet at once when you have finished the present one, ie do not have a gap between packets. This will mean you may not have a period until the end of two packets but this does you no harm. Nor does it matter it you see some bleeding on tablet taking days. If you are using everyday (ED) pills—miss out the seven inactive pills.*

It is believed that seven days gives sufficient time for restoration of contraception in the vast majority of cases. When pills are omitted at the end of a packet, the new advice also avoids the illogicality of permitting the woman to take a already inadvertently taken (by the missed pills). The same advice is recommended, modified as appropriate, in other situations where the bioavailability of contraceptive steroids is reduced: such as vomiting, severe diarrhoea, and drug interactions.

Devised originally by Pincus, it is clear that the pill-free interval potentially impairs the efficacy of the combined contraceptive pill. It can also be associated with certain side-effects, such as withdrawal headaches. On the other hand there are both proven and probable benefits.

There is the regular reassurance of a withdrawal bleed. Secondly, a lesser total quantity of artificial steroids is ingested per year. But, possibly most significant, is the finding that certain metabolic variables altered by the combined pill show a tendency to return to normal by the end of the pill-free week. This may imply an important benefit to health, and possibly to reversibility, by the monthly 'rest' from its systemic actions. However, there exist special indications for either eliminating the pill-free interval, or for reducing it to four or five days.

Introduction

During the 30 years since the combined oral contraceptive pill (COC) or pill was first introduced, the question has often been asked, by women and researchers 'Why is it that conception can apparently follow the missing of just one pill, when the overwhelming majority of women routinely miss seven pills in each 28 day cycle with impunity?'[1] I have been arguing since the beginning of this decade that 'it is precisely because of this seven day break that most pregnancies occur,'[2] and that the pill omissions of greatest concern are those that lead to a lengthening of the pill-free interval (PFI). The time of risk is at the end of the lengthened PFI, but the causation of the lengthening can *either* be by delay in re-starting a new packet or by

day break.

The evidence for these statements is presented below and is becoming stronger with better research design and the use of new tools such as ultra-sound scanning. However, the 'acid test', namely the occurrence of pregnancy following missed pills, is extremely difficult to apply-chiefly because the worst pill-takers are also those who are worst at recalling which particular pills they omitted. In addition, until recently they would not even have been asked by the investigator about missed pills at the end of the packet *before* their last 'period' (withdrawal bleed). Yet available ancedotal evidence (see for example Table 1) links in well with what is now known about the pharmacology.

An elementary point is also worth making, which is valid without any assumptions about mechanisms. During the PFI, each day by which the interval is lengthened distances a woman's genital tract further from the last pill taken and hence from its contraceptive effects. Thus, lengthening the PFI must always increase the conception risk. In fact by the end of any lengthened pill-free interval not only is breakthrough ovulation more likely, but also the well known adjunctive contraceptive actions, particularly on the cervical mucus,[3] will be exerting their least effect.

Physiology and pharmacodynamics

Until recently, few researchers took account of the PFI, whether in devising or analysing their studies. As early as 1980 we showed how endogenous gonadotrophin and oestradiol levels tend to rise during the PFI from the very low levels found during pill taking, the rise being much more marked in some women than others.[4] Indeed it has been shown that by the seventh pill-free day some women have gonadotrophin and oestradiol levels similar to those seen in untreated women in the early follicular phase of a normal menstrual cycle.[5] Other endocrine studies[6–12] have confirmed that in some women, especially on low dose pills, there is a tendency for regular restoration of pituitary and ovarian activity.

There is naturally biological variation, many cycles showing quiescence of the ovaries at all times, but others showing sufficient ovarian activity to cause concern that for them, the seven days may be close to the limit that could be

al[11] identified a sub-group of five out of 31 subjects in which plasma oestradiol (E2) levels rose as high as 1200 pmol/l. In both this group and the remainder they found a statistically significant linear increase with time in E2 levels during the pill-free week. This rise would obviously be of greater relevance to contraception in the high E2 group, and in a later study[12] the same researchers were able to show in one subject out of 10 that prolongation of the pill-free period from seven to nine days led to surges of luteinising hormone and marked follicular plus (inadequate) luteal activity in two of three cycles. The remaining cycles in that study were characterised by a varying degree of follicular activity with no luteal function. None of the subjects with a lengthened PFI had a normal ovulatory cycle in this small study, but the results were interpreted as 'suggesting that repeated prolongation of the pill-free period. . . might result in a gradual increase in ovarian activity.'

The hormone studies in this area up to 1983 were reviewed by Fraser and Jansen (59 references).[13] They reached the conclusion that 'the most hazardous times to miss pills are at the beginning or the end of a monthly course.'

More recently, these observations have been confirmed by ultrasound (U/S) scanning for ovarian follicular activity. Nine Van de Vange and her co-workers[14] showed that with modern ultra-low dose pills, particularly the levonorgestrel triphasics, there was evidence of the growth of follicles in over half the normal COC-cycles studied. Pre-ovulatory size follicles (diameter 18 mm or more) were detected in no less than 27–31 per cent of cycles, and follicular cysts were observed in 14 out of 210 cycles. Unfortunately they did not specifically relate these findings to the pill-free interval. But they found a highly significant correlation between maximum follicular diameter and maximum E2 level measured, implying follicular activity as the basis for the rising oestradiol levels previously shown during the PFI.[4–12]

Molloy *et al*[15] found multiple ovarian follicles by the end of the PFI in every one of 19 women. However, by the seventh day of the new pill pack the follicular appearances had returned to the dormant condition shown in the first scan, just before the PFI (apart from one subject whose largest follicle had reduced in size from 8 to

Table 1 *Some relevant cases of unplanned pregnancy in users of combined pills at the Margaret Pyke Centre*

	Pills omitted or affected (D = day)	Causation	LMP	Remarks
Ms GE (Ovranette)	D1, D2, D3	Forgot to take her pills when she went away	28.12.80 (*Previous* to pill omissions)	12½/52 gestation on 13.3.81
Ms LC	D1, D2, D3, D4	Forgot to take her pills when she went away	23.5.81 (*Previous* to pill omissions)	11/52 gestation on 5.8.81
Ms KL (Microgynon)	D1–5	Antibiotic treatment (Doxycycline) for sinusitis, from D23 through WTB, to D5 of new packet	*Previous* to the affected pills	Patient a reliable pill-taker (midwife)
Ms LJ	D1, D2, D3	She had got the message to wait for WTB to *finish* after each cycle of pill-taking, leading to 9–10 day gaps between packets.	*Previous* to pill omissions	
Ms NB (Brevinor)	D19, D20	Having forgotten pills towards the end of a packet, BTB commenced. It merged with her next "period".	LMP was the WTB *subsequent* to pill omissions	Unprotected intercourse took place subsequent to the 10 days of BTB + WTB
Ms GF (Eugynon 30)	D19 and D21	Vomited D19 pill. Forgot D21	LMP was the WTB *subsequent* to pill omissions	
Ms DC (Logynon)	D20 and D21	Missed last two pills	LMP was the WTB *subsequent* to	*Had serial ultrasound (U/S) scans* On D 24 (5th day since last pill–12 mm follicle) On D 27 (8th day since last pill–16 mm follicle) On D 31 (12th day since last pill–corpus luteum on scan) *Research case*—advised but failed to take extra precautions. Pregnancy confirmed three weeks later + U/S scan.

NOTE: D1–21 are days on which pill-taking *should* take place.
D22–28 are days of the pill-free interval (PFI).

with only three of 19 women producing a largest follicle greater than 7 mm in diameter by the end of the PFI. More recent unpublished studies have given ample confirmation of this restoration of

than 120 women all scanned on the seventh day of their PFI, follicles greater than 10 mm in diameter were identified in no less than 23 per cent. While it is by no means certain that these

disturbed ovulation leading to functional cyst formation, the congruence of these ultrasound studies with the endocrine studies is striking, and the paramount significance of the pill-free interval when considering 'missed pills' is confirmed.

A most interesting new study[18] considers the effect on the hypothalamo-pituitary-ovarian axis of deliberately creating a seven day pill-free interval at various stages in the pill-taking cycle. The 36 women recruited to the study were divided equally between two types of pill (Microgynon^{R} and Trinordiol^{R}). In Group 1 medication was begun routinely on the day following the usual pill-free interval, but stopped after seven days; Group 2 took the pills for 14 days and Group 3 (the control group) for 21 days. Levels of gonadotrophins, oestradiol (E2) and progesterone were measured during the final week of pill therapy and daily for the seven days after stopping the pill. They observed, like other workers,[11] that E2 levels both during and after pill taking were higher in a sub-group than in the remainder of the population, and this was much more marked in users of the lower dose compound (Trinordiol^{R}). But only one of the latter, in Group 1 having taken seven days of pills, showed a rise in plasma progesterone during the subsequent pill free seven days and this cycle was abnormal; with excessively high oestrogen levels and a peak measured progesterone concentration of 6.8 nmol/l. This is a low value for the relevant day of the luteal phase.[19] The authors conclude that 'normal ovulation is a rare event in the week after cessation of either of these pills, even if only seven days of medication have been taken'.

Chowdhury *et al*[20] however, showed elevation of plasma progesterones in far more women when pills were missed (10 out of 35 women in the first cycle and five out of 19 in the second). There are still reasons for believing that the women could not have conceived, since the endometrium continued to be suppressed and there was a persistent marked progestagenic effect on the cervical mucus. However, the rate of elevated progesterones was much higher than in any other study (and included one case out of 10 even in the correctly-treated control group). This presumably reflects individual variation in different populations (see Conclusion 1 below).

Another factor may be the COC used, combined with ethinyloestradiol 30 ug, in fixed dose for 21 days out of 28. Norethisterone acetate is a pro-drug rapidly converted to norethisterone, and this has a much shorter elimination half-life (5–12 hours) than levonorgestrel (11–20 hours).[21] Wang *et al*[11] recorded an even higher value after administration of 150 μg of the latter, and found measurable levels six days after the last tablet.

Why do the biochemical studies to date fail to show any convincing return of fertility when volunteers deliberately miss their tablets?

There are several answers to this important question. First, as just noted, many studies have chosen to use levonorgestrel-containing fixed dose brands. Because of the long half-life of levonorgestrel, these may well have a higher margin-for-error than pills containing other progestogens. Secondly, only a tiny minority of studies have focused specifically on pill omissions which lengthen the pill-free interval. But most importantly, biochemical studies are by definition small studies. In the context of enormous individual variation they are unlikely to include sufficient representatives of the only subjects who matter. It is well known that pill-omissions are extremely common as shown by a study of 161 women in Glasgow of whom 27 per cent admitted missing pills in the past three months yet pregnancy rarely results.[22] For most women the pill is "fail-safe"; the problem in this research is to identify the vulnerable minority. Even among them within-patient (cycle-to-cycle) variation means that in any one-cycle biochemical study the critical observations may be missed.

A tenable hypothesis is that the vulnerable minority are those with the lowest blood levels of the exogenous hormones.[23] This group is probably largely co-incident with the sub-group[4,5 11–13,18] with the highest levels of endogenous oestradiol especially at the end of the pill-free interval; and these are also the women whose ovaries show the greatest follicular activity and the largest individual follicle-like structures detected by ultrasound.[14–17] These are the women who should be deliberately selected by preliminary screening before any future studies are started; and the latter should concentrate on tablet

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