

Low Dose OCP's, Cycle Control, Compliance and Pregnancy Protection



**Southern Ontario
Fertility Technologies**

Introduction

A Brief Historical Perspective

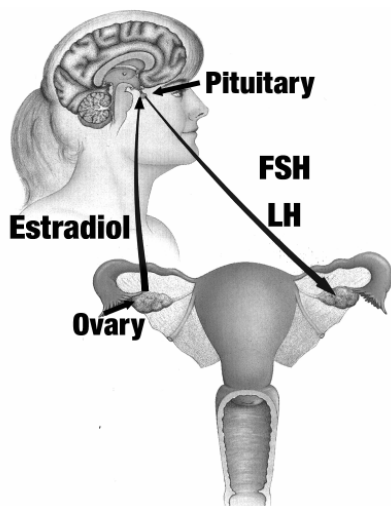
Oral contraceptives (OCPs) were originally **introduced in 1958**. At that time they were designed to mimic the usual 28 day cycle in order to make them more acceptable. This was done by taking the “pill” for 21 days and having a 7 day pill free period. The original oral contraceptives contained estrogen and progesterone in **much higher doses** than today’s pills. During the 7 day pill free time a withdrawal period occurred which mimicked normal menstruation.

In general, the development of OCPs over the last 45 years has been a **continual lowering of both the estrogen and progestin** components of the pill. This has been done both to minimize the serious but rare complications of the pill as well as the more common but less serious complications. The original “pill” contained 150ug of estrogen (mestranol) and 9.85 mg of norethynodrel and today’s pills contain as low as 20ug of ethynl estradiol and 100ug levonorgestril. Many pills have remained monophasic, meaning the same dose of estrogen and progestin is found in all pills but biphasic and triphasic formulations have been developed in further attempts to lower the does of hormones.

During most of the development of the OCPs the **basic format of 21 days on and 7 days pill free has been maintained**. This is not physiologically necessary as the bleeding occurring during the pill-free is not the same as the bleeding that occurs during a spontaneous cycle. Moreover, humans are the only animals that menstruate in the whole animal kingdom. Although monkeys have vaginal bleeding, this occurs at the time of ovulation. Sloughing of the endometrial lining and therefore **periods are not necessary**.

How the Pill Works and the Relative Importance of Follicle Suppression

The pill is very effective contraception and probably **works at several levels**. To understand how the pill works, it is necessary to briefly review how normal pregnancies occur.



Menstruation and ovulation are complex processes depending on the action of hormones released from the ovary, pituitary and hypothalamus. An imbalance in the levels of these hormones can disturb normal ovulation and can contribute to infertility. The first day of the cycle is considered the first day of bleeding sufficient to require sanitary protection as long as it occurs before midnight. All of the reproductive hormones are at their lowest level at this point in the cycle. **Follicle stimulating hormone (FSH)** is then released by the pituitary and stimulates both oocyte (egg) maturation and production of **estrogen (estradiol)**. The estradiol “feeds-back” to the pituitary to cause a decrease in the secretion of FSH. When the FSH and estradiol are at a

certain level and a mature follicle is present in one of the ovaries, a rapid rise of LH occurs (the **LH surge**), causing the final growth of the follicle, maturation of the egg and rupture of the follicle (ovulation).

The **progestin component** of the oral contraceptive is believed to inhibit the LH (and therefore, the LH surge) which is felt by most to be the main hormonal contraceptive action of the pill. Without a full LH surge, the egg is not released from the ovary (ovulated) and pregnancy cannot occur.

Estrogen was initially put in the oral contraceptive pill for cycle control. Estrogen causes the growth of the endometrium (lining of the uterus) so that when it and progestin are withdrawn, the endometrium is shed and menstruation occurs. Without estrogen, the endometrium would be



too thin to shed with withdrawal of progestin only. However, estrogen also inhibits FSH, which is necessary for follicle growth and probably egg maturation. The original high dose pills probably completely inhibited follicular development because of their high estrogen content. Historically, as the dose of estrogen became lower and lower and ultrasound became better, it was observed that lower doses of estrogen allowed some follicles to develop and become larger.

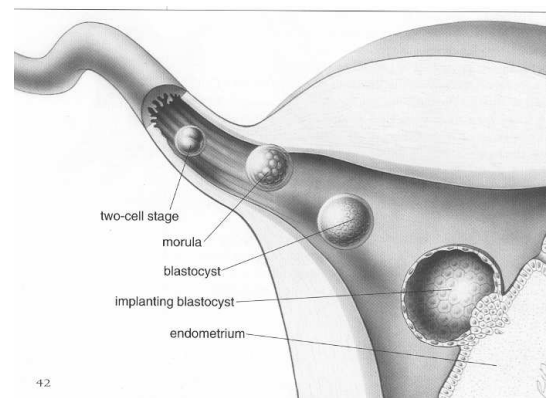
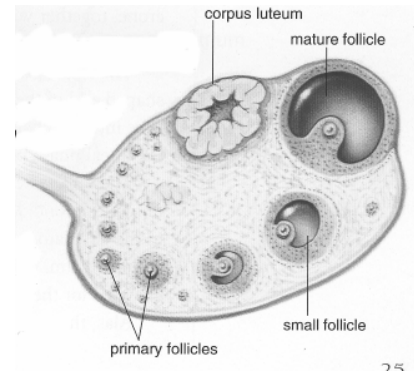
Follicle Development When Using the Pill

In 29 studies which looked at follicle development, 20 of them demonstrated follicle development to **10 mm in diameter**. Ten millimeters is the diameter at which follicles become physiologically able to be selected for further development and perhaps maturity and ovulation. A few of these follicles went on to develop to **14 mm** and then regressed. Still fewer follicles developed to **16 to 20 mm**, the stage at which they could contain a mature egg, but failed to demonstrate ovulation. In very rare circumstances, the follicle was felt to ovulate or rupture either because of the detection of a LH surge or the ultrasound demonstration of a collapsed follicle.

The maximum diameter that follicles appear to be able to develop to is reversely proportional to the estrogen component of the pill. Slightly more and larger follicles were noted in 20 ug pills than in 30-35 ug pills in three different studies, however, the **difference was not striking**. More striking was the more frequent development of follicles associated with longer pill free periods. Women who began their pill on day 5 of the cycle developed many larger follicles than those who began on day 1.

In fact, the most critical time for the development of 10 mm follicles is the **7 day pill-free** time. Up to 86% of cycles on any dose pill will demonstrate development of these size follicles in the 7 days! With the use of the higher dose pills in the 60s, the development of these potential follicles was probably of little consequence. However, with lower dose pills (20-35ug), some of these can grow. Most will regress once they reach 14 mm but some will grow to pre-ovulatory size and occasional ovulations have occurred. Very rarely ovulation has been documented both on 20 and 35 ug pills.

Shortening the pill free time from 7 days to 3 or 4 days drastically reduces potential 10 mm follicles. Administration of low dose estrogen



alone appears also to decrease the number of potential follicles but is probably not practical in clinical situations. Eliminating the pill-free period seems to almost eliminate the formation of these follicles.

Additional Mechanisms of Contraception with the Pill

For a normal pregnancy to occur, many things have to happen. The oral contraceptive pill is **believed to work by a number of mechanisms**. Sperm has to be ejaculated into the vagina, travel through the cervical mucous, uterine cavity and into the fallopian tubes. The pill may effect cervical mucous, cervical dilatation and the movement of the sperm through the fallopian tubes. The egg has to mature in the follicle in the ovary, be released by the ovary (ovulated) and be picked up and transported in the fallopian tube were fertilization occurs. Inhibition of follicle development and blunting or elimination of the LH surge are important. However, the pill also changes transport and perhaps pickup by the fallopian tubes. Lastly, the fertilized egg (embryo) has to be transported through the fallopian tube into the uterus and implantation has to occur. Again, fallopian tube transport may be affected and definitely the ability of implantation to occur is effected. All of the mechanisms probably contribute to the efficacy of the pill.

Contraceptive Reliability

The bottom line is the **pearl index**. The pearl index is the number of pregnancies occurring in 100 woman years on the pill. This is extremely low with all modern OCPs but **has not been demonstrated to increase as the estrogen dose decreases**.

The pearl index is calculated in ideal circumstances, when patient compliance is excellent. **What can be expected if pills are missed?** Most pregnancies on the pill probably occur in the circumstances of missed pills. This is most sensitive if the missed pill extends or is close to the pill-free time. This is certainly true if the missed pill(s) occur in the first 7 days of starting the cycle. It is also true if the last few pills of the cycle are missed, thus extending the pill free time. Pills with lower estrogen doses may be more sensitive to this, but this has not been proven and no difference in contraceptive efficacy has ever been demonstrated.

Compliance and Low Dose Pills

The major problem with the pill is compliance. None-compliance increases the number of **unwanted pregnancies** which amount to 82% of all pregnancies in woman under 15 years old and 78% of all pregnancies in women 15 to 19 years old. Forty two percent of all these pregnancies are aborted! Those that do not elect to abort these pregnancies are faced with unexpected major life changes including marriage, raising a child as a single person, changes in educational goals or in work position.

Side effects or perceived side effects of oral contraceptives can effect compliance. **Fear of weight gain** has become a much more important consideration in recent years. Forty four percent of women under 20 years old are trying to loss weight and 26% are trying not to gain weight. A survey administered to under 20 year olds in 1990 demonstrated that 11% were concerned with weight gain if they started the pill. The same survey completed in 2000 demonstrated that that number had increased to 28% and in 2004, this has probably increased again. In fact it had become the major reason that young women state for not starting the pill.

Weight gain has not been demonstrated in 7 different clinical studies utilizing low dose (35 or less) pills. It probably was an issue with higher dose pills but with new lower dose pills does not appear to be a real issue. Still, probably the lowest dose the best.

Nausea has been found to be significantly reduced in both clinical trials which addressed the issue in 20ug pills as compared to 35 ug pills.

Breast tenderness and bloating were both found to be significantly less as well with 20 ug estrogen pills as compared to 35 ug pills.

Irregular bleeding has always been a side effect with the pill and contributes to non-compliance. Theoretically, the amount of breakthrough bleeding should be increased with lower estrogen doses. With the conventional 21 day on 7 days off, cycle control was actually found to be better with the 20ug pill as compared with a 35 ug pill.

Newer Cycling Regimes

As outlined before, 28 day cycling is not necessary and was initially developed to make oral contraceptives appear more natural and therefore more acceptable.

In some circumstances, severe endometriosis for example, it would be beneficial for a woman to have no period since they are very painful. However, usually, if a woman is placed on the pill continuously, some breakthrough spotting or bleeding will occur.

This is not because the endometrium builds up but is in contrast, because the endometrium becomes thinner. Different women probably have different stabilities to their endometrium and some women will start this breakthrough bleeding much earlier than others. For example, the following graph was produced when **31 patients with severe endometriosis were placed on continuous OCP ...**

Month	% Bleeding
1	22.6
2	10.7
3	4.2
4	27.3
5	50
6	60

A similar pattern has been observed by other investigators. This lead to a trial in which 63 day cycles were attempted. The logic behind this was the bleeding patterns in the chart above – were the bleeding each month for the first three months decreased but then increased in the fourth month. The patient would begin the pill and take 21 out of the same package, but then instead of taking 7 days off, the patient would start a second package and similarly a third. This constituted 63 days in a row of the pill and then the patient would take 7 days off (the 63-7 regime). This was very beneficial for patients with endometriosis and other conditions were it was beneficial to avoid a period as they would only have 3 or 4 periods a year instead of 13. The following table demonstrates the **bleeding pattern in consecutive cycles in patients using the “63-7 regime”...**

Cycle	% Bleeding
1	27.3
2	7.3
3	9.1
4	0

This chart demonstrates that after the first 63 day cycle, breakthrough bleeding decreases to very acceptable levels by the second cycle. The regime was initially used by women with conditions such as endometriosis, who were trying to reduce the number of menstrual cycles. It became very widely accepted and in fact was used by many women who just preferred to have fewer periods!

The most recent development in cycling regimes is one that **treats the individual as an individual rather than forcing her to conform to the average.** The one problem with the “63-7 regime” is that women appear to have different endometrial stabilities. Although bleeding levels fall to very acceptable levels usually by the second cycle, they don’t for all women. A newer approach is to start the pill continuously with instructions for the woman to stop the pill if

there is three days of consecutive bleeding (bleeding being defined as having to use more than a panty liner) or five days of consecutive spotting. The woman then stops the pill for 5 days and allows the sloughing of the endometrium. Five days was chosen as opposed to seven days because of the potential of follicle development in the pill-free time and will be discussed in more detail in the section discussing contraceptive efficacy of the new cycling regimes.

Once the sloughing of the endometrium has occurred in the five days of stopping the pill, the woman then begins the pill again continuously until the cycle has to be repeated. With this regime, the following average times of being able to take the pill continuously are in the following chart...

Attempt	# Of Days
1	61.2
2	84.3
3	100.2
4	102
5	118
6	134
7	155

As you can see from the chart, the average woman would get 61.2 days in the first continuous attempt; interestingly very close to the 63 days of the “63-7 regime”. **This increased progressively each cycle.** The average is probably an underestimate as each cycle an increased number of the women would not bleed again. Therefore a number could not be assigned to them for the number of days they were able to continue the pill without interruption and they were dropped from the calculation.

On the other hand, there are women **with very unstable endometrium.** We have all had them in our practice and become frustrated trying to prescribe the oral contraceptive to them because they bleed no matter which pill they are on. This newest cycling regime has become very useful for these women! It has been my experience that using the cycling rules exactly like they are laid out will enable almost any woman to have reasonable control of her cycling. **A case history is presented in the box to illustrate this.**

Contraception Effectiveness with the Newer Cycling Regimes

All commercially available oral contraceptive have very low pearl indexes based on 21 days on and 7 day off regimes. Pearl indexes have not been established for these newer cycling regimes. However, referring back to our earlier discussion, for a pregnancy to occur, a breakthrough ovulation must occur. Questions have been raised, as the estrogen level of the pills drop that follicles may be allowed to develop more frequently. However, a larger risk factor in having a follicle develop during the cycle is the pill-free time. The pill-free time has probably become more important since the dose of the pill has decreased.

Studies have consistently demonstrated that shortening the pill free time, allows fewer follicles to develop. This is why in the newest cycling regime, we have chosen a 5 day off period rather than a 7 day off period. Missed pills are most likely to allow follicle development and therefore a pregnancy of they extend the pill-free time. In other words, pills missed at the end of the cycle or shortly after starting the pill are the most critical.


The newer cycling regimes have not had pearl indexes calculated for them. However, it seems logical, because both the “63-7” and the “individualized” regimes shorten the pill-free

Case Presentation

Miss W K – 19 years old, sexually active

Irregular Bleeding with 7 Different OCP’s

Start Continuously
 First Cycle – 13 Days!!!
 But Follow Protocol ++++
 Second – 17, Third – 24,
 Fourth – 33, Fifth – 67,
 Sixth – 66, Seventh – 89,
 Still on Eighth at 100



time (7 to 5 days) and in some cases may eliminate it; they probably give equal or better protection. With the newest regime, several of my colleges and I, will advise women that one they can continue the pill for 21 days without having to stop, it is likely (but not proven) as effective at preventing pregnancy. No pregnancies have occurred on the regimes to my knowledge.

A Final Word about Compliance

It should be remembered that the **pill has many benefits**. It prevents unwanted pregnancies, and also ectopic pregnancies. It decreases ovarian cysts and the newer cycling regimes may do this even more effectively. Many studies have demonstrated a decrease in the risk of ovarian and endometrial cancer. The pill has been demonstrated to improve bone density and this may be extremely important with the number of women who are underweight and therefore predisposed to lower bone densities. The pill (all pills) decrease acne and the progression of hirsutism.

The pill decreases pain with periods and the newer cycling regimes may add to this advantage as they allow even fewer periods. The pill also decreases benign breast disease, rheumatoid arthritis, and colorectal cancer. Fewer women have anemia because periods on the pill tend to be less intense. The pill also allows better cycling control and the newer regimes, again may add substantially to this benefit.

If these benefits are kept in mind and the negatives are reduced, compliance will likely be maximized.

Jim Martin ©

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