SIXTY YEARS OF THE COMBINED ORAL CONTRACEPTIVE PILL

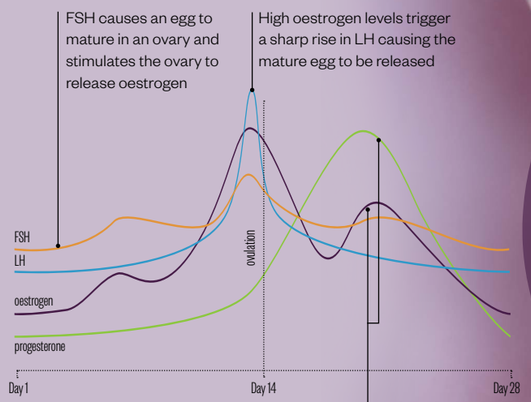
The first combined oral contraceptive pill was licensed for 'menstrual irregularities' in 1957, and contraception three years later. Since then, millions of women have taken 'the pill'.

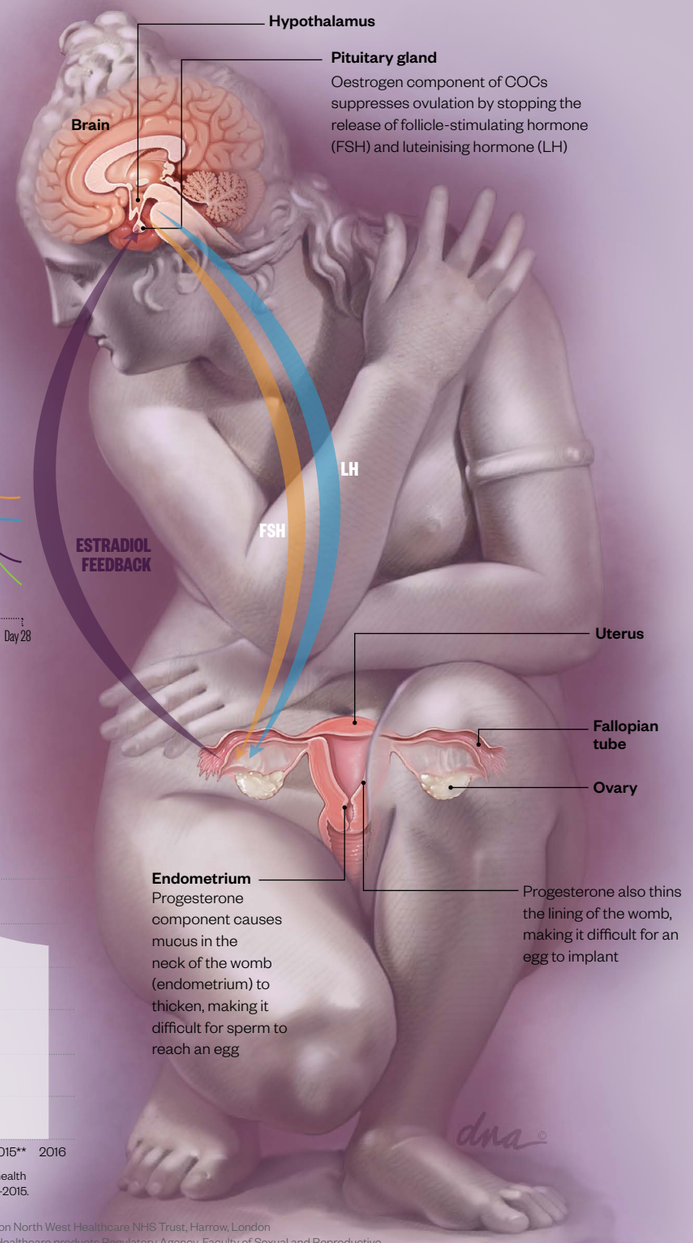
DAWN CONNELLY

HOW COMBINED ORAL CONTRACEPTIVES WORK

Combined oral contraceptives (COCs) contain synthetic versions of the sex hormones oestrogen and progesterone, steady levels of which convince the pituitary gland of a pregnancy.

Hormones and the menstrual cycle





ENDURING POPULARITY OF THE PILL

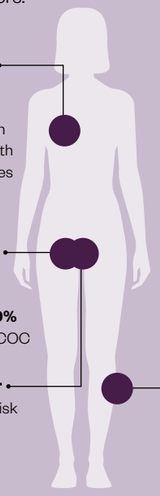
There has been little change in the proportion of women using oral contraceptives over the past ten years.

* Data show uptake of oral contraceptives for women in contact with sexual and reproductive health services in England. **Methodology for determining method of contraception changed in 2014–2015.

Editorial adviser: Nuttan Tanna, pharmacist consultant, women's health and older people, London North West Healthcare NHS Trust, Harrow, London
Sources: British National Formulary, NHS Digital, European Medicines Agency, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare. Illustration: Alex Baker. Infographic: Maria Gonzalez

RISKS WITH TAKING COMBINED ORAL CONTRACEPTIVES

COCs increase the risk of blood clots and some cancers, but reduce the risk of other cancers.



Breast cancer
In the UK, around **1%** of breast cancers in women are associated with oral contraceptives

Ovarian cancer
The risk of ovarian cancers is **reduced by 50%** after >5 years of COC

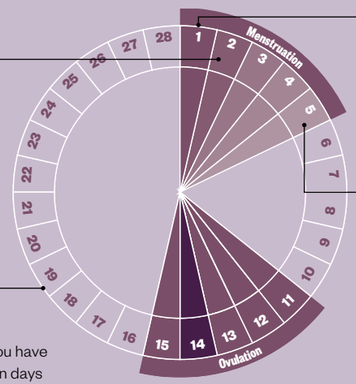
Cervical cancer
Cervical cancer risk is **doubled** after >5 years of COC

Venous thromboembolism (VTE)
VTE risk is increased but is small compared with the risks during pregnancy and immediately after giving birth. The risk varies depending on the type of progestogen in the pill. The risk of VTE is highest in the four months following initiation of COCs

Women **not using** a combined hormonal pill/patch/ring and not pregnant	About 2 out of 10,000 women
COC containing **levonorgestrel**, **norethisterone** or **norgestimate**	About 5–7 out of 10,000 women
COC containing **etonogestrel** (ring) or **norelgestromin** (patch)	About 6–12 out of 10,000 women
COC containing **drospirenone**, **gestodene** or **desogestrel**	About 9–12 out of 10,000 women
COC containing **chlormadinone**, **dienogest** or **nomegestrol**	Not yet known
Pregnancy	29 per 10,000 women years
Immediate postpartum period	300–400 per 10,000 women years

TYPES OF PILLS

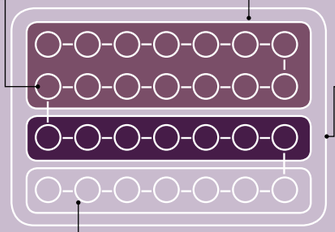
There are two main types of COCs: monophasic (contain the same amount of hormones in each pill) and phasic (contain different amounts of hormones).



Missed pill advice

If only one active pill is missed, take the missed pill straight away and further pills as usual. No extra precautions are needed. If more than one pill is missed, follow advice below. This advice doesn't apply to Qlaira, Zoely, Eloine and Daylette — consult product literature.

Missed pills on week 2:
- Take the most recently missed pill straight away and further pills as usual
- Extra precautions (condoms) are needed for the next 7 days



Missed pills on week 1:
- Take the most recently missed pill straight away and further pills as usual
- Extra precautions (condoms) are needed for the next 7 days
- Emergency contraception is recommended if there has been unprotected sex

Missed pills on week 3:
- Take the most recently missed pill straight away and further pills as usual
- Omit the pill-free interval (or inactive pills)
- Extra precautions (condoms) are needed for the next 7 days

DISCOVERY AND DEVELOPMENT OF THE PILL

Progesterone was first synthesised in the 1950s and was licensed as an oral contraceptive in 1960.

1950s

1951: Carl Djerassi, a chemist at pharmaceutical company Syntex, creates a progesterone pill by synthesising hormones from yams

1952: Chemist Frank Colton at the pharmaceutical company Searle also develops a synthetic progesterone pill

1954: Biologist Gregory Pincus and gynecologist John Rock conduct the first human trials on 50 women in the US. The pill is contaminated with oestrogen during synthesis but purifying it leads to breakthrough bleeding so it is retained

1956: After large clinical trials in Puerto Rico, the pill is found to be 100% effective

1957: Enovid 10mg (9.85 mg norethynodrel and 150 µg mestranol; Searle) is approved by the US Food and Drug Administration (FDA) for "menstrual irregularities". It is released onto the British market as Enavid

1960s

1960: The FDA approves contraception as an additional indication for Enovid 10mg

1961: Conovid 5mg is approved by the British Family Planning Association. Serious concerns are raised after three fatal cases of blood clots in women taking COCs

1967: Epidemiological studies link the pill with thrombosis

1970s

Second generation pills are launched, which contain lower amounts of hormones

1974: Free contraception is introduced in the UK leading to increased uptake

1980s

Third generation pills are launched to reduce androgenic and metabolic side effects

1990s

1995: The UK Committee on Safety of Medicines says third generation COCs should not be used first line because of the risk of blood clots. This "pill scare" is thought to lead to an increase of 9% in the abortion rate in 1996

1999: The Medicines Commission says third generation pills can be prescribed first line after all

2000s

2001: The EMA reviews third generation COCs and confirms a small increased risk of VTE compared with second generation pills. Fourth generation COCs are released

2009: The first COC containing the oestrogen estrodiol is launched

2010s

2013: The EMA reviews third and fourth generation COCs and concludes that their benefits continue to outweigh their risks, and the well-known risk of VTE with all COCs is small