Progestiiniehkäisyn vuotoprofiili

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Progestiinien historiallinen jaottelu

I polvi 1960-luku
- Noretisteroni ja noretisteroniasetaatti
- Lynestrenoli
- Megestroliasetaatti

II polvi 1970-luku
- Norgestreeli ja levonorgestreeli
- Syproteroniasetaatti?

III polvi 1980-luku
- Desogestreeli ja gestodeeni
- Norgestimaatti

IV polvi 2000-luku
- Drosperinoni ja dienogesti

Progestiinien ”sukupuu”

PROGESTIINIT

TESTOSTERONI-DERIVAATAT

Estraanit

Noretisteroni

Noretisteroni-asetaatti

Lynestrenoli

Gonaanit

Levonorgestreeli

Gestodeeni

Desogestreeli (-Etonogestreeli)

Norgestimaatti

PROGESTERONI-DERIVAATAT

Pregnaanit

Syproteroniasetaatti

Dydrogesteroni

MPA

SPIRONOLAKTONI

Drospirenoni

Paljonko progestiinia tarvitaan?

OVULAATION ESTO mg/pv	ENDOMETR.TRANSF. mg/cycle
-progesteronia 300	200
-LNG 0.05	5-6
-Gestodeeni 0.04	2-3
-drosperinoni 2	40-60

Mitä missäkin progestiiniehkäisyssä/ehkäisimessä on?

- MIRENA: Levonorgestreeli 52mg, 20mikrog./24h
- IMPLANON: Etonogestreeli 68mg, 25-45mikrogr./vrk
- JADELLE: Levonorgestreeli 75mgx2, 25-100mikrogr./vrk (ent. Norplant)
- Depo-Provera: Medroksiprogesteroniasetaatti150mg(1ml)

- Cerazette: Desogestreeli 75mikrogr./tabl/vrk
- Microluton: Levonorgestreeli 30mikrogr./tabl/vrk
- Mini-Pill: Noretisteroni 0,35mg/tabl/vrk

Vertailuksi kliinisessä käytössä yleiset progestiinit

- Terolut: Dydrogesteroni 10mg
- Orgametril: Lynestrenoli 5mg
- Primolut: Noretisteroni 5mg
- Primolut Nor: Noretisteroni 10mg
- Lugesteron: Progesteroni 100 tai 200mg
- Provera: Medroksiprogesteroniasetaatti 5 tai 10 mg

Mechanism of normal menstruation (1)

- Menstruation occurs as a universal endometrial event following the withdrawal of estrogen and progesterone subsequent to a normal ovulatory cycle.
- Disruption of a regulated sequence of molecular, cellular and vascular events can lead to a range of menstrual disturbances.
- Estradiol and progesterone probably act predominantly through their receptors. Two subtypes of each receptor have been identified, but the exact role of these in the endometrium remains to be clarified.

Mechanism of normal menstruation (2)

- The first morphological effect of hormone withdrawal is schrinkage of the tissue due to fluid absorption and spiral arteriole vasoconstriction, probably predominantly under the influence of prostaglandin PGF2 and endothelin-1, leading to reduced bloodflow.
- The arterioles undergo episodic vasoconstriction and relaxation leading to endometrial ischaemia and reperfusion damage, contributing to local release of a range of substances including cytokines, such as tumour necrosis factor aplpha, and other signalling molecules.
- The vasoconstriction process is limited predominantly to the first 24h.
- Haemostatic mechanisms are very important in limiting the volume of blood lost at menstruation.

Mechanism of normal menstruation (3)

- With further schrinkage and a combination of apoptosis and necrosis, a variable quantity of the functional layer breaks down into fragments which are shed into the cavity and expelled. A variable quantity of blood and tissue fluid is also lost during this process.
- Prolonged vasoconstriction, release of local growth factors and an effect of increasing estradiol terminate the blood loss and lead to epithelial repair.
- Angiogenic factors like vascular endothelial growth factor(VEGF) are probably very important in the repair process.
- Hypoxia is one of the most potent stimuli of VEGF

The irregular bleeding

- The cause of the irregular bleeding is not fully understood, but recent evidence suggests that an increase in endometrial vascular fragility

  might precipitate vessel breakdown and, hence, breakthrough bleeding.

Disturbances of vaginal bleeding patterns are almost inevitable in users of modern contraceptive implants (and Mirena), and there are no devices that can guarantee regular bleeding or even amenorrhea.

These bleeding disturbances are not known to threaten the health of contraceptive users, although they may lead to further investigations to rule out cervical or even endometrial pathology. Their major significance is the degree to which bleeding disturbances are disliked by women, leading to rejection or discontinuation of these methods.

Regular patterns of vaginal bleeding are central to beliefs concerning fertility, absence of pregnancy, and reproductive health for women from many cultures.
In addition, for some
women the presence of irregular or unpredictable bleeding is a barrier to social, sexual, and cultural activities and, hence, represents a major disruption to their lives.
Because
irregular bleeding may also be a feature of infection of the genital tract, and (rarely) of malignancy, this symptom may also prompt additional investigations, such as high vaginal and endocervical bacteriology, cervical cytology, colposcopy,
or even endometrial biopsy.

The maximum disruption of bleeding
occurs in the early months of use, with between 40 – 70% of
discontinuations in clinical trials caused by these disturbances.
The extent to which bleeding disturbances lead to implant removal in normal clinical practice is less clear, but
it is likely that the extent of dissatisfaction with bleeding patterns in implant users exceeds that of actual removals
because many women will tolerate irregular bleeding because
of the other advantages of implants

Irregular bleeding in the users of progestin only contraceptives

- Recent advances in understanding of the mechanisms of

this irregular bleeding are mostly drawn from studies of LNG-releasing systems.

The reduction in blood loss with the LNG IUS (Mirena) is related to changes in a complex series of molecular mechanisms.

Mirena is associated with the dramatic 95% reduction in volume of menstrual blood loss.

This unpredictable light bleeding and spotting is caused by continuous exposure of the endometrium to relatively constant doses of progestogen, with simultaneous exposure to low levels of estrogen.

This results in a variety of endometrial histologigal pictures which are broadly described as “suppressed secretory” but sometimes verge on complete atrophy. Surface breakdown of the endometrium is erratic and does not occur synchronously over the whole surface.

In trials comparing Implanon to Norplant, Implanon was consistently shown to induce more amenorrhea and less frequent bleeding than Norplant.

The incidence of prolonged bleeding is similar with both devices and decreases with time.

Irregular bleeding/LNG

In most studies, Norplant users were found to have a thin endometrium, regardless of bleeding patterns or estradiol/ progesterone levels.

However, some authors do report a positive association between endometrial thickness, peripheral estradiol levels, and number of bleeding days.

A number of studies were carried out in implant users to investigate the relationship between vaginal bleeding patterns

and ovarian function, endometrial thickness, and LNG serum levels.
In longitudinal studies, it was found that
women who had similar hormonal environments could ex-

perience very different bleeding patterns; for example, low estradiol levels and the absence of luteal activity could be associated with amenorrhea, frequent bleeding, or prolonged
bleeding patterns.

Because endometrial vascular and epithelial breakdown must occur before vaginal bleeding is seen, the focus of recent investigations into implant-related irregular bleeding has focused on endometrial blood vessels and the local control of their growth, breakdown, and repair.

Hysteroscopic observations have suggested that endometrial bleeding is focal following exposure to both low and high dose progestogens. There is insufficient information about the pattern of vessel breakdown in normal menstrual cycles to know whether focal bleeding usually occurs or is peculiar to BTB.

Current understanding is that BTB arises from abnormal endometrial vessels situated in an abnormal endometrial environment.

Sequence of events leading to BTB

If the endometrium contains comparatively more microvessels with comparatively less structural support and increased statement and activation of proteolytic molecules able to break down vessels, in conjunction with compromised
hemostatic mechanisms, this may induce and perpetuate BTB. This process of vascular breakdown may also act as a stimulus to vascular repair and angiogenesis.

BTB is likely to arise as the final point in a complex and multi-factorial process that may be activated by exposure to exogenous sex steroids, particularly progestogens.

The management of BTB

Supplemental estrogens have been given to women using progestogen-only contraceptives to try to improve bleeding patterns.
However, there is no evidence that estrogens improve bleeding patterns beyond the duration of their use . Similarly, it is common in clinical practice to change contraceptive or HRT preparations to those containing
different preparations and doses of estrogens and progestogens,
but there is no consistent evidence that this significantly improves bleeding patterns.

The natural history
of BTB is to gradually improve over time.

- Flavonoids, part of the vitamin B complex, have been shown in controlled trials to increase peripheral capillary resistance and to improve the systemic symptoms of capillary fragility, such as epistaxes, petechiae, and conjunctival hemorrhages.

- Recent pilot data have suggested that oral vitamin E (an antioxidant)

given during bleeding episodes may reduce bleeding in users of low-dose progestogens. The results of an on-going clinical trial are awaited to confirm this observation.

- The prostaglandin synthetase inhibitor mefenamic acid has been used to control irregular bleeding secondary to Norplant use. In a double-blind, placebo controlled study, 34 women who took mefenamic acid were significantly more likely to stop bleeding and had longer bleeding-free intervals than did the placebo group.

The effects of Implanon® on menstrual bleeding patterns

Diana Mansour et al.,The Eur.J of Contraception and Reproductive Health care

- Data from 11 clinical trials were reviewed (N =923). Assessments included
- bleeding-spotting records, dysmenorrhoea, and patient-perceived reasons for discontinuation.
- Bleeding patterns were analysed via reference period (RP) analyses.

Implanon

- Bleeding day: any day with vaginal discharge containing blood that required more than one sanitary towel or tampon per day.

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Spotting day: any day with vaginal discharge containing blood that required at most one sanitary towel or tampon per day.

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Bleeding-free day: a day during which neither bleeding nor spotting was entered in the diary.

- B-S episode: one or more consecutive days during which bleeding or spotting was entered in the diary, bounded by bleeding-free days.
- If a B-S episode started in an RP and continued into the next one, it was counted in the RP in which it started.
- The characterization of clinically important types of bleeding patterns was based on the original World Health Organization (WHO)-recommended definitions:

. Amenorrhoea: no bleeding or spotting days throughout the 90-day RP. .

Infrequent bleeding: less than three B-S episodes in a 90-day RP, excluding amenorrhoea.

Implanon

- use was associated with the following bleeding irregularities:

  amenorrhoea (22.2%) and infrequent (33.6%), frequent (6.7%), and/or prolonged bleeding (17.7%).

  In 75% of RPs, bleeding-spotting days were fewer than or comparable to those observed during the natural cycle, but they occurred at unpredictable intervals.

  The bleeding pattern experienced during the initial phase predicted future patterns for the majority of women.

  The group of women with favourable bleeding patterns during the first three months tended to continue with this pattern throughout the first two years of use, whereas the group with unfavourable initial patterns had at least a 50% chance that the pattern would improve.

  Only 11.3% of patients discontinued owing to bleeding irregularities, mainly because of prolonged flow and frequent irregular bleeding.

  Most women (77%) who had baseline dysmenorrhoea experienced complete resolution of symptoms.

Conclusion

- Implanon use is associated with an unpredictable bleeding pattern, which

  includes amenorrhoea and infrequent, frequent, and/or prolonged bleeding.

  The bleeding pattern experienced during the first three months is broadly predictive of future bleeding

  patterns for many women.
- Effective preinsertion counselling on the possible changes in bleeding patterns may improve continuation rates.

Implanon

- Bleeding patterns become unpredictable and irregular, occasionally with bleeding occurring more frequently and/or becoming prolonged or infrequent, with episodes of amenorrhoea.
- The total measured volume of endometrial blood loss in women using subdermal progestogen implants is usually significantly smaller

  than their natural menstrual loss.

Implanon

- The mechanisms behind the bleeding pattern disturbance are still not completely understood but appear to be the combined result of fluctuating ovarian estradiol secretion and continuous progestogenic exposure of endometrial glands, stroma and vasculature.
- There is increasing evidence that this leads to disturbed endometrial angiogenesis, with fragile, thin-walled surface vessels, lack of pericytes, defective basement membrane, altered migratory leukocytes, and disturbed matrix metalloproteinase release.

Implanon results

Dysmenorrhoea

- Changes from baseline to end of treatment in dysmenorrhoea: At baseline, 48.7% of subjects reported dysmenorrhoea.
  Among this cohort of women, 77% reported that their symptoms resolved, and 6% reported decreased severity.
  Dysmenorrhoea developed or became worse in 5.5% of women.

Haemoglobin

- To assess whether blood loss associated with the use of Implanon resulted in anaemia, haemoglobin blood levels were measured at baseline and at the end of treatment in several studies.
- The mean haemoglobin concentration was 133 g/l (n 504, SD 9.8) at baseline and 129 g/l (n 68, SD ¼9.2) at end of treatment.

Implanon

- Breakthrough bleeding arises from abnormal endometrial vessels embedded in an abnormal endometrial environment.
- Although in normal menstrual cycles bleeding appears to originate from spiral arterioles, breakthrough bleeding during progestogen use arises from a dense network of small, thin-walled, dilated superficial veins and capillaries.

  The integrity of these vessels is compromised by alterations in their basement membranes and pericytes. Alterations in several angiogenic factors suggest that abnormal endometrial angiogenesis may be the common denominator to those changes.
- Endometrial haemostasis may also be impaired owing to changes in several vasoactive substances (endothelins, tissue factor, nitric oxide) and a bleeding-prone superficial vascular network results. This network is embedded in an endometrial environment that provides less structural support, partly because of the changed proportions between vascular and structural components but also because of impaired stromal integrity.
- The latter may be the result of increased levels of cytokines and matrix metalloproteinases (MMPs) derived from an increased number of endometrial leukocytes, resulting in a loss of extracellular matrix.

Implanon

- Among Implanon users, endometrial histology assessed after one and two years of use revealed mainly inactive or weakly proliferative endometrium and an endometrial thicknesses of less than 4 mm as determined by ultrasound.

  Immunohistochemistry for progesterone receptor (PR), oestrogen receptor (ER) and vascular endothelial growth factor (VEGF) on endometrial biopsies of Implanon users after one year of treatment revealed a reduction in glandular VEGF without a change in endothelial cell density and an increase in glandular PR.

- In an ovarian and endometrial ultrasound study, subjects with bleeding disturbances appeared more likely to have increased follicular diameter and endometrial thickness, which suggests that incomplete ovarian suppression with associated increased ovarian oestradiol levels may contribute to bleeding disturbances.

Implanon

- Treatment or prevention of progestogeninduced irregular bleeding. Varying results have been reported with estrogens, COCs, additional progestogen, PR modulators, selective ER modulators (tamoxifen), vitamin E, nonsteroidal anti-inflammatory drugs, and doxycycline (as an MMP inhibitor).

  Some of these are effective short-term therapies for stopping a particular bleeding episode, but none provide useful medium-or long term benefits. Therefore, the evidence obtained so far with any treatment is not sufficiently strong to recommend the routine use of any of these.

In fact, effective patient counselling on the likely changes in the vaginal bleeding pattern still appears to be the most effective method to increase continuation rates on progestogen-only contraception, including Implanon.

References

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