

Premeno[®] duo - First dual-action vaginal suppository

1. Physiology of the vaginal wall:

- Makeup and function
- The changes during the various stages of a woman's life
- The defence: the vaginal flora

2. The active substances in Premeno duo

Hyaluronic acid

- Moisture and elasticity
- Wound-healing and defence against infections

Lactic acid / Sodium lactate

- Formation
- Significance for defence against infections

3. The galenics: composition of the vaginal suppositories

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Makeup of the internal vaginal wall and vaginal secretion

Multilayered, non-horny pavement epithelium

Reproduction is rapid: approx. 10-15 cells/week

Contains no glands: lubrication takes place by means of transudation.

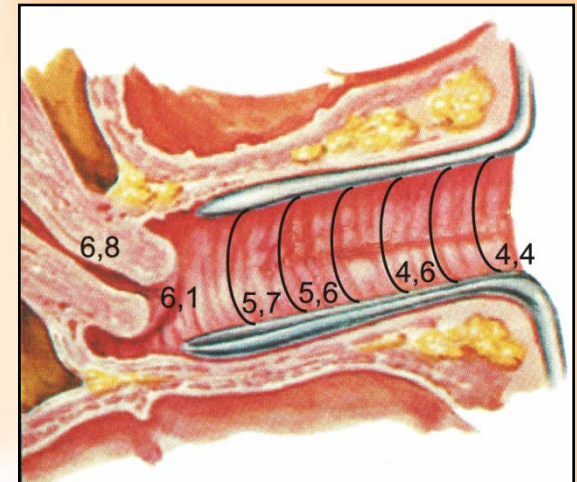
„Normal“ fluid level: approx. 0.8g [1]

It has been known since 1877 that vaginal secretion gives an acid reaction.

The reason is 6-18mg lactic acid and other organic acids

Distribution of the acid and consequently the pH is uneven (see fig.)

[1] A.Meisels, J. Repr. Med. 1, 603 (1968)



pH distribution in the vagina

S. Nolting Epidemiologie der Pilzkrankungen, 1978

Bild: Netter, Gynäkologie, 2006

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The shape of the vaginal wall and the composition of vaginal secretion are subject to ovarian hormone influences.

Oestrogens:

- improve vaginal blood flow
- stimulate epithelialisation
- increase transudation
- stimulate the storage of glycogen in the vaginal skin



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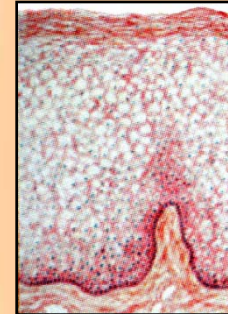
The vaginal epithelium during the various stages of a woman's life (1)

(1) The vaginal epithelium is most pronounced during pregnancy.

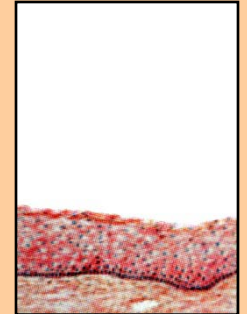
(2) The oestrogen level falls after giving birth.
The epithelium shrinks.

(3) Thanks to her mother's oestrogen, the new-born girl's vaginal skin is as well pronounced as her mother's.

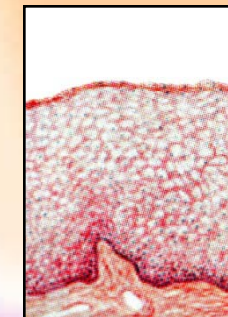
(4) After approximately 4 weeks, the infant experiences her „first menopause“. Until she reaches puberty, her vaginal epithelium and flora are similar to that of a postmenopausal woman. [1]



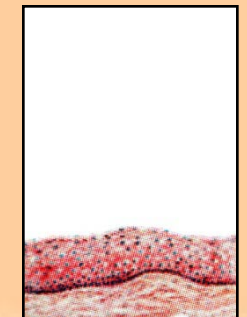
(1) Pregnancy



(2) Lying-in



(3) New-born



(4) Pre-puberty

[1] Mendling, Vaginose, Vaginitis, Zervizitis und Salpingitis, 2. Auflage 2006

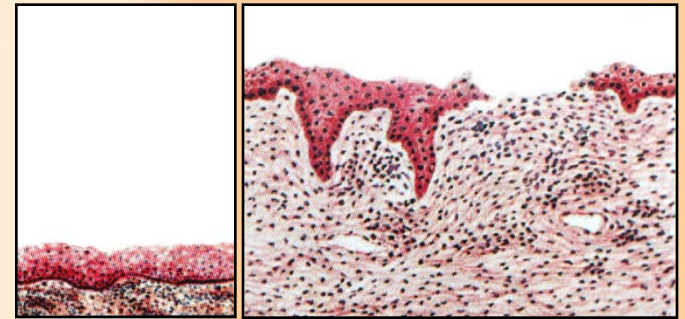
All fig. from Netters, Gynäkologie, 2006

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The vaginal epithelium during the various stages of a woman's life(2)

Fig.5: atrophy of the epithelium due to a lack of oestrogen:

- loss of lubrication
- irritation of the vaginal wall plus itching and pain (during intercourse),
loss of libido
- damage to the epithelium plus petechial haemorrhaging



(5) Atrophic changes of the vaginal epithelium during the menopause

Fig.: Netters, Gynäkologie, 2006

Formation of atrophic vaginitis:

The weakened and atrophic vaginal floor becomes infected

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The defence: the vaginal flora

Healthy vaginal skin contains approx. 10^9 various types of organisms, including facultative pathogens.

Lactobacilli (Döderlein's lactic acid bacilli) protect this sensitive equilibrium through:

- lactic acid production
- production of H_2O_2
- formation of „bacteriocines“
- formation of biosurfactants

If this equilibrium is upset, bacterial vaginitis may result.

Pathogenic organisms grow up to a thousandfold. (*Gardnerella vaginalis*)

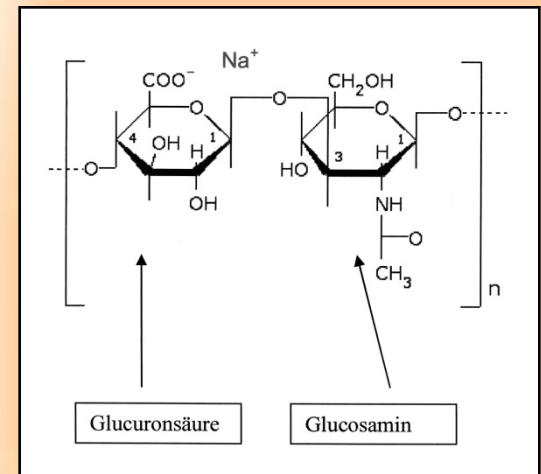
The number of lactobacilli drops and the pH rises to above 4.5.

The formation of amines results in an unpleasant odour.

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The active substances in Premeno Duo: **Hyaluronic acid (1)**

- Discovered in 1934, its structure was not elucidated until 1954 however.
- Accounting for approx. 70%, is the largest carbohydrate component in the extracellular matrix.[1]
- Makeup: macromolecular chain consisting of two glucose derivatives. The chain length varies greatly and is between 15 and 5000 disaccharide units long
- Belongs to the most hygroscopic molecules in nature: 1g of HA is able to bind 3 kg of water. [1]



[1] T.Friedel, Physiologie und Pathophysiologie des Haut-und Narbengewebes, Akademie für Handrehabilitation, 2002

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Hyaluronic acid (2)

- Forms a 3-dimensional network between cells.
- Determines the biomechanical functional capacity of the skin through its concentration and hydration.
- The stiffening rate of collagen increases in the absence of hyaluronic acid. Skin elasticity decreases.

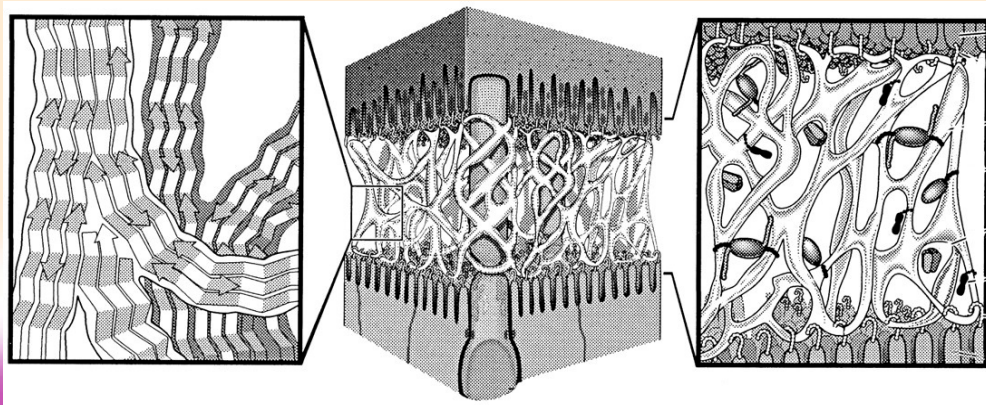


Fig.1



Fig.2

Fig 1: J.G. Hollyfield: Hyaluronan and the Functional Organization of the Interphotoreceptor Matrix, 1999

Fig 2: Denise Smith: HA illustration from various REM images taken in synovial fluid. From J.E.Scott 1998

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Hyaluronic acid (3)

-It is today considered proved that hyaluronic acid regulates cell development and stimulates wound healing [1,2]

- Stimulation of fibroblast proliferation
- Acts as a radical catcher and is anti-inflammatory
- Regulates cell regeneration and cell migration
- Encourages neoangiogenesis

-Forms a natural barrier against invading organisms

[1] T.A.Dechert et al.: Hyaluronan in human acute and chronic dermal wounds, Wound Rep Reg 2006 14: 252-258

[2] J.Chen et al.: Functions of hyaluronan in wound repair; Wound Rep Reg.. 1999;7:79-89

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Hyaluronic acid (4)

- Current studies show hyaluronic acid to have an inhibiting effect on *Candida albicans* in human, oral epithelial cells [3]
- In vitro studies substantiate the excellent penetration of hyaluronic acid through the vaginal skin [4]

[3] A.Sakai et al.: Potential role of high molecular weight hyaluronan in the anti-*Candida* activity of human oral epithelial cells; *Medical Mycology*, 45: 73-79

[4] G.Sandri et al.: Mucoadhesive and penetration enhancement properties of three grades of HA using porcine buccal and vaginal tissue; *JPP* 2004,56: 1083-1090

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The active substances in Premeno Duo: lactic acid

Lactic acid is a major factor in maintaining vaginal defences against infection.

Treating an excessively high pH is a long-known recommended method for preventing bacterial vaginosis [1,2]

Factors leading to too high a pH and increasing the risk of infection as a result (e.g.):

- Low oestrogen level (e.g. menopause, hormone therapy)
- Psychosocial stress
- Antibiotic therapy or the use of nonoxynol-9 (A-Gen 53) [3]

[1] Mendling, Vaginose, Vaginitis, Zervizitis und Salpingitis; 2.Auflage 2006

[2] Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; AWMF-Leitlinien 06/2008

[3] B.Richardson:Use of Nonoxinol-9 and changes in vaginal Lactobacilli; The J. of Inf. Diseases; 1998;174:441-5

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The galenics: composition of the vaginal suppositories

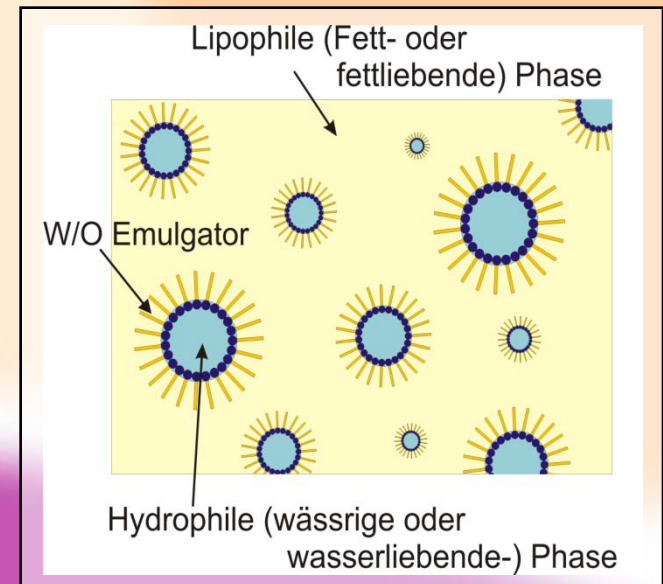
Weight: 2g, simple to use

Combination of melting and dissolving suppositories; therefore contains water-soluble and fat-soluble components in a w/o emulsion (cream ovulum)

Crucial for good absorption:
hyaluronic acid is not soluble in the matrix. It is evenly suspended:
d=40-50µm

Lactic acid/sodium lactate buffer produces a pH of 4.5

Contains no stabilisers or preservatives



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Summary (1)

Adjuvant treatment for atrophic, dry vaginal skin

- during or after the **menopause**,
- after **labour**,
- during **breast-feeding**,
- when taking **hormone preparations**,
- for **psychological disorders** (stress),
- or after **cancer treatment** (chemotherapy)

Initial reports on its use and studies substantiate the effectiveness of hyaluronic acid suppositories and gels for vaginal dryness [2,3]

Assists in the healing processes of the damaged vaginal wall

[T.A.Dechert / J.Chen, s.o.]

[2] M-K. Tea: Journal für Fertilität und Reproduktion, 2006(16) 16-19

[3] G.Morali: Open, Non-controlled clinical studies to assess the efficacy and safety of a Medical Device in Form of a Gel topically and intravaginally used in postmenopausal women with genital atrophy; Drug Res. 56,No.3,2006

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Summary (2)

Effective against *Candida albicans* – the organism that causes vulvovaginal mycosis. [A. Sakai, s.o.]

Restores a „healthy“ pH through lactic acid substitution. Improves susceptibility to infection. Supportive treatment of bacterial vaginal infections.

It has been able to be demonstrated that vaginal dryness and the increased risk of infection are often to be attributed to the same hormonal causes.

The simultaneous use of hyaluronic acid and lactic acid is therefore an ideal, complementary combination.