
Progesterone

Physiology

Progesterone is produced in the cortex of the adrenal glands in both sexes as precursor of the other steroid hormones synthesized at this site. In addition, the major quantity of progesterone in females is produced in the Thecalutein- and the Granulosaluteincells of the Corpus luteum in the ovaries and, during pregnancy, in the placenta. Additionally, small amounts of progesterone are produced in the testicles of males and also in the brain of both sexes.

The most important role progesterone plays during the menstrual cycle of females is transforming the mucous membrane of the uterus from the proliferation to the secretion phase and therefore to prepare the uterus for the implantation of a fertilized ovum. During early stages, progesterone is also responsible for the maintenance of the pregnancy.

The following figure summarizes endocrine levels during the menstrual cycle and its effect on the ovaries and the endometrium of the uterus.

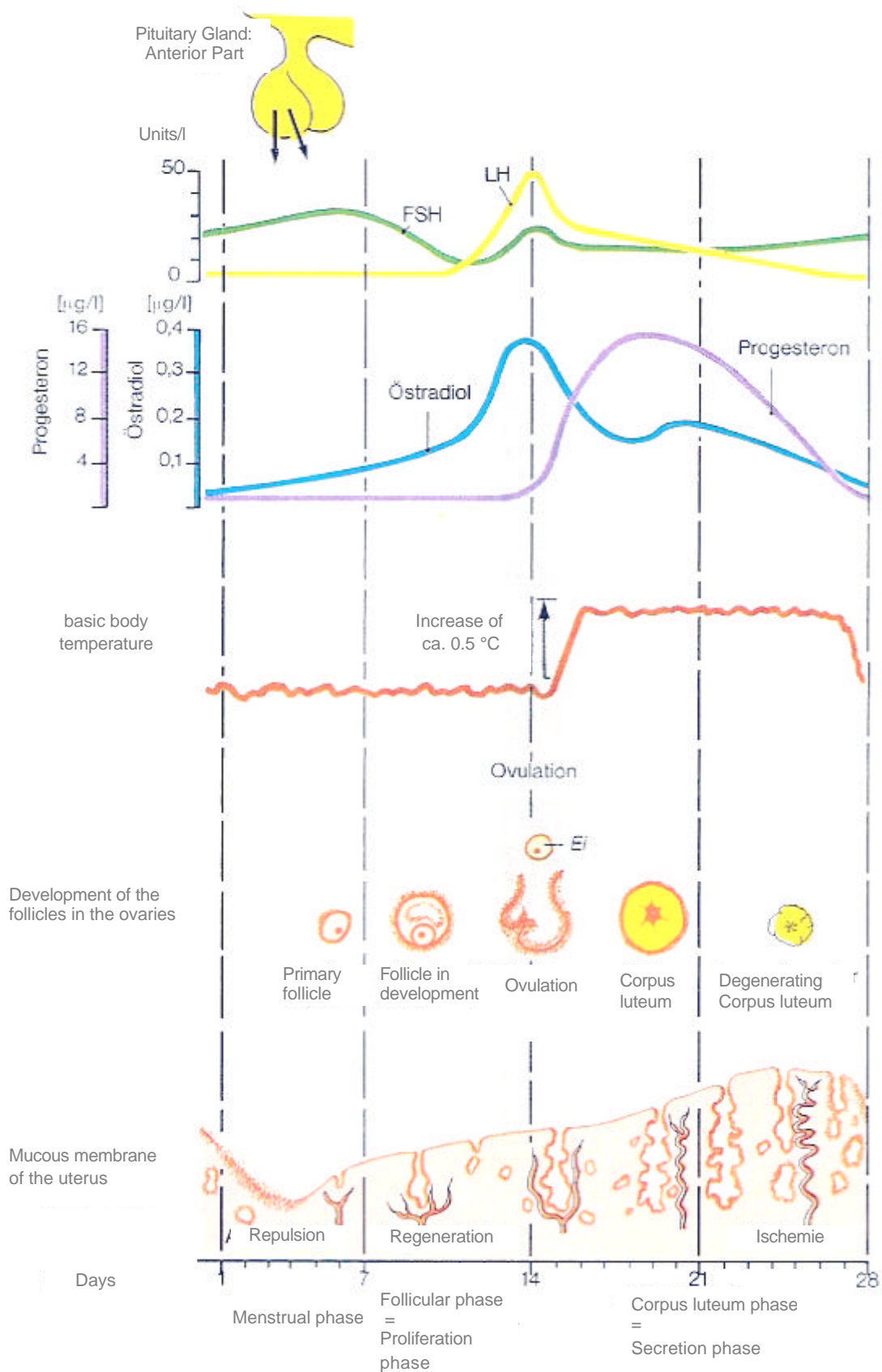


Fig. 43: Menstrual cycle in women (S. Silbernagl and A. Despopoulos, 1983)

In the figure 43 the curves of the hormones are idealized. Normally the hormone levels have a distinct diurnal fluctuation with a wavelength of about 90 to 300 minutes depending on the phase of the cycle. This fluctuation, especially of GNRH (gonadotropin releasing hormone) from the hypothalamic region is important for the receptors on the target cells (of the pituitary glands). The fluctuation of the GNRH level is linked to the release of FSH and LH as well as estradiol and progesterone.

The following figure shows the diurnal fluctuation of the progesterone concentration in plasma and in saliva of a woman during the 21st day of the cycle. Regarding this fluctuation a multiple collection of samples during the day is recommended to assess an actual progesterone level for that day.

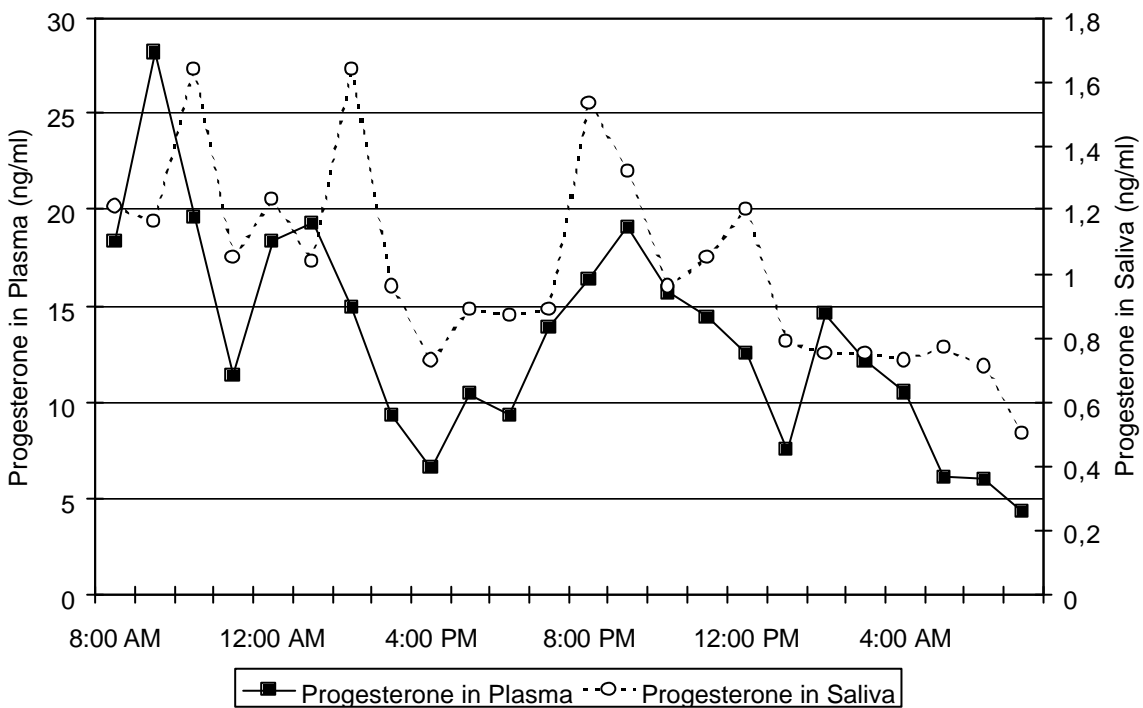


Fig. 44: Diurnal fluctuation of the progesterone level in a woman (T. M. Delfs et al., 1994)

In the blood circulation 1 – 3 % of the progesterone is not bound to proteins and therefore only this small portion is endocrine active within the target cells. The greatest fraction of the circulating progesterone is bound to CBG (corticoid binding globulin) and albumin, similar to the situation of cortisol. As with the other steroids only the free progesterone is released with the saliva and so the evaluation of the salivary hormone level is a convenient and reliable method to assess the active portion of this hormone.

In the following figures the salivary progesterone and estradiol profiles of women in the menstrual cycle are shown:

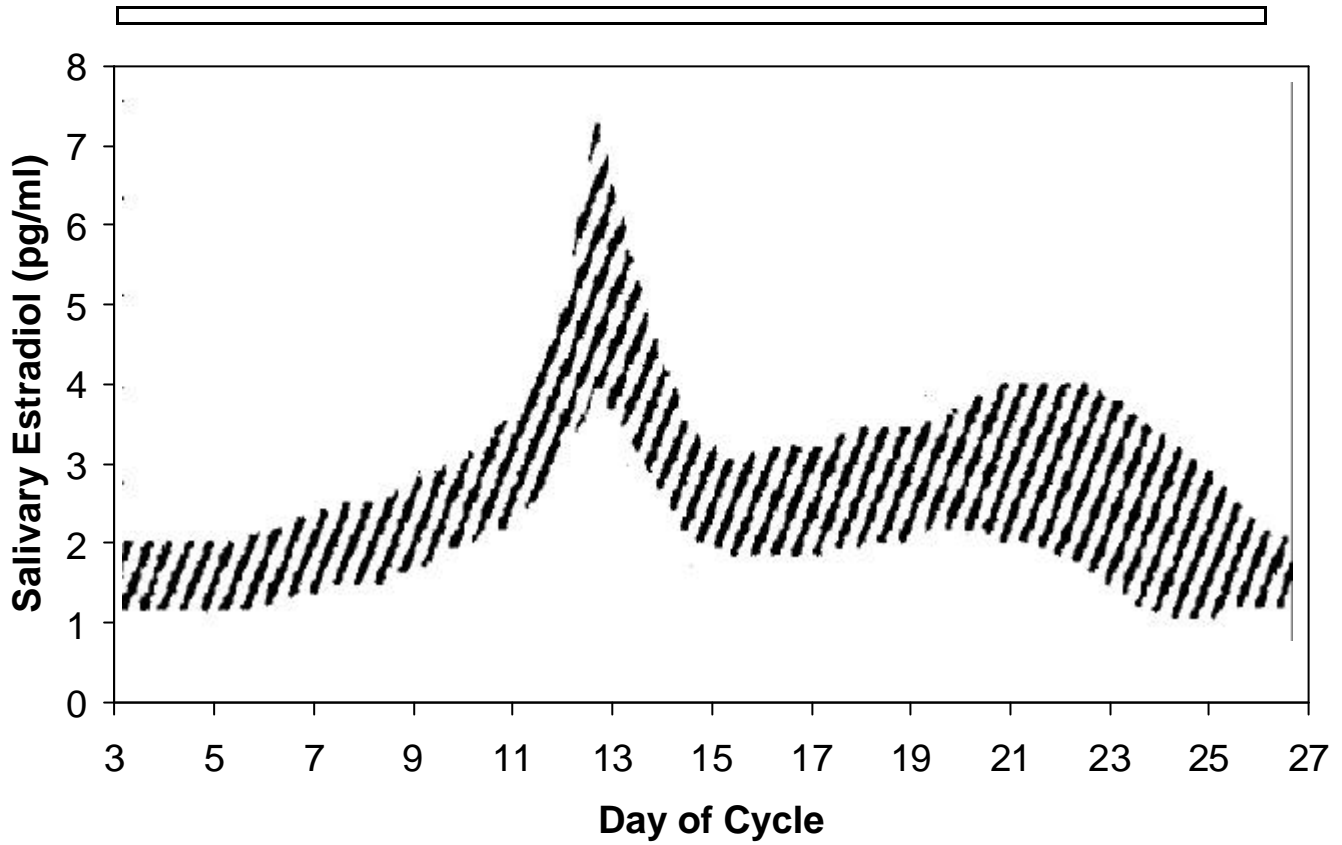


Fig. 45: Monthly profile of the salivary estradiol during the menstrual cycle of the woman (Collins, J. J., 2000)

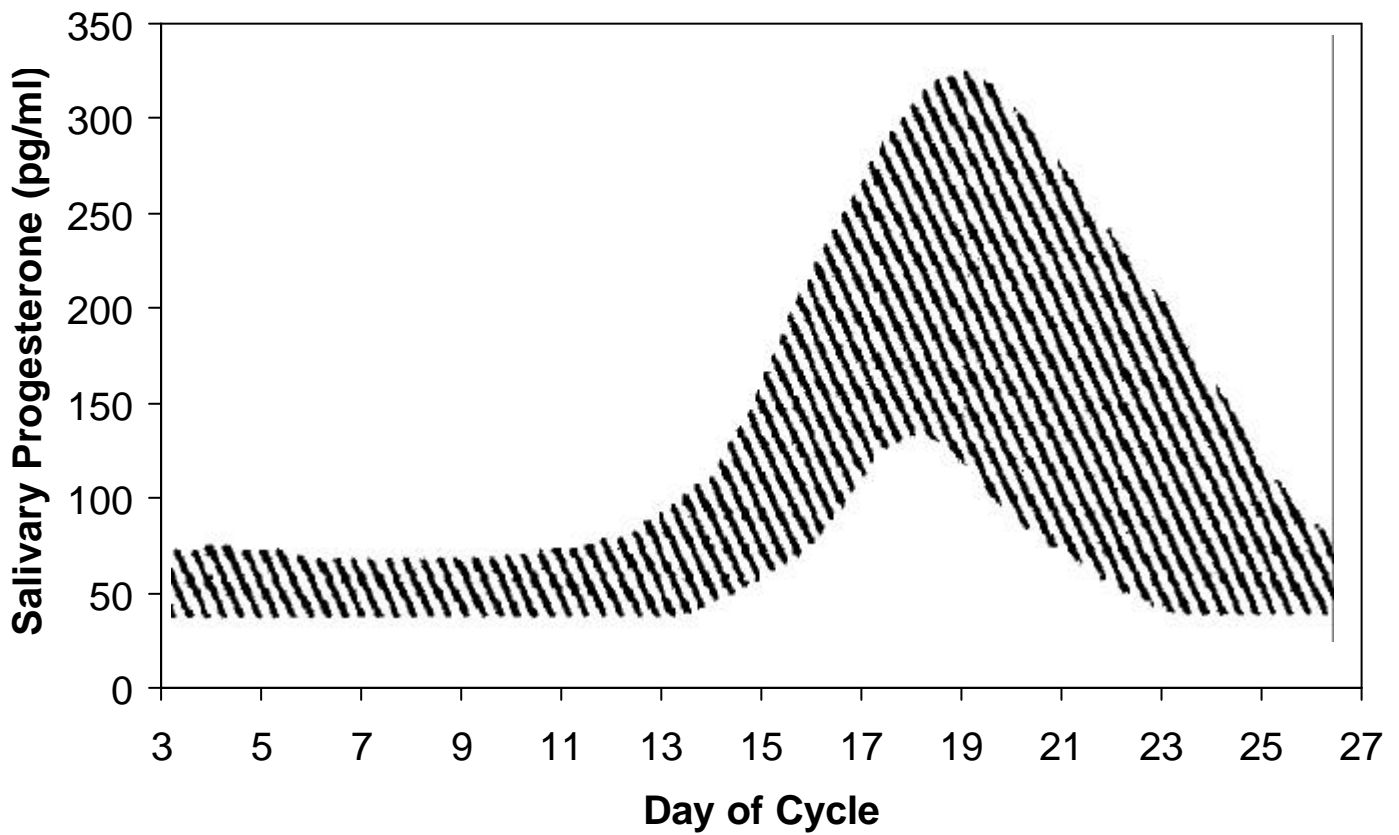


Fig. 46: Monthly profile of salivary progesterone during the menstrual cycle of the woman (Collins, J. J., 2000)

Indications

Regarding the above mentioned physiological role of progesterone the main indication for assessing its concentration is the dysregulation in females at puberty, in premenopause and during perimenopause. In addition, there are some other indications such as control of early pregnancy, evaluation of some ovarian neoplasms etc. In anti-aging medicine it is sometimes necessary to evaluate the progesterone level before and during replacement therapy.

Implantation of the ovum in the endometrium of the uterus will not be possible if the progesterone concentration is absolutely too low. However, it is much more common that the progesterone level will be within the normal range but the shape of the progesterone curve during the cycle is irregular: So a possibility exists that luteal phase will be too short because of an early degeneration of the corpus luteum. The same consequence might result from a premature luteinisation. On the other hand, if luteinisation begins too late after ovulation, it may result in insufficient preparation of the mucous membrane for implantation.

To assess a complete progesterone profile during a cycle repeated samples have to be taken. Regarding the above mentioned diurnal fluctuation of progesterone a collection of at least 3 samples per day is recommended. This might be very inconvenient for the patients if blood samples are taken and therefore saliva collection represents a good alternative.

The following figure illustrates the possibilities of abnormal progesterone profiles in women.

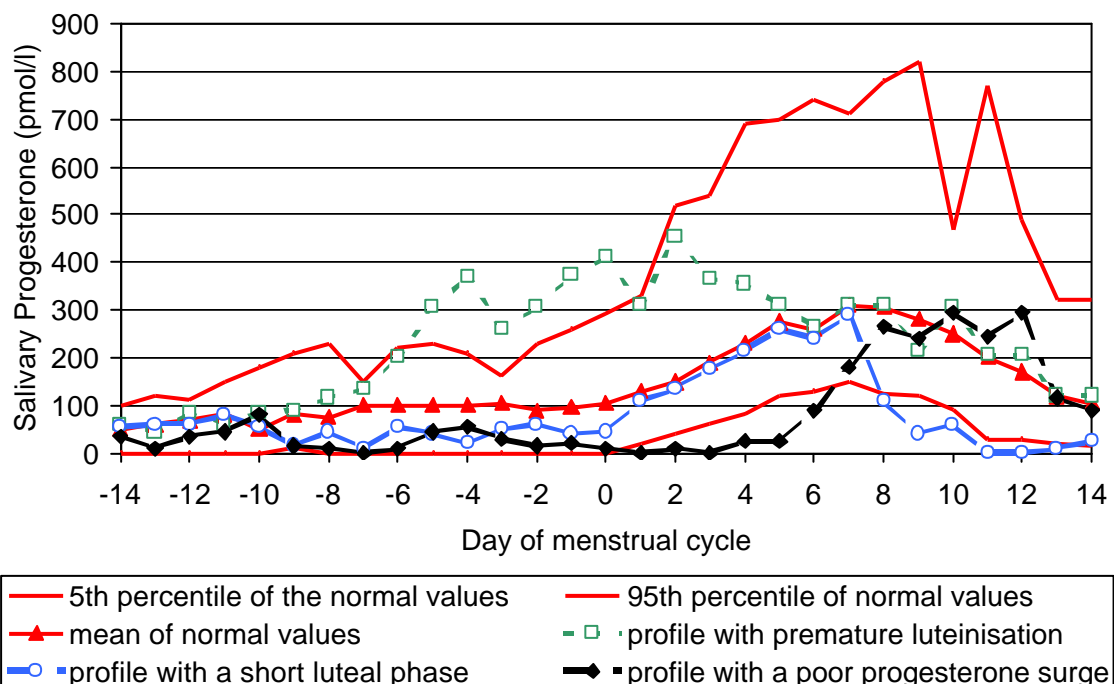
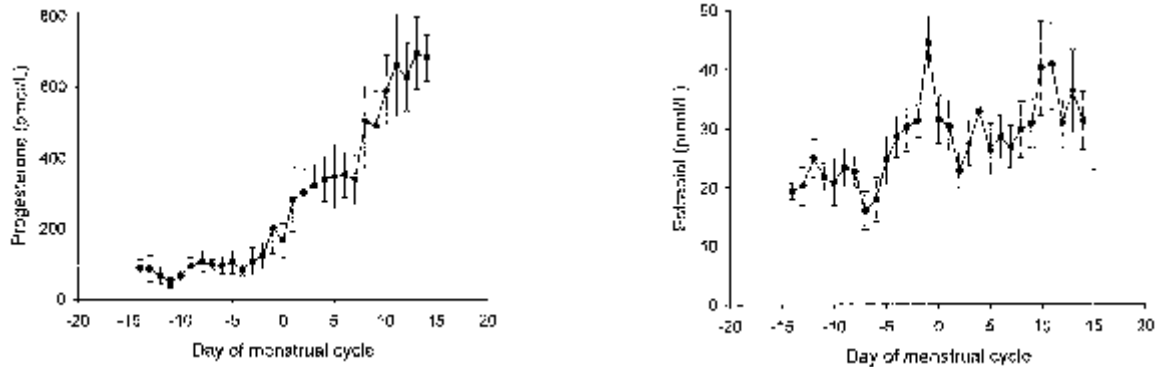
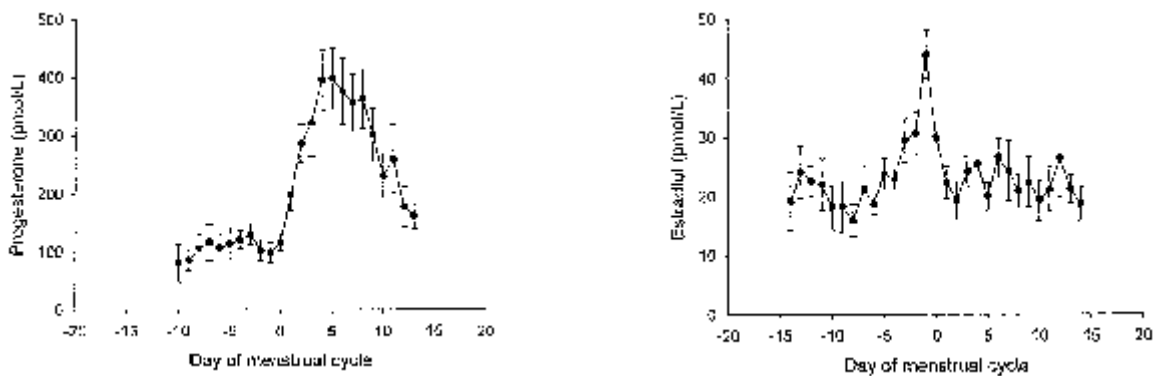


Fig. 47: Salivary progesterone profiles during the menstrual cycle of women. Day 0 is the day of ovulation; day -14 is the day of bleeding (Bolaji et al., 1992)

The assessment of salivary progesterone (and estradiol) is also appropriate to differentiate between conception and non-conception cycles in women. Whereas the estradiol peak just before ovulation is similar in both kinds of cycles, the progesterone concentration decreases in non-conception cycles after the first increase of about 7 days following ovulation. In conception cycles a



Conception Cycles: Progesterone (pmol/l) and Estradiol (pmol/l) levels in saliva samples of 11 women (mean \pm SE); Day 0 = day after midcycle peak of



Nonconception Cycle: Progesterone (pmol/l) and Estradiol (pmol/l) levels in salivary samples of 11 women (mean \pm SE); Day 0 = Day after midcycle peak further increase can be observed.

Fig. 48: Salivary estradiol and progesterone levels in conception and non-conception cycles of women (Yu-cai Lu et al., 1999)

Normal ranges

The following is an example of a saliva collection schedule used by a group of laboratories. Variations in collection schedules can be assumed for special studies.

Saliva Collection:	
- Cycle mapping:	- at least the 20 th to 23 rd day after menstrual flow
	- in irregular cycles preferably 2, 10, 12, 14, 16, 18, 24 days after bleeding
	- early in the morning (8 am); preferably mixed saliva from 3 collections in the morning
- menopause	- (without cycle symptoms) day 2 is the start of sampling
	- in replacement therapy, 8 – 12 hours after application
	- for continuous transdermal patches, preferably 24 – 48 hours after application

The following “values” may only be regarded as a guideline because of variables such as choice of diagnostic reagent kits and population bias.

	Values (ng/ml)
Women:	
Premenopausal	
follicular phase	< 0.1
luteal phase	0.1– 0.5
Postmenopausal	< 0.05
with oral replacement*	0.1 – 0.5
replacement with transdermal cream*	1.0 – 10

* Levels 8 – 12 hours after application

Literature

1. Collins, J. J. Salivary Hormone Testing: Science, Benefits, Limitations & Clinical Applications. *Anti-Aging Medical News*, Winter 2000
2. Laine, M. A. et Ojanotko, A. O. Progesterone Metabolism in Human Saliva in Vitro. *Journal of Steroid Biochemistry and Molecular Biology* **70**: 109 – 113, 1999
3. Lu, Yu-cai et al. Salivary Estradiol and Progesterone Levels in Conception and Nonconception Cycles in Women : Evaluation of a New Assay for Salivary Estradiol. *Fertility and Sterility* **71**: 863 – 868, 1999
4. Lu, Yu-cai et al. Direct Radioimmunoassay of Progesterone in Saliva. *Journal of Immunoassay* **18**: 149 – 163, 1997
5. Sumiala, S. et al. Salivary Progesterone Concentrations After Tubal Sterilization. *Obstet Gynecol* **88**: 792 – 796, 1996
6. Delfs, T. M. et al. 24-Hours Profiles of Salivary Progesterone *Fertil Steril* **62**: 960 – 966, 1994
7. Lipson, S. F. et P.T.Ellison. Reference Values for Luteal Progesterone Measured by a Salivary Radioimmunoassay. *Fertil Steril* **61**: 448 – 454, 1994
8. O'Rorke, A. et al. Development and Validation of a Monoclonal Antibody Enzyme Immunoassay for Measuring Progesterone in Saliva. *Clin Chem* **40**: 454 – 458, 1994
9. Wingfield, M et al. Follicular and Luteal Phase Salivary Progesterone Profiles in Women with Endometriosis and Infertility **8** : 21 – 25, 1994
10. Harris, B. et al. Cardiff Puerperal Mood and Hormone Study : 1. Saliva Steroid Hormone Profiles in Late Pregnancy and the Puerperium: Endocrine Factors and Parturition. *Horm Res.* **39**: 138 – 145, 1993
11. Finn, M. M. et al. The Frequency of Salivary Progesterone Sampling and the Diagnosis of Luteal Phase Insufficiency. *Gynecol Endocrinol* **6**: 127 – 134, 1992
12. Lipson, S. F. et P. T. Ellison. Normative Study of Age Variation in Salivary Progesterone Profiles. *J. biosoc. Sci.* **24**: 233 – 244, 1992
13. Vuorento, T. et I. Huhtaniemi. Daily Levels of Salivary Progesterone During Menstrual Cycle in Adolescent Girls. *Fertility and Sterility* **58**: 685 – 690, 1992
14. Li, T. C. et al. The Relation Between Daily Salivary Progesterone Profile and Endometrial Development in the Luteal Phase of Fertile and Infertile Women. *British Journal of Obstetrics and Gynaecology* **96**: 445 – 453, 1989
15. Meulenbergh, P.M.M. et Hofman, J. A. Salivary Progesterone Excellently Reflects Free and Total Progesterone in Plasma during Pregnancy. *Clin Chem* **35**: 168 – 172, 1989
16. Vuorento et al. Daily Measurements of Salivary Progesterone Reveal a High Rate of Anovulation in Healthy Students. *Scand J Clin Lab Invest* **49** : 395 – 401, 1989
17. Lenton E. A. et al. Measurement of Progesterone in Saliva : Assessment of the Normal Fertile Range Using Spontaneous Conception Cycles. *Clinical Endocrinology* **28**: 637 – 646, 1988
18. Luisi, M. et al. Radio-Immunoassay of Salivary Progesterone for Monitoring Ovarian Function in Female Infertility. *Ann. Biol clin.* **45**: 449 – 452, 1987