

MITOTIC ACTIVITY IN THE EPITHELIUM OF REPRODUCTIVE ORGANS OF PREGNANT MICE

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It is known that during pregnancy the hormone balance in female mammals undergoes significant changes. New organs, such as the corpus luteum and the placenta, appear in the organism. The periodic production of estrogens and of progesterone is replaced by a continuous production of these hormones. Chorial gonadotropins are produced in large amounts, the polactin of the hypophysis is produced towards the end of pregnancy. The mitotic activity in the epithelium of the vagina, uterus and mammary glands is regulated by the female sex hormones [2, 3, 4], and consequently the hormone changes which occur during pregnancy must have an effect on the proliferative processes in these organs.

We could find no relevant investigations on the uterine and vaginal epithelium in literature. The mitotic activity of the mammary gland epithelium during pregnancy has been studied in three publications [1, 5, 7] but this needs a further study.

The purpose of this work was to determine the mitotic activity in the epithelium of the vagina, uterus and mammary glands at different stages of pregnancy.

EXPERIMENTAL METHOD

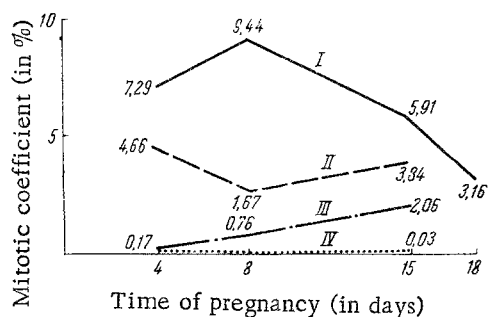
Mature female mice in a state of estrus, weighing 25 grams, were placed in a cage with males overnight. In the morning females with vaginal plugs were separated. Mice were killed on the 4th, 8th and 15th days of pregnancy and sometimes on the 18th day. Each group consisted of not less than 9 animals. The vagina, uterus and the second and third pectoral mammary glands were fixed in Zenker's fluid. The portion of the uterus dissected was between two fetal vesicles, or more often between the last fetal vesicle and the oviduct. The middle third of the vagina was taken for study. The mitotic activity in the epithelium of the mammary glands, vagina, uterus and uterine glands was determined by a method described previously [3].

The data obtained were subjected to statistical analysis by the method of Fisher-Student.

EXPERIMENTAL RESULTS

At all stages of pregnancy the mitotic activity in the epithelium of uterine glands was the lowest (Fig. 1). On the fourth and 15th days of pregnancy mitosis was seen only in one out of 10 and 11 animals respectively. On the 8th day of pregnancy there was no mitosis in any of the 10 animals examined.

In the epithelium lining the uterine lumen the mitotic activity throughout pregnancy also remained low, but somewhat higher than in the epithelium of uterine glands (figure). On the 4th day it constituted on the average 0.17%. On the 8th day 0.76% and on the 15th day 2.06%. The difference in mitotic activity between the 4th and the 8th days was not statistically significant ($P = 0.06$). The increase in mitotic activity on the 15th day of pregnancy as compared with that on the 8th day was statistically significant ($P = 0.0001$).



Mitotic activity in the epithelium of mammary glands (I), vagina (II), uterus (III) and uterine glands (IV) at different periods of pregnancy in mice.

In the epithelium of the uterus and the uterine glands of non-pregnant mice the maximal mitotic activity reached 12-16% (bordering between meta-estrus and diestrus). This indicated a sharp decrease of mitotic activity during pregnancy; this decrease was most pronounced in the epithelium of uterine glands.

The mitotic activity in the vaginal epithelium during pregnancy was considerably higher than that in the uterine epithelium (figure). Thus, on the 4th day of pregnancy it constituted on the average 4.66%, on the 8th day it fell to 1.67% and on the 15th day rose again to 3.84%. The differences were statistically significant ($P = 0.002$). During pregnancy the mitotic activity in the vaginal epithelium was considerably lower than that in non-pregnant mice. On the 4th and the 15th day of pregnancy it was similar to that in non-pregnant mice in the period of meta-estrus, and approximately 4 times lower than that during the period of pro-estrus.

The mitotic activity in the epithelium of mammary glands during pregnancy was high, and especially so during the first half of the pregnancy (figure). On the 4th day of pregnancy it constituted on the average 7.29% and on the 8th day 9.4%. However, the difference between these two values was not significantly statistical ($P = 0.03$). On the 15th day of pregnancy the mitotic activity fell to 5.91%. This fall was statistically significant ($P = 0.005$). On the 18th day there was noted a further statistically significant fall of this value to 3.16% ($P = 0.001$).

It must be noted that in our previous publication [5] the mitotic activity in the mammary gland epithelium in mice on the 18th day of pregnancy was too high, it seemed that at the end of pregnancy it rose instead of falling. This is not in accordance with the published results [7, 8]. The results of this investigation, which was conducted on a larger number of animals and with improved techniques, have shown that the mitotic activity in the mammary glands of pregnant mice remains high for a long time as compared with that in non-pregnant mice, reaching its maximum at half-term and then gradually decreasing until the termination of pregnancy.

In our previous studies [4] we have made certain conclusions regarding the effect of female sex hormones on the epithelium of reproductive organs and on the activity of the epithelium in different organs. It has been shown that estrogens and progesterone stimulate the mitotic activity in the epithelium of reproductive organs. However, when these steroid hormones are injected either in large doses or for a prolonged period of time, an opposite effect takes place, i.e., the mitotic activity becomes inhibited. Another relationship, which has been confirmed in all the experiments, consists of the fact that in order to maintain the mitotic activity in the epithelium of various non-reproductive organs, a different level of the estrogen stimulus is necessary. The highest estrogen concentration is necessary for the mammary glands, somewhat lower for the vaginal epithelium, and lower still for the uterine epithelium. The lowest estrogen concentrations are necessary for the stimulation of mitoses in the epithelium of uterine glands. The lower the threshold concentration of estrogens stimulating mitoses in a given organ, the earlier occurs an inhibition of the mitotic activity in that organ when the estrogen concentration is increased.

In the light of the above-mentioned relationships we will now attempt to evaluate the results obtained in the present investigation.

It is logical to assume that during pregnancy, which is characterized by an increase and a continuous production of estrogens and of progesterone, the effect of these hormones on the mitotic activity in the epithelium of the uterus, and the vagina would be inhibitory. This has been confirmed in our experiments. As was to be expected, the degree of the inhibitory effect is progressively lower along the following series: uterine gland epithelium, uterine epithelium, vaginal epithelium. In the mammary gland epithelium, which requires relatively higher concentrations of the ovarian steroid hormones for the stimulation of the mitotic activity, the latter was the highest.

While in non-pregnant mice during corresponding stages of the estrus cycle the mitotic activity in the uterine and vaginal epithelium exceeds many times that in the mammary glands epithelium, the reverse is true during pregnancy.

The lowering of the mitotic activity in the mammary gland epithelium during the second half of the period of pregnancy is apparently related to the effect of prolactin and the beginning of the secretory function of the

epithelium. Our investigations and those of Lazarev [6] have shown that prolactin is not to be regarded as a hormone which stimulates the proliferation of the mammary gland epithelium, as is commonly stated in foreign literature [9, 10].

At this stage of our studies we do not have all the necessary data in order to analyse the changes in the curves for mitotic activity of the vaginal and uterine epithelium at different stages of pregnancy.

The regular changes in the intensity of the proliferative processes in reproductive organs are of paramount importance in the continued existence of a species. Due to this the proliferative processes in reproductive organs of female mammals, as well as spermatogenesis and oogenesis, are apparently subjected to a specific hormonal control.

SUMMARY

The authors determined the mitotic activity of the epithelium of the mammary glands, vagina, uterus and the uterine glands at various periods of pregnancy in female albino mice. As shown, mitotic activity of the mammary glands epithelium exhibited a marked rise during the first half of pregnancy and declined smoothly during the second half. Mitotic activity of the epithelium of the vagina, uterus and the uterine glands decreased. Reduction of mitosis is mostly marked in epithelium of the uterine glands, less in the uterine epithelium and even less in the vaginal epithelium. A different level of mitotic activity in the epithelium of reproductive organs during pregnancy is explained by different sensitivity of the epithelium these organs to mitosis-stimulating and depressing action of female sex hormones.

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