Granulocytes in the endometrium of post-partum women

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Summary. Endometrial samples of women at various stages of gonadal activity after parturition were examined for the presence and numbers of endometrial granulocytes. Although samples at all the stages contained significant numbers of the granulocytes (i.e. >7/high-power field), the 100% values for late-proliferative and adaptation hyperplasia were significantly higher than the values for the resting (81-8%), early (82-4%) and mid- (87-9%) proliferative and secretory (83-3%) phases. We suggest that this correlates with the suggestion that the granulocytes constitute a receptor system for oestrogens.

Introduction

A possible explanation of the mechanism of menstruation, suggested by Dallenbach-Hellweg (1964, 1974), suggested that the reticulum network of the human endometrium is disintegrated by relaxin which is released by so-called endometrial granulocytes or K (Kornchenzellen) cells under progestagenic influence. Our previous investigation (van Bogaert, 1975) was unable to confirm this view.

The exact origin, identity and function of endometrial granulocytes is still debatable. The cells were suggested as resulting from the differentiation of endometrial stroma (Dallenbach-Hellweg, 1974), connective tissue or smooth muscle cells (Bjersing & Borglin, 1964). Others supported the view that the granulocytes are wandering cells (Andrews, 1951; Bjersing & Borglin, 1964). These granulocytes have also been described in ectopic endometrium (Hughesdon, 1976), in the myometrium (Bjersing & Borglin, 1962) and in the Fallopian tubes (van Bogaert, Maldague & Abarca, 1978a; van Bogaert, Maldague & Staquet, 1978b) as well as in the glandular epithelium of the human endometrium (van Bogaert et al., 1978a). While some authors (Brosens, Robertson & Van Assche, 1974; Dallenbach-Hellweg, 1974; Hellweg, Félin & Ober, 1960; Kazazz, 1972, 1975) have stressed the need for a progestagenic influence, others have shown a positive relationship between the increase of endometrial granulocytes and an oestrogenic influence in rodents (Baker, Bergman & Paul, 1967; Bjersing & Borglin, 1964) and women (Bjersing, 1977; van Bogaert, 1975). In order to substantiate our previous findings in anovulatory cycles (van Bogaert, 1975), we have now studied the appearance and increase of endometrial granulocytes after childbirth, i.e. after a prolonged period of ovarian refractoriness followed by a gradual recovery of gonadal activity.
Materials and Methods

Endometrial biopsies were collected from 93 non-lactating post-partum women, who agreed to take part in a study on the appearance of the first ovulation after childbirth (van Bogaert, De Ridder & Van der Pas, 1977). The biopsies were obtained during the 6th week after parturition. No oestrogen estimations were carried out, because plasma levels do not reflect accurately the actual tissue concentration (Batra, Grundsell & Sjöberg, 1977).

The specimens were fixed in Bouin’s fluid, subjected to routine histological procedures and stained with haemalum and eosin. Normal proliferative patterns were classified as early, mid- and late stages, as recommended by Noyes, Hertz & Rock (1960). Another type of proliferative pattern consisted of the so-called adaptation hyperplasia, which is an irregular developing proliferation with cystic dilatation, supposed to ensue when an oestrogenic stimulus lasts abnormally (Dallenbach-Hellweg, 1974). Secretory changes were also recorded using the criteria of Noyes et al. (1960). Finally, specimens devoid of proliferative or secretory changes were labelled ‘resting-phase pattern’, as defined by Beuselinck (1967), i.e. a poorly developed mucosa with scarce glands lined by a single layer of epithelial cells with elliptic nuclei and no mitotic activity.

The endometrial granulocytes have been described previously (Hamperl & Hellweg, 1958; Kazzaz, 1972, 1975; Dallenbach-Hellweg, 1974; van Bogaert, 1975). Although phloxine-tartrazine demonstrates them nicely, the granulocytes are easily recognizable even when routinely stained with haemalum and eosin. The nucleus is small and may be round, reniform or irregular; chromatin content is dark. Bright red, coarse refractile cytoplasmic granules are usually located in front of a nuclear recess.

The presence of at least 7 endometrial granulocytes per high-power field (10 × 40 magnification) was considered significant (Kazzaz, 1972; van Bogaert, 1975).

Results

The distribution of the three basic endometrial patterns is reported in Table 1. Very few of the patients had luteal changes, and <25% of the subjects were still in a period of low ovarian activity; the majority of women had proliferative patterns. The granulocyte counts are shown in Table 1.

<table>
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<tr>
<th>Table 1. Relationship between endometrial pattern and the occurrence of a significant number of endometrial granulocytes in 93 women</th>
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<td>Endometrial pattern</td>
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<tr>
<td>Resting phase</td>
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<td>Proliferative phase</td>
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<td>Adaptation hyperplasia</td>
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<td>Secretory phase</td>
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A significant number occurred in most of the specimens, regardless of the endometrial pattern. The only luteal-phase endometrium which did not contain any granulocytes showed signs of chronic endometritis.
A paired $t$ test of the significant results revealed that the data of late proliferation and adaptation hyperplasia were significantly different ($P < 0.005$). There was no significant difference between rest phase and early proliferation or between early and mid-proliferation (paired $t$ test).

**Discussion**

Three basic problems are related to the occurrence and significance of endometrial granulocytes: the identity of the cell, the nature and function of its cytoplasmic granules, and the influence of hormones.

The identity of this cell has been investigated in various mammals. In the spayed mouse (Baker et al., 1967) and rat (Bjersing & Borglin, 1964) eosinophilic granulocytes appear in the uterus after administration of oestrogens. Furthermore, the peroxidase activity in the mouse uterus is proportional to the number of eosinophilic granulocytes (Baker et al., 1967). In the mouse at least, therefore they appear to stem from or be identical with true eosinophilic leukocytes. “Leucocyte-like cells” in heifer oviducts were considered by Nellor (1968) as atypical lymphocytes or lymphoblasts. In human genital tract tissues leucocyte-like cells or endometrial granulocytes have been observed (Andrews, 1951; Bjersing & Borglin, 1962; van Bogaert et al., 1978a, b), and considered to be wandering cells (Andrews, 1951). The absence of peroxidase activity in these granulocytes (Hamperl & Hellweg, 1958) militates against them being eosinophilic leukocytes, although the possibility that these cells are related to and perhaps represent transformed eosinophilic leucocytes cannot be dismissed. Peroxidase activity is normally absent or low in lymphocytes (Bloom & Fawcett, 1975), but the absence of eosinophilic cytoplasmic granules in lymphocytes suggests that the endometrial granulocytes are distinct entities. The hypothesis of a macrophagic cell (Salm, 1962) must also be considered. Padykula & Campbell (1976) have shown that raising oestrogen levels increases the number of macrophages in the rat endometrium and that these macrophages are involved in the cyclic stromal renewal of the uterus, by means of their phagolysoosomal system and lysosomal enzymes. An hormone-dependent acid phosphatase content has been reported by Baron & Esterly (1975) in human endometrial mononuclear cells. The cells were described as having an appearance similar to lymphocytes, monocytes and histiocytes; but unfortunately, the magnification of the micrographs is too low to determine whether the cells are endometrial granulocytes. Human (More, Armstrong, Carty & McSeveney, 1974) and rhesus monkey (Cardell, Hisaw & Dawson, 1969) endometrial granulocytes have been studied by electron microscopy. The discoid cristal, a characteristic of blood eosinophils (Bloom & Fawcett, 1975), was not identified; the granules had the appearance of lyosomes or dilated cisternae of the Golgi-complex or of the endoplasmic reticulum.

The basic function of endometrial granulocytes, according to Dallenbach-Hellweg (1964, 1974), would be the destruction of the endometrial reticulum network by the release of relaxin from the granules. However, the hypothesis of the existence of an “eosinophil receptor system” for oestrogens involved in the early oestrogen action in the uterus (Bjersing, 1977) is more attractive than the relaxin hypothesis. The endometrial “eosinophils” are labelled by tritiated oestrogens, but not by progesterone (Tchernitchin, Tsang, Stumpf & Gurpide, 1973; Tchernitchin, 1974). However, this might be interpreted either as a preliminary to hydrolysis of the steroid, or as the result of a metabolic stimulation (Brökelman, 1969). If endometrial granulocytes act as a local oestrogen receptor, their gradually increasing number under progressively rising oestrogen levels is in agreement with the autoregulatory effect of oestrogens on their own receptor (Jänne, Kontula & Vihko, 1975). The increased numbers of endometrial granulocytes in the luteal phase reported by Dallenbach-Hellweg (1974) might possibly be the result of the oestrogenic stimulus brought about by the luteal peak of oestradiol reported by Gurpide, Tseng & Gusberg (1977).
Since no clear link could be demonstrated between the percentage of granulocyte-like cells and inflammation (van Bogaert et al., 1978b), but the present study shows some increase in relation to proliferative changes of the endometrium, we support the view of a possible role for endometrial granulocytes in the action of oestrogens in the female genital tract.

References


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