Introductory Remarks:

These images are from clinical trial endometrial samples collected by catheter biopsy. They are presented with a ***low power section view*** with selected higher power images to show detailed morphology. To put the biopsy cassette structure in perspective, a "composite" ***low power section view*** has a 2-millimeter bar and a 2 millimeter circle since this is the size of the sampling "pore" used in catheter biopsy. Review of the images will confirm that many fragments are about 2 mm wide. These samples were collected at 13 weeks of therapy and it is fair to say that regardless of dose (5 mg or 10 mg) the result was a similar degree and range of morphology. It should be noted that there are common features of this compound class (as summarized by a panel of expert endometrial pathologists, including this author), but the degree to which each of these features is expressed is variable within the individual subjects regardless of dosages. Because these compounds have a partial progestational effect (thus a partial anti-estrogenic effect), a degree of estrogenic effect will often co-exist, likely due to each subject's estrogen levels as well as their tissues' sensitivity to each hormone. In any case, these compounds often create a confusing pattern of coexistent "estrogen dominant" and "progesterone dominant" changes in both glands and stroma. You should review the pamphlet information provided for ESMYA™ in addition to this information. In subjects on both doses of ESMYA™ only about 60% showed these changes after 3 months of therapy; thus these changes can be absent or very subtle.

This author and others involved in analyzing these cases have seen both short (3-6 months) and very prolonged (1-2 years) therapy with other PRMs. Most subjects on prolonged therapy had excellent response and control of bleeding, but a subset of subjects developed thickened endometrium requiring biopsy. In all cases, the benign thickening was an extreme expression of these changes without premalignant change. Additionally the vast majority of all subjects treated (regardless of duration) reverted to a normal cycling endometrium after cessation of therapy, with only a few requiring mechanical curettage to remove persistent vascularized stroma. After a consensus conference of an international panel of endometrial experts at the US National Institutes of Health, the term ***PRM Associated Endometrial Change (PAEC)*** was used to describe the spectrum of features seen in a series of cases from subjects in several clinical trials on a variety of doses of several PRMs. The marked endometrial thickening seen in some subjects on prolonged therapy did result in the subsequent approach of intermittent therapy with treatment limited to 3-month intervals (followed by a similar duration without therapy to allow the resumption of menstrual cycles to slough the endometrial tissue).

It is clear to all who have seen these changes that the patterns are not commonly seen in routine clinical material. However, after seeing this effect for several years, this author began to recognize a rare "routine" clinical patient with a history of abnormal uterine bleeding that had a similar pattern. In most cases, but not all, the treating clinicians confirmed that a progestational agent was used to try to stop the bleeding.

Thus when seen, these unusual features will be confusing and may result in a diagnosis of another condition that shares some features in common with PAEC. Therefore these example show how these samples can be confused with more common benign conditions including disordered proliferative endometrium, endometrial polyps and simple endometrial hyperplasia.

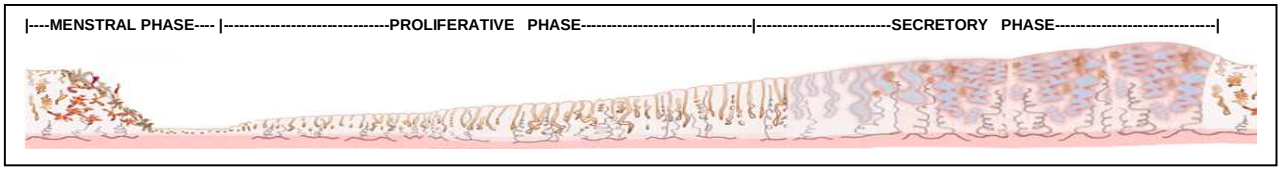
To give the users of this endometrial educational set a complete experience, the ***low power section view*** images are **composited** with the high power images so the changes seen at higher power can be related to the overall biopsy. Additional ***low power section view*** images with **annotation** are provided to allow an appreciation of the frequency and degree of cystic glands and the overall variability in gland density, size and shape. Similarly, these images will aid in understanding the distribution and character of the stromal changes, which are subtle at low power.

It is suggested that users consider how variable these changes can be between subjects. ***What the user will not see in these images is how PAEC develops in the uterine cavity and how prolonged exposure can result in an exaggerated thickening.*** *Thus, the following illustrations compare and contrast what happens in the conditions that can be confused with PAEC and what the endometrium might look like intact and with prolonged exposure (*E=estrogen and P=progesterone).

ILLUSTRATIONS OF ENDOMETRIAL GROWTH:

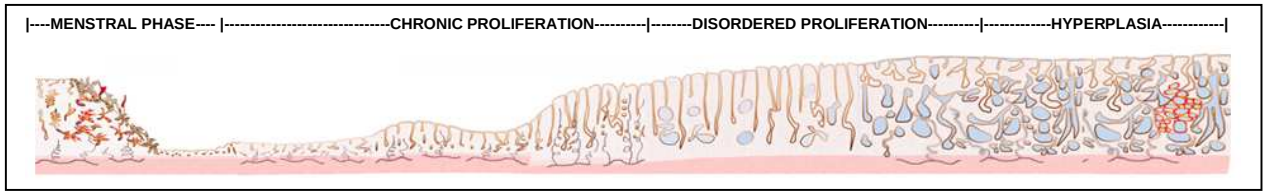
Normal cycle = E → E+P → Withdrawal → Menses = Normal Cycles

With regular shedding, the endometrium is "reset".



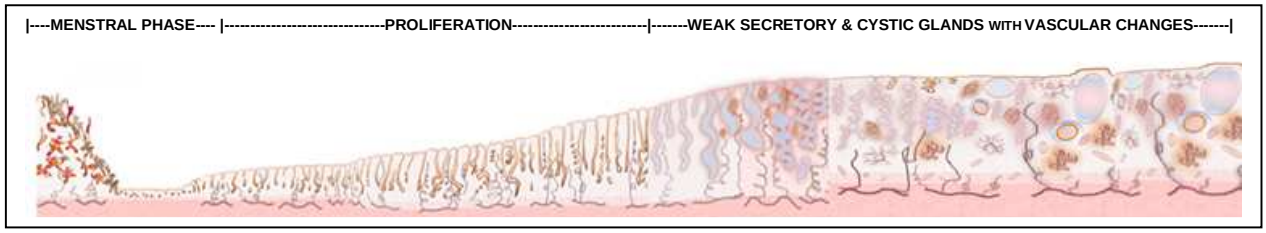
Perimenopause = E only → Chronic Proliferation = Disordered Proliferation or Hyperplasia

With continued growth, the endometrium overgrows.



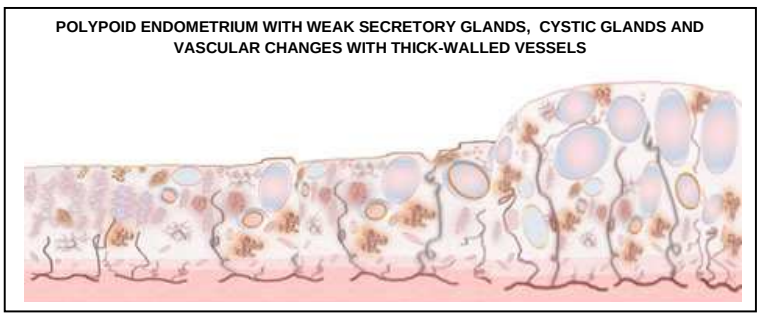
PAEC = E + PRM (Weak Combined Effect) → Anovulation
Discontinue PRM → Return to cycling if physiologic

With weak dual stimulation for 3 months, the endometrium in some subjects can form cystic glands and unusual proliferating vessels.



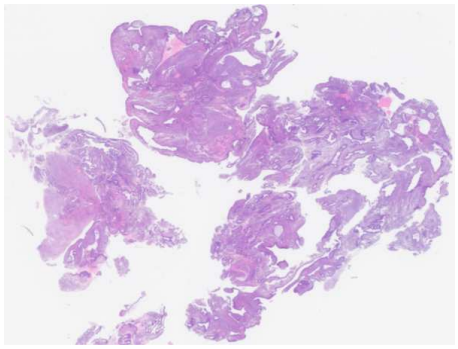
Chronic PAEC → Anovulation → 6 mo. → 12 mo. → Discontinue PRM → Return to cycling if physiologic but may require physical curettage to remove larger vessels

With chronic weak dual stimulation, the endometrium can form a polypoid growth from markedly cystic glands and unusual proliferating, often thick walled vessels.



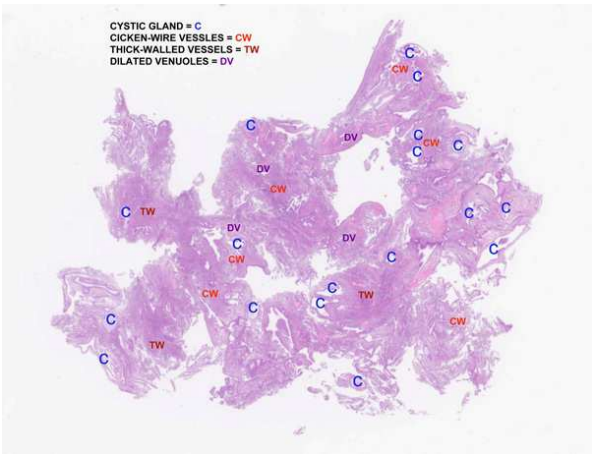
Consider reviewing each of the PAEC cases starting with the **low power section view** to see how PAEC can have cystic glands with variable density, shape and size. In stromal dominant areas, there is more likely stroma with proliferation of vascular elements.

Low Power Section View

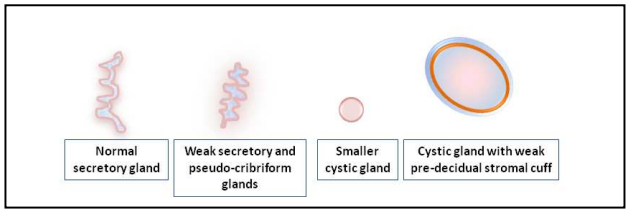


Next review the **"features" low power view** images to see the frequency of the various PAEC changes illustrated.

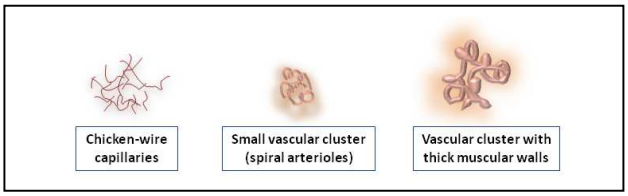
"Features" Low Power View



Next review the intermediate to high power images by using the "composite" view where you can click on the frames of higher power images to display. Notice the range of epithelial differentiation (secretory, inactive or weakly proliferative) and glandular morphology (cystic, accordion-like or tubular). In some cases a stromal reaction forms a "cuff" around a few cystic glands.

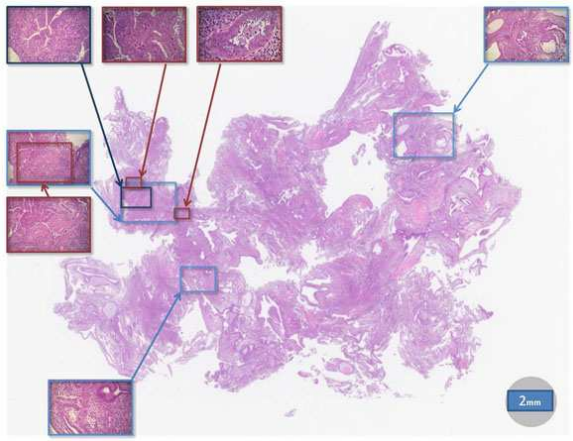


Less frequently you will have areas of stromal/vascular growth patterns (dilated venous channels, chicken-wire capillary proliferations, "spiral arteriole-like" vascular clusters and larger thick-walled vessels).



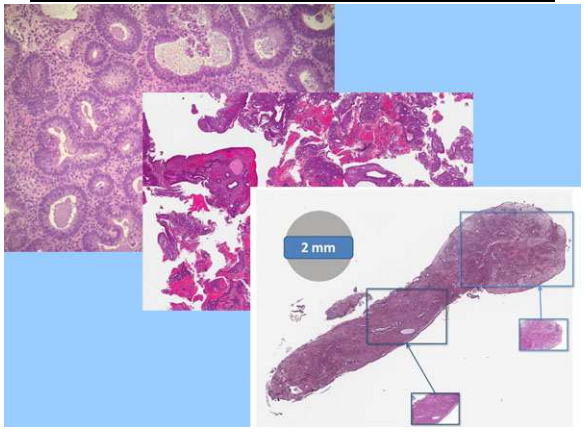
What you should appreciate is that although each case differs in degrees of change, almost all express most of the changes.

"Composite" Low Power View – "click to view"



Finally, review the illustrations on how PAEC can share features with lesions that are common in clinical material and will be in the differential diagnosis. Several examples of these diagnostic patterns from non-clinical trials samples are provided for reference.

"Hyperplasia, Disordered Proliferation and Polyps"



A distinctive feature of PAEC is weakly secretory patterns (accordion-like secretory glands with vascular proliferations) ***coexistent with features expected in unopposed estrogen effect*** (cystic glands, disordered glands, dilated venous channels).

Then users compare the changes of PAEC with some examples of benign endometrial polyps, disordered proliferation and simple hyperplasia. It should be obvious at the lowest power that PAEC cases can appear similar to disordered proliferation due the cystic glands. However the epithelium on higher power is not as proliferative in PAEC as in cases of disordered proliferation.

In cases of PAEC with thick-walled vessels, fragmented samples can have similarities to a small polyp. This is because thick-walled vessels between two cystic glands can be extracted as a column of stroma with a central vessel and lined on two sides by epithelium. This is additionally problematic because catheter biopsies may not remove much of a large polyp and since a catheter aspirates out 2 mm "cores" of tissue, the fragments of relatively normal endometrium can mimic the shape of a tiny polyp.

Simple hyperplasia can be a concern in areas of PAEC where there are relative crowded clusters of smaller tubular glands with areas of cystic glands and dilated venuoles. The inactive to weakly secretory epithelium with little or no mitoses and limited number of crowded glands in PAEC will aid in the differential diagnosis.

The following case descriptions are provided to aid in your review of this condition. These are not in any specific order so table below shows how these cases illustrate this condition. This author considers PAEC changes are more characteristic when the progestational features dominate over the estrogenic features, which makes the complex of findings more characteristic.

- **Characteristic PAEC: 1, 3, 5, 10**
- **PAEC with estrogenic features: 2, 7**
- **PAEC with limited features: 4, 6, 7, 8, 9, 12**
- **PAEC in scant samples: 11, 13**

CASE DESCRIPTIONS

CASE 1: PAEC – dose of 5mg for 13weeks
This case is quite typical of PAEC with mainly progestational features. Scattered moderate to large cystic glands are lined by mainly weakly to moderately secretory epithelium with some accordian-shaped glands. This case also has multiple areas of vascular change with both the chicken-wire capillary proliferations and thick-walled arterioles.

CASE 2: PAEC – dose of 5mg for 13weeks
This case is not as typical of PAEC as **CASE 1** because it seems to have mainly estrogenic features. Scattered moderate to large cystic glands are lined by mainly inactive to weakly proliferative. This case has several areas of vascular change, but dilated venules are most common. This case would likely be called disordered proliferation by most pathologists.

CASE 3: PAEC – dose of 5mg for 13weeks
This case is similar to **CASE 1** with scattered moderate to large cystic glands lined by mainly weakly to moderately secretory epithelium with some accordian-shaped glands. This case also has several areas of vascular change with both the chicken-wire capillary proliferations and thick-walled arterioles. This case also has some ciliated metaplasia.

CASE 4: PAEC - dose of 10mg for 13weeks
This case has more limited features with scattered moderate to large cystic glands lined by mainly weakly secretory epithelium. Only rare vascular changes (chicken-wire capillary proliferations) are present.

CASE 5: PAEC - dose of 10mg for 13weeks
This case is different than **CASE 1** in terms of the cystic glands, which are limited, but the epithelium is mainly weakly to moderately secretory epithelium with some accordian-shaped glands. A couple cystic glands are surrounded by a circumferencial cuff of spindle shaped stromal cells, a distinctive but occasional finding in PAEC. This case also has numerous areas of vascular change with both dilated venules and clusters of small to larger thick-walled arterioles.

CASE 6: PAEC - dose of 5mg for 13weeks
This case is similar to **CASE 4**. It has limited features with scattered moderate to large cystic glands lined by mainly inactive epithelium. Only rare vascular changes (chicken-wire capillary proliferations) are present.

CASE 7: PAEC - dose of 5mg for 13weeks

This is another case with more limited features and very disrupted tissue pattern. There are only scattered intact moderate sized cystic glands lined by mainly weakly inactive epithelium with areas of apoptosis. Only rare thick-walled arterioles are present.

CASE 8: PAEC - dose of 5mg for 13weeks

This is another case with more limited features. There are numerous cystic glands centrally in the sample, lined by mainly inactive to weakly secretory epithelium. A few areas with chicken-wire capillaries and a dilated venule are present.

CASE 9: PAEC - dose of 5mg for 13weeks

This is another case with more limited features. There are scattered cystic glands, lined by mainly inactive to weakly secretory epithelium. A few areas with chicken-wire capillaries and some small cystic glands with stromal cuffs lined by metaplastic epithelium are present.

CASE 10: PAEC - dose of 5mg for 13weeks

This is a case with more progestational features. There are numerous moderate sized cystic glands, a few with stromal cuffs and lined by metaplastic epithelium. The epithelium is mainly inactive to weakly secretory and there are a few areas with accordian-shaped glands. In the stroma there are a multiple areas with thick-walled vessels.

CASE 11: PAEC - dose of 5mg for 13weeks

This is a case with scant tissue, but there are numerous moderate sized cystic glands. The epithelium is mainly weakly secretory and there are a few areas with accordian-shaped glands. In the stroma there is only one area with chicken-wire capillaries.

CASE 12: PAEC - dose of 10mg for 13weeks

This case has more limited features with scattered moderate to large cystic glands lined by mainly weakly secretory epithelium. In areas the glands are crowded. No definite vascular changes are present.

CASE 13: PAEC - dose of 5mg for 13weeks

This is a case with very scant tissue, but there are intact cystic glands present. The epithelium is inactive to weakly secretory. In the stroma there are areas of chicken-wire capillaries, thick-walled vessels and a dilated venule.

The Comparison Cases: Examples of disordered proliferation, hyperplasia and endometrial polyps are provided for comparison. These come from routine clinical work at a reference laboratory with a high volume of gynecologic pathology samples. Although these are typical of many cases, they are not meant to provide the full spectrum of changes that might be seen in these conditions.