The Arias-Stella Reaction: Facts and Fancies Four Decades After

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Summary: Since its first description more than four decades ago, the atypical endometrial change associated with chorionic tissue effect has been widely confirmed in the literature. However, errors and inaccuracies in text books and other publications often occur. This review clarifies some of these misconceptions and presents a summary of new data on the histologic and immunohistochemical characteristics of the change. A brief discussion on the pathogenesis and biologic significance of the alteration is included. **Key Words:** Arias-Stella Reaction– Atypical endometrium–Endometrial change.

Forty-six years ago, I bravely knocked on the door of Dr. Fred W. Stewart's office. He was the Chairman of the Pathology Department of Memorial Hospital for Cancer in New York City. I had been a fellow in Pathology for 2 months and finally I was reaching my main goal at this famous hospital**:** to consult with the Pathologist then considered one of the foremost in tumors diagnosis in the United States on two cases that I had seen while a medical student back home in Perú and that had been diagnosed by my seniors as forms of early endometrial cancer. However, given the uniqueness of the changes, and because one case was associated with an intramural chorioadenoma destruens and the other with an ectopic pregnancy, I thought that this was some form of an endometrial reaction resulting from the chorionic hormonal stimulation.

I expected that Dr. Stewart would send me to the bibliographic references, which I had searched in vain for more than 2 years. His answer, left me dumbfounded: “I don’t know! Javier -you have something to study”. The rest of the story is not for this occasion, but I have recreated the background, development and immediate corollary in the form of a story for medical students, which will soon published (1).

The initial publication appeared in the *Archives of Pathology in 1954* (2) and it is interesting today to recall the very first reaction in the literature. Dr. Emil Novak, the author of the textbook *Gynecological and Obstetric Pathology*, which during my youth was considered to be the Bible, was among other things the editor of the *Survey of Obstetrics and Gynecology*. He made the following comments when my article was published (1,3):

“This is an interesting study, but one upon which it would be difficult to comment unless one had made similar studies, which no one appears to have done…”

“While I have examined many thousands of endometria including many containing trophoblastic rest, after miscarriage hydatidiform mole, chorioadenoma destruens, or choriocarcinoma, I cannot say that I have noted the particular cellular changes which Arias-Stella has described.”

“To show how foolish an objection this last statement is, I may say also that I examined many ovaries before 1921, and that not a few of them showed endometrium, but I did not appreciate the importance and the frequency of endometriosis until after Sampson’s first publication in 1921, nor did anyone else.”

“Similar confessions could be made about other pathologic, or for that matter, clinical entities, for which we are all now on the alert.”

Dr. Novak was not a formal pathologist, as we understand it today. He practiced clinical gynecology in Baltimore and because he had helped Dr. Cullen, who had organized the gynecologic pathology laboratory at Johns Hopkins, he was now its director -a common situation in the early years of surgical pathology. It is therefore not surprising that pathologists of his time viewed him with reservations and that his gynecology peers did not let him admit patients to Johns Hopkins (4).

Looking back, his sincere, humble, and wise comment, as well as the magnitude and quality of his contributions to science, leave no doubt that he knew very well the trade of pathology. He deserves the recognition that is owed to him by our community of pathologists.

Since my first report, the original description has been widely confirmed and mentioned in the literature (references in [5]), although errors and inaccuracies occur in some textbooks and publications. Common misconceptions are to consider the change, exclusively, a hypersecretory phenomenon, or a nonspecific regressive alteration due to fetal death, trophoblastic disturbance, or decreased hormonal levels (6,7). Some have, equivocally, stated that "the occurrence of mitosis in carcinoma and its absence in the Arias-Stella reaction is important for the differential diagnosis" (8). This article summarizes the most recent contributions to the literature, both mine and those of other investigators, and attempts to clarify the pathogenesis.

DEFINITION

The main characteristic of the reaction is cellular enlargement, mainly of the nucleus, to double or many times normal size. Without the presence of nuclear

enlargement, the phenomenon cannot be diagnosed. Hypertrophied nuclei can show an ovoid or round shape with granular or vesicular viable chromatin, an irregular outline and a hyperchromatic appearance or a compact, pyknotic pattern (Fig. 1).

Mazur, et al. (9) have used the term "optically clear nuclei" to describe an aspect of the alteration, which is characterized by centronuclear vacuolization, resulting from the replacement of the chromatin by a net of fine filaments. Another morphological variant is the occurrence of intranuclear cytoplasmic invaginations–pseudoinclusions. One or another of these alterations of the macronuclei has been confused with herpetic endometritis (10) (Fig. 2).

Usually the alterations are focal; they involve a group of glands or only some part of them. Occasionally, they can be quite extensive or "florid". It is important to emphasize that the presence of hypersecretory glands alone does not constitute the phenomenon. The presence of hypersecretory foci in the gestational endometrium was described by Opitz at the beginning of the last century (11).

HISTOLOGIC VARIANTS

Even though at the beginning we described two forms of the alteration (2), and later on we recognized a third form (12), accumulated experience allows us to distinguish the five histologic variants: 1) minimal atypia; 2) early secretory pattern; 3) secretory or hypersecretory pattern; 4) regenerative, proliferative, or nonsecretory pattern; 5) monstrous cell pattern. The variants are a function of comparison with the phases of normal endometrium and degree of atypicality.

Minimal Atypia

Minimal atypia is the pattern usually seen at the beginning of gestation. The nuclear enlargement is minimal and occurs in limited foci (Fig. 3). Because the decidual reaction is absent or is not conspicuous in the early stages of gestation, the diagnosis of minimal atypia may have a special practical meaning. This is what we have found in some women who have been evaluated for infertility (Table 1).

Early Secretory Pattern

The early secretory pattern resembles normal early secretory endometrium at day 17-18 of the menstrual cycle. In these cases, nuclear enlargement is marked and the endometrial cells show subnuclear or subnuclear and supranuclear vacuoles (Fig. 4). The nuclei are centrally located. The cells are frequently arranged in a palisading fashion, with the nuclei at the same level. The affected glands can show intraluminal papillary projections.

Since the original description, my colleagues and I pointed out the occurrence of mitosis in the phenomenon and, more recently, that they can be normal and abnormal (Tables 2 and 3) (13). It is precisely in this model of presentation that they are more frequent and abnormal (Fig. 5). It is understandable why this histologic variant is the one most likely to be confused with adenocarcinoma. In my experience this model has been common in cases of uterine abortion and ectopic pregnancy.

Secretory or Hypersecretory Pattern

Secretory or hypersecretory pattern is the classically recognized form of reaction. The glandular cells display intense and diffuse cytoplasmic vacuolization, which

predominates as a distinct morphologic feature. The enlarged and hyperchromatic nuclei are usually pyknotic (Fig. 6). Focally, one can distinguish cells that are less vacuolated and show a dense cytoplasm (Fig. 7), which is due to their different histochemical composition.

The comparative epithelial immunohistochemical profile of the normal functional endometrium with the atypical change has demonstrated that the epithelial membrane antigen (EMA) and the CK7 give an intense and homogenous reaction in both normal endometrium and the Arias-Stella Reaction (ASR) (Table 4). The vacuolization that characterizes the hipersecretory pattern of the atypical change highlights the increased membranous localization of staining with these markers, creating a "chicken-wire" pattern (Fig. 8).

Ultrastructural studies done by de Brux (14), Thasher and Richart (15), and Salazar and Burgess (16) have shown few organelles and sparse particles that resemble granules of ribonucleic acid in the clear cells, and a conspicuous Golgi apparatus, vesicles of endoplasmic reticulum, numerous mitochondrial crests, and Palade grains in the dark cells. One detail that has been found repeatedly is the presence of parallel rows of rough endoplasmic reticulum (Fig. 9), which is a characteristic described in various tumors of Mullerian origin. This variant is found mainly in uterine abortions.

Regenerative, Proliferative or Nonsecretory Pattern

In the regenerative, proliferative or nonsecretory pattern there is usually no evidence of secretory activity, or it is minimal in the glandular cells. The enlarged nuclei display a vesicular configuration or a granular chromatin with a well-

delineated nuclear membrane. The glands are similar to those observed in the proliferative or regenerative endometrium (Fig. 10). I have found this variant in cases of hydatidiform mole, choriocarcinoma, ectopic pregnancy, and uterine abortion.

Monstrous Cell Pattern

In rare cases, the monstrous cell pattern, which is usually focal, affects the whole endometrium. The histologic section is dominated by the presence of giant and bizarre nuclei, which involve all the cells in the glands. (Fig. 11). The atypical nuclei show a dense, homogeneous chromatin and, frequently, pseudoinclusions. This model of atypia originates problems of histologic interpretation. In our experience, my colleagues and I have found it in 0.5% of florid alterations.

LOCATION OF THE CHANGE

Even though the alteration was originally described in the functional endometrium, which is more sensitive to hormonal effects, today we have proved that when the stimulation is intense, the change can also occur in less sensitive basal regions. From the beginning my colleagues and I pointed out that not only the glandular but also the covering epithelium could be affected and that the alteration occurred in both the endocervix and the tubal epithelium (17,18).

In recent years our observations and those of many authors have demonstrated that under the stimulation of chorionic tissue –gestational condition or trophoblastic proliferation– the change can be observed in many territories and lesions, including endometriosis (peritoneum, subcutaneous, umbilical) (19); endocervical polyps

(20,21); vaginal adenosis (22,23); germinal inclusion cysts (ovary) (24); para-ovarian and para-tubaric cysts (25); and mucinous cystoadenoma (26).

It is interesting that Albukerk and Berlin (27) have described nuclear changes that resemble the Arias-Stella reaction in the luteal cyst of the gestation and that Clement and Scully (28) described similar atypias in luteinized follicular cysts of gestation and puerperium.

CHRONOLOGY BETWEEN THE PRESENCE OF CHORIONIC TISSUE AND ARIAS-STELLA REACTION

Two questions that must be answered is: How early in the gestation and how late after delivery does the endometrial atypia occur? Fortunately, studies by Holmes and Lyle (29) and Dahlerup and Jorgenson (30) and the review by Oertel (31) of material that Hertig examined to elucidate the early stages of human embryogenesis have answered these questions.

PRACTICAL VALUE OF THE ARIAS-STELLA REACTION

The accumulated information shows that in certain clinical situations, finding the Arias-Stella reaction can be specially significant, as an isolated histological sign, or as part of a group of changes, in making a diagnosis. According to our experience and that of other investigators, the change has been of histologic diagnostic significance for recognizing early uterine pregnancy (12), ectopic pregnancy (32,33), trophoblastic tumors (indirect evidence), and postabortion or postpartum metropathies. Histologic differential diagnosis can be problematic in the following

conditions: metastatic Adenocarcinoma versus foci of endometriosis in pregnancy (5); endometrial Adenocarcinoma versus florid Arias-Stella reaction (8,34); Adenocarcinoma versus Arias-Stella reaction infallopian tube (35); and atypical mucinous cystoadenomas, germinal inclusion cysts, and paratubal cysts in pregnancy and puerperium (26).

It is interesting to note that in recent years there has been special emphasis in finding the change in the endocervix and recognizing atypical cells in Papanicolau smears.

Schneider (36) has found the alteration in the endocervix in 17 of 191 uteri, which were removed during gestation, proving that the proximal segment of the cervical canal was the most frequent location. Cove (37) and Rhatigan (38) have described cases of endocervical Arias-Stella reaction that caused confusion with premalignant or malignant conditions. The same problem was encountered by Cariani and Guderian (39) and McCormick and Menaci-Williams (40) in endocervical polyps with Arias-Stella reaction. McCormick and Menaci-Williams reported the occurrence of tripolar mitoses, confirming our finding of abnormal mitosis in the reaction.

In my experience the endocervical Arias-Stella reaction, whether in normal mucosa or polyps, frequently shows the monstrous cell pattern (Fig. 12), and gives rise to the differential diagnosis with neoplastic processes. The gestational state is often ignored and it is the debate over the nature of the cervical lesion that reveals the pregnancy conditions.

Hilrich and Hipke (41) were the first to show that atypical endometrial cells could appear in Papanicolau smears. Since then, many observers have verified the same finding (42,43). Albukerk and Gnecco (44) pointed out that the abnormal cells in the Papanicolau smear could be confused with neoplastic cytology and that they are found more frequently in cases of ectopic pregnancy, in which the lack of a uterine-placental barrier makes it easier for desquamation and passage of the cells to the vaginal fundus.

In recent years, Pisharodi and Jovanoska (45), Mulvany et al. (46), Yates et al. (47), and Michael and Esfahani (48), have reported observations showing that the abnormal cytology due to Arias-Stella reaction, of the endometrium or the endocervix, in pregnant women, originates problems of cytologic interpretation. We have verified this occurrence in Figure 13 illustrates one such cases.

Recently, because of similar experiences, Benoit and Kiny (49) recommended including Arias-Stella reaction cells among the atypical glandular cells to be considered in Papanicolau smears from women in pregnancy or puerperium.

PATHOGENESIS

An understanding of the mechanism of enlargement of the nucleus and the unique histologic reaction is essential. Three basic facts must first be mentioned:

1. Nuclear hypertrophy is due to an increase in the contents of DNA. The finding of double Barr corpuscle by Dahlerup and Jorgensen (30), the karyometric studies of Chiara (50) and the Fulgen microspectrocytophotometric

determinations of Wagner and Richart (51) early established that nuclei enlarge because of polyploidism and that aneuploidism does not exist.

2. The aspect of the histological reaction is evidence of occurrence of proliferative and secretory stimuli, acting simultaneously.
3. The change can be present in normal physiologic conditions, including term pregnancy (52), postpartum (30), therapeutic abortion (51,53), and early normal pregnancy (12).

The glandular changes in the endometrium are a consequence of the action of estrogens and progesterone. The former stimulate cellular proliferation and the latter stimulate secretory activity (54,55).

With this background, since my first observations I postulated that estrogen and progesterone are, in some way, involved in the pathogenesis of the change. Early on, using human chorionic hormones and estrogens, I was able to obtain, experimentally, proliferative and secretory activity simultaneously in normal rats, and, using estrogens and progesterones in castrated rats to induce the same changes. In these experiments I also observed focal nuclear enlargement (56,57). In 1966, experimental studies by Dr. Dallenbach (58) confirmed these findings.

Since then I have performed some experiments on humans. Administering a combination of estrogens and progesterone to postmenopausal women who were going to have hysterectomies, I was able to induce, after 1 month of treatment in some of them, endometrial changes that were focal and suggestive of the Arias-Stella reaction (5).

In another experiment, due to the action of high doses of estradiol and hydroxyprogesterone, I was able to produce focal changes that were similar to the endometrial atypia (5).

Conversely, since the observations of Dockerty et al. (59) and Azzopardi and Zayid (60) it has been recognized that therapy with synthetic progesterone-estrogen can induce endometrial changes of the Arias-Stella reaction type. Recently, Huettner and Gersell (61) have reported the induction of what they consider Arias-Stella reaction in eight postmenopausal or perimenopausal women who received treatment with progestational hormones.

Since the classic studies by Good and Moyer on the *Macaca mulata*, it has been shown that by adjusting the doses of estrogens and progesterone, it is possible to obtain, experimentally, secretory or proliferative endometrial responses (62).

All of the above supports, my proposition that the pathogenesis of the phenomenon depends on a balance of these two hormonal effects.

How do we continue exploring along these lines of thought?

Today, we know more about the hormonal mechanisms. In the case of female hormones, we know that there are cellular receptors, that estrogens stimulate the synthesis of DNA, RNA and proteins, by a chain reaction mechanism, and that progesterone reduces the synthesis of DNA and RNA (63-65). We know the cell cycle and we can identify, in tissues, some of the factors of intermediation (Fig. 14). Therefore, there is room for further investigation. We have investigated, using immunohistochemical methods, the presence of estrogen and progesterone receptors and markers of cellular proliferation, Ki-67 and proliferating cell nuclear antigen

(PCNA), in 20 cases of florid Arias –Stella reaction, compared with findings in the normal phases of the endometrium and in endometrial hyperplasia.

In the absence of an accepted standardized method for evaluation immunohistochemical reactions, we have adopted the method recently proposed by Allred et al. (66) for scoring the immunostaining signal for estrogen receptors and progesterone receptors in breast cancer. In each case the best stained fields were chosen for the evaluation. In the Arias-Stella reaction we found that the estrogen receptors and the progesterone receptors (Table 5) had a total score less than in the normal functional phases and in hyperplasia.

Score for the cellular proliferation markers (Table 6) were also less than in the proliferative phase, but nevertheless, higher than those of the normal secretory phase. To summarize, the results of the immunohistochemical study shows that:

1. Estrogen and progesterone receptors (Fig. 15) are present in the foci of the endometrial atypia.
2. The positive reaction for the proliferative factors, such as antigen Ki-67 and PCNA (Fig. 16), is also present in these foci. It should be stressed that estrogen receptors, progesterone receptors, Ki67, and PCNA have been found present in enlarged typical Arias-Stella reaction cells (Fig. 17).

These results are, in essence, in agreement with the immunohistochemical study recently reported by Doss et al. (67).

Steroid hormones can act by either of two ways: the nongenomic mechanism or the classical, or genomic, form (68). The nongenomic effects are fast -occurring in seconds or minutes- are highly specific, do not require nuclear receptors, and do not induce RNA or protein synthesis.

The nature of the Arias-Stella reaction corresponds to that of a long duration process -days, weeks or months- and as we have demonstrated above, it is accompanied by the involvement of receptors and growth factors that lead to DNA synthesis. Therefore, the evidence supports the view that the steroid action in the Arias-Stella reaction follows, basically, the classic genomic path.

All of these findings suggest that the pathogenesis is related to the effects of estrogen and progesterone acting simultaneously, but as highlighted in the immunohistochemical study, with a higher estrogen weighting than found in the normal secretory phase. This imbalance would be a determining factor, through intermediary mechanisms, to induce the increased synthesis of DNA that leads to the occurrence of polyploidism.

It is interesting to note that recently, the late Mexican Professor Márquez-Monter et al. (69) compared the macronuclei of the Arias-Stella reaction to those seen in megaloblastic anemia, suggesting that in some cases, they result from a change in the cellular cycle by mutation of the “check point” bound to the mitogenic factor, which determines the continuation of DNA synthesis. It cannot be ruled out if in these hormonal interactions there is a role for factors directly derived from chorionic tissue.

CELL BIOLOGY

How DO WE locate this alteration from the perspective of cell biology? The characteristics that we have highlighted reveal and adaptive, controllable, and reversible cellular reaction induced by hormonal actions that comprise proliferative and antagonistic stimuli. Because the cells that modify are mature cells that are not replaced, it is not a form of metaplasia.

If the variability in the shape and size of the cells, the pleomorphism and hyperchromasia, and the presence of atypical mitosis could suggest a dysplasia, the DNA polyploid contents, absence of aneuploidy, and absence of progression would not correspond with this process (Fig. 18, Table 7) (70).

At this level of knowledge, the accumulated information leads us to think of a singular form of transdifferentiation: conversion of a differentiated cell into another differentiated cell. In this case it would be called "atypical transdifferentiation (Fig. 18).

This atypical transdifferentiation, which is characterized by polyploidism, absence of aneuploidism, and absence of progression of lesions, and which is found in tissues that are sensitive to antagonistic hormonal factors, would also occur in other areas, including atypical cells in seminal vesicles (71,72); monstrous cellsin epididymis and duct deferens (73,74); atypical cells in lutein cysts in pregnancy (27); atypical cells in luteinized follicle cyst of pregnancy and puerperium (28); and bizarre, benign cells in tyroid (dyshormogenetic goiter) and other endocrine organs (75).

CONCLUSION

All of the above information allows us to conclude that the description of endometrial atypia, associated with the effect of the chorionic tissue, has had until now, practical significance in gynecologic and obstetric pathology. Owing to its peculiar relation to the synthesis of DNA, it is possible that elucidating the pathogenesis of the changes will have even greater importance in the scope of cell biology. This is the challenge for future generations.