

## CERVICAL CYTOLOGY IN FOLIC ACID DEFICIENCY OF PREGNANCY

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Pregnancy offers a great strain on the body, for a two celled embryo becomes a two billion celled foetus. There is rapid proliferation of various maternal tissues and haemopoietic system, and the normal replacement of body tissue has to be continued. In consequence there is an exceptional demand for folic acid because of role of folates in cellular reproduction and tissue growth. In a country like ours where nutrition is substandard there is a possibility of folic acid deficiency in its period of maximum demands resulting in a number of complications like antepartum haemorrhage and toxæmia of pregnancy. (Stone, 1967, 1968).

Folic acid deficiency results in defective cellular growth. This is reflected in tissues which grow rapidly resulting in cytological abnormalities not only in bone marrow but also in other actively proliferating cells. The present study consists of an analysis of 80 cases with 20 controls in which morphological alterations in cervical cytology were studied with a view to establish its diagnostic sensitivity in

the assessment of folic acid deficiency. It was also studied to see if such changes would revert back to normal after therapy.

The cases were selected from antenatal patients attending the out-patients department and admitted in wards of S. N. Hospital, Agra. The cases were divided into two main groups:

The cervical smears were stained by Papanicolaou's stain and the following changes were studied.

(a) Abnormal cells were usually isolated but occasionally clusters were seen.

(b) They were predominantly oval or round with well defined cell borders.

(c) Multinucleated cells—upto four nuclei were seen in single cell, (Fig. 1).

(d) Cytoplasmic vacuolization was another striking feature. Single and multiple vacuoles were present. These vacuoles were large in contrast to the small peripheral vacuoles observed in cell degeneration, (Fig. 2).

(e) Cells were grossly enlarged, the nuclear cellular ratios were increased as compared to normal squames but were less than those of the cells originating from severe dysplasia, (Fig. 3).

(f) Nuclei were round or oval and nuclear borders were distinct.

This study was supplemented by a

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complete blood examination, peripheral blood smear and bone marrow study. Since biological tests to find out folic acid deficiency and FIGLU test require detailed laboratory procedures simple tests of polymorph lobe average was utilized to establish the folic acid deficiency. A previous investigation established that polymorph lobe count above 3.62 is diagnostic of folic acid deficiency in pregnancy, (David, *et al*, 1968).

After establishing folic acid deficiency the patients were given folic acid 15 mg. daily and after varying intervals blood smear and cervical smears were repeated to see remission of changes.

#### Observations

As evident from Table I, 70% cases in control group had 0-3% cells with two

or more nuclei while in the study group, 40% cases had smears with 3-6% abnormal cells, 35% smears had 7-9% abnormal cells and even more than 16% abnormal cells were seen in some. In contrast none of the smears in control group showed more than 6% abnormal cells.

#### Vacuolation

As evident from Table II most of the smears in the control group had less than 2% vacuolated cells, while the percentage of vacuolated cells were significantly high in the study group.

#### Big Cell with Hyperchromatic Nuclei

Cells with bigger size and hyperchromatic nuclei were seen in greater number in the folate deficient group than in the non-folate deficient group. 22.5% had

TABLE I  
Showing Incidence of Bi- and Multi Nucleated Cells

Cell percentage	Control Group		Study Group	
	No. of cases	Percentage	No. of cases	Percentage
0-3	14	70	7	8.75
4-6	6	30	32	40.0
7-9	-	-	28	35.0
10-12	-	-	10	12.5
13-15	-	-	2	2.50
More than 16	-	-	1	1.25
Total	20	100	80	100.0

TABLE II  
Showing Incidence of Vacuolation in Cervical Cells

Cell Percentage	Study Group		Control Group	
	No. of cases	Percentage	No. of cases	Percentage
0-2	21	26.25	18	90.00
3-4	35	43.75	2	10.00
5-6	15	18.75	-	-
7-8	7	8.75	-	-
9 or more	2	2.50	-	-
Total	80	100.00	20	100.00



TABLE III  
Showing Incidence of Big Cells with Hyperchromatic Nuclei in Cervical Cells

Cell Percentage	Study Group		Control Group	
	No. of cases	Percentage	No. of cases	Percentage
0-2	18	22.50	17	85.00
3-4	36	45.00	3	15.00
5-6	19	23.75	-	-
7-8	4	5.0	-	-
9 or more	3	3.75	-	-
Total	80	100.00	20	100.00

smears with 0 to 2% cells having hyperchromatic nuclei, while 45% had 3 to 4% cells having hyperchromatic nuclei and 23.75% cases had 5 to 6% cells with big hyperchromatic nuclei, while none in the control group had more than 4% cells with hyperchromatic nuclei.

#### Remission of changes after Folic Acid Therapy

In the study group, 56 cases were followed after folic acid therapy. Out of these, 39 cases (72.57%) showed remission of polymorph lobe average below the

average norm, while 48 cases showed remission of cervical cytology indicating that the changes in cervical cell appear much earlier than in the polymorph lobe average.

Table V shows remission of changes in blood and cervical cells after different periods of therapy. Depending upon the severity of deficiency the percentage of abnormal cervical cells diminished after 15 mg. folic acid corresponding to diminution of polymorph lobe average below the normal.

TABLE IV  
Showing Remission of Changes After Folic Acid Therapy

No. of cases followed-up	Remission of polymorph lobe average		Remission of cervical cytology	
	No. of cases	Percentage	No. of cases	Percentage
56	39	72.57	48	87.5

TABLE V  
Showing Remission of Changes After Different Duration of Therapy

Duration of therapy in days	Polymorph lobe average		BL + Multinucleated cells		Vacuolated cells		Big cells with hyperch. nuclei	
	Before	After	Before	After	Before	After	Before	After
days	3.91	3.40	6.43	2.26	3.43	1.14	3.71	0.71
8-14 "	3.80	3.30	7.33	2.00	4.11	1.73	4.98	1.32
15-21 "	3.85	3.01	9.40	3.25	3.75	1.40	4.80	1.50
22-28 "	3.94	3.60	6.15	3.85	3.43	1.86	5.23	1.41

### Discussion

Folic acid is of paramount importance in desoxyribonucleic acid synthesis which gives cells its life. A deficiency of this is believed to produce a variety of clinical manifestations. According to Beck (1964) deficiency of folic acid results in impaired and therefore inadequate DNA synthesis. Consequently cells accumulate with a complement of DNA that is insufficient for replication. This may lead to asynchronous maturation in which nuclear development slows while cytoplasmic growth and function proceeds. The morphologic expression of this biochemical defect is reflected in rapidly proliferating cells that is blood cells in the bone marrow. In the present study the effect of folic acid deficiency is studied on cervical epithelium which is in a state of rapid proliferation during pregnancy.

The present study reveals morphological alteration in cervical cytology of patients with folic acid deficiency during pregnancy. As shown in Tables I, II and III the percentage of cells showing vacuolation bi, tri and multinucleated cells and big cell with hyperchromatic nuclei was much higher in the folate deficient group than in the control indicating that these are the manifestations of folic acid deficiency. It is confirmatory with the work of Van Niekerk (1962, 1966) and David *et al*, (1969). All the cases after establishing folic acid deficiency were given 15 mg folic acid daily and followed at variable intervals. 87.5% cases showed

reversion to normal cervical morphology, and this reversion to normal started as early as 7 days after therapy, thus indicating that changes in cervical cytology revert to normal before any evident blood change.

### Summary

As with other epithelia of the body that of the female genital tract undergoes morphologic alterations, prompt evidence of it appearing in the exfoliated cellular material. There are definite morphological alterations in cervical cells in pregnant women having folic acid deficiency which are reversed by folic acid therapy in matter of days implicating folate deficiency in the pathogenesis of these changes. Assuming the diagnostic sensitivity of cervical cytology is approximately equal to that of polymorph lobe average cervical cytology preparations might be expected to reflect early development of folate deficiency.

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*See Figs. on Art Paper III*