during pregnancy is therefore necessary in order to eliminate the serious foetal consequences which emergency obstetrical interventions cannot avoid, even if they are correctly carried out.

SUMMARY

The authors carried out a detailed analysis of 345 obstetric interventions in a group fo 2277 deliveries. The strong emphasis on prophylactic measures led to a high percentage of cesarean sections. Only one fourth of the obstetrics interventions was carried out under emergency conditions. More extensive observation during pregnancy and delivery would eliminate many foetal deaths which even obstetrical procedures cannot avoid.

Translated by Samil Pabyrn Foundation

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The pathological and clinical significance of high degree cervical dysplasia: an inquiry on 235 cases

by
G. D. MONTANARI and G. R. MONTANARI

The present evaluation of the clinical and pathological significance of high degree cervical dysplasia is based on colposcopic, cytological and, where indicated, histological examination of 52,843 patients, either hospitalized or out-patients of the Istituto di Clinica Ostetrica e Ginecologica of the University of Padua from the 1st March 1964 to the 31st December 1970.

We assessed as dysplastic all changes of differentiation of the squamous epithelial lining of the uterine cervix other than carcinomas *in situ*. These variations may be high degree or low degree; these terms are to be preferred to suspected or non-suspected dysplasia. In fact they are confined to describing the histological appearance of the lesion without expressing any opinion regarding prognosis ([1]).

High degree dysplasia is a rare lesion. We saw only 235 cases out 52,843 patients examined. The incidence is therefore of the order of 0.44%.

The age at which high degree dysplasia of the cervix is most often observed is between 35 and 40 years. The age distribution of the 235 consecutive cases studied by us is given in Fig. 1.

The cause of high degree cervical dysplasia is not known. There are, however,

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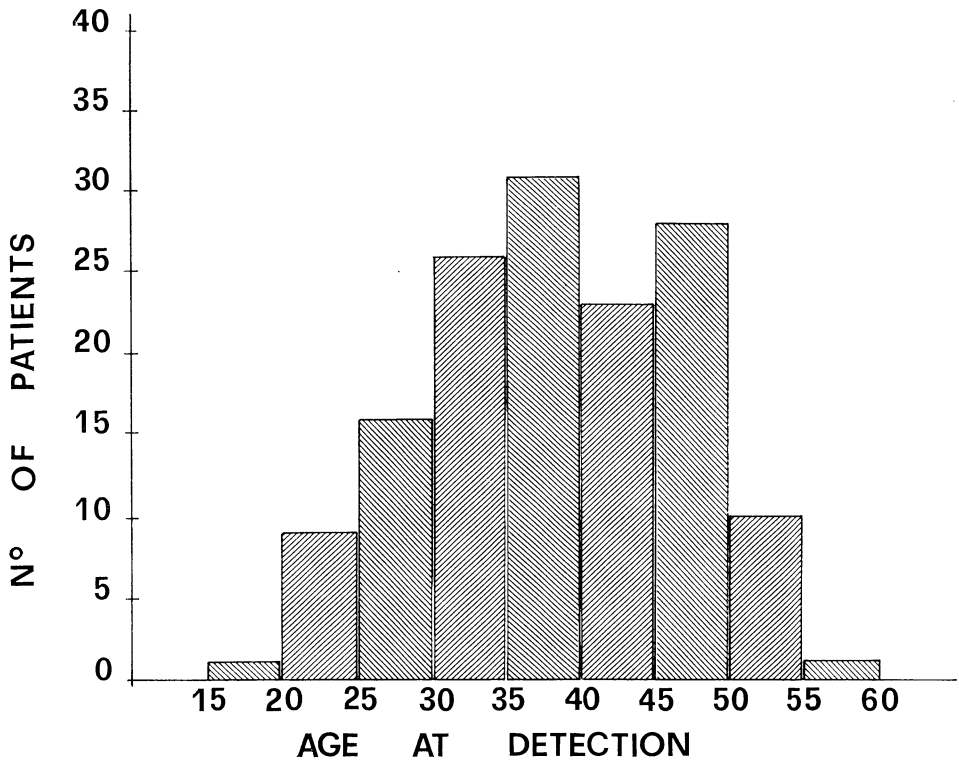

FIG. 1 - The age distribution of high degree cervical dysplasia.

some factors which appear to be significant. As regards parity (Fig. 2) a striking feature is the relatively high number of cases of dysplasia among women who have never been pregnant. Moreover, the incidence of colposcopic leucoplakia is higher in patients affected by primary sterility than in non-sterile nulligravidae or patients who have had one or more pregnancies (Fig. 3). Histologically, colposcopic leucoplakia in sterile patients is found to be low degree dysplasia in 81% of cases; high degree dysplasia in 5% of cases; and simple cervical dystrophy in the remaining 14%. Much of the dysplasic pathology in sterile patients is associated with raised or persistent estrogen production ([2]).

The present study is retrospective. It was not, therefore, possible to establish at what age the patients had their first intercourse. An indirect evaluation of the « precocity in sexual relations » factor can be obtained by taking into account the age when the patient married. In Fig. 4 can be seen a higher incidence of high degree dysplasia among patients who married at an early age.

HISTOGENESIS AND MORPHOLOGY

In order to try and clarify the nature of high degree dysplasia, it is necessary to refer to its histogenesis ([3]). That is to say that it is necessary to evaluate the mechanism of epidermization of the ectopias and similar disorders. As is well

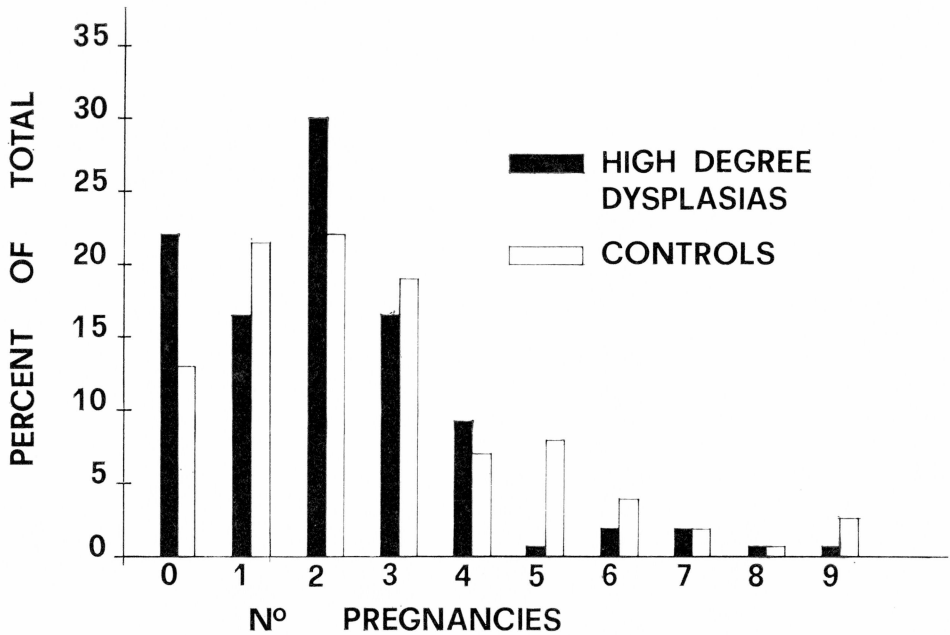

FIG. 2 - Parity in patients with high degree dysplasia.

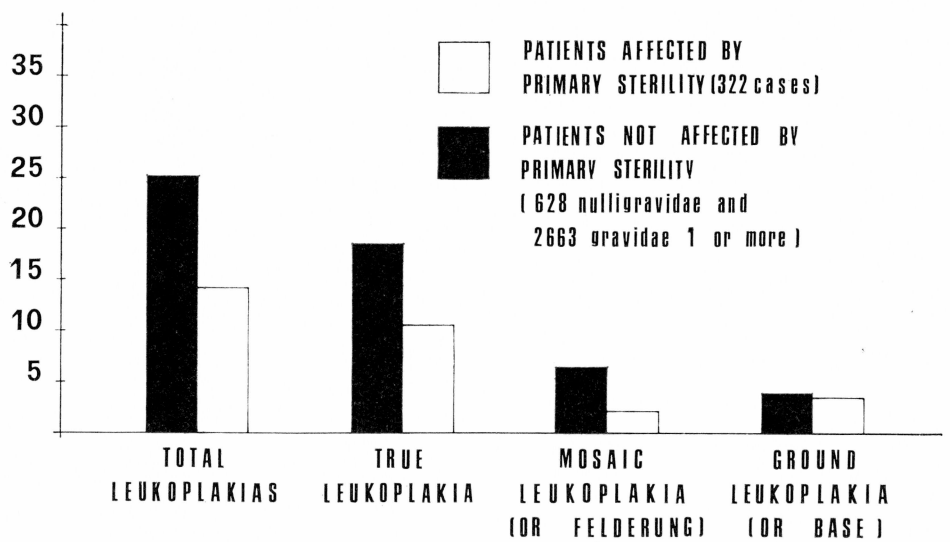

FIG. 3 - Incidence of colposcopic cervical leucoplakia in patients affected by primary sterility and in controls.

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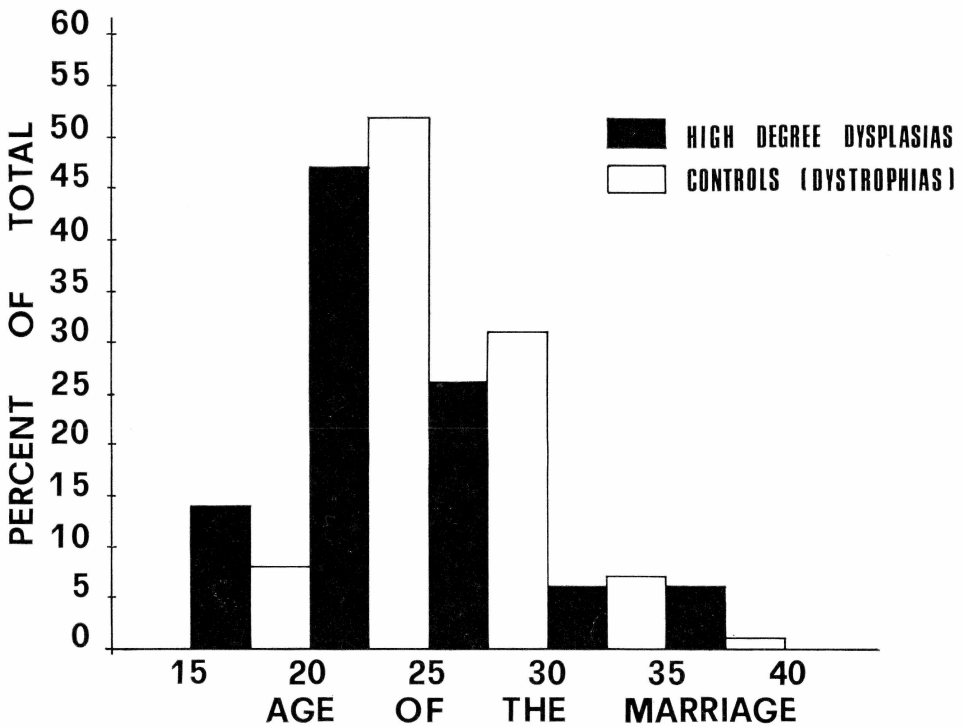

FIG. 4 - Age of the marriage in patients affected by high degree dysplasia and in controls.

known, such epidermization takes place also through processes of epidermoid metaplasia which have as their starting point the undifferentiated and ambivalent subcylindrical reserve cell. By this, we refer to the capacity which this cell possesses for differentiating itself either into a squamous direction or in a cylindrical direction. The reserve cells, as they multiply, become more and more evident and arrange themselves in more and more numerous strata beneath the cylindrical epithelium. Subsequently, spaces and bridges occur among these cells; that is to say that a process of differentiation has begun which becomes more and more marked and is also accompanied by signs of maturation and cell growth. With the beginning of stratification a flat polystratified epithelium is created which differs little from the normal. There are four factors which condition the formation of a metaplastic epithelium:

a) differentiation, characterized by the appearance of spaces and bridges between the cells;

b) growth, which involves the ordered succession from the bottom upwards of cells of progressively increasing volume;

c) stratification, which orders the less deep cells into strata which are more and more horizontal, i.e. parallel to the basal membrane; and finally

d) maturation, which consists of the concomitant evolutive modification of the nucleus and cytoplasm. This modification has its point of arrival the superficial cell with acidophile cytoplasma and pyknotic nucleus.

When, during development of the metaplastic process, one or more of these factors does not intervene, intervenes out of turn or in a discordant manner, an abnormal structure is formed, that is to say, a dysplastic epithelium appears.

What are the causes which are able to alter the metaplastic process and thus bring about its evolution in a dysplastic direction? The one most frequently quoted is hormonal imbalance, which can occur in two main forms: the first of these is the protracted absence of the rhythmic alternation of estrogen and progesterone incretion. It is a continual transgression of the law of sexual rhythm, which for the uterus represents an antitumoral defence mechanism ([4]). The other form of hormonal imbalance which may come into play in the genesis of dyplasia is that which is observed both in pregnancy and also in women under prolonged therapy with estrogen-progesterone combinations. Raised or persistent production of estrogens can seldom give rise to hyperplasia of the reserve cells which if it comes up against epidermoid differentiation will give rise to low degree dysplasia. If, on the other hand, such epidermoid differentiation develops slowly and tentatively, the syndrome of high degree dysplasia may occur. Progesterone, by blocking the maturative action of the estrogens, promotes atypical evolution of the processes of epidermization of ectopias with hyperplasia of the deeper layers, and makes it impossible for the nuclei to retract normally. Thus pregnancy and conditions where the taking of drugs imitates the hormonal substrate act on the cervical epithelium like a trigger, giving rise to a pathological tendency, in the same way as other latent lesions, such as diabetes, are manifested. The second cause which can induce the metaplastic process to evolve in a dysplastic manner is irritation and inflammation. This often occurs in conjunction with the previous cause and is above all linked with cervico-vaginal trichomoniasis.

In order to undestand the morphology of dysplastic lesions and grade the intensity of such epithelial reactions we must again have recourse to their histogenesis. Repeating what we have already said, we shall talk of low degree dysplasia when the results of histological examination show the following: differentiation, even if more or less slow to develop, finally occurs; cell growth is complete or almost so; stratification, although delayed, appears in the end; only maturation is completely changed. What characterizes high degree dysplasia, on the other hand, is that its architecture, as opposed to that of low degree dysplasia, is very dissimilar to the architecture of the normal polystratified squamous epithelium. Differentiation is in fact slow or scarcely indicated. Growth is completely stagnant at the basal cell stage. Stratification is therefore absent, delayed or scarcely begun. Finally maturation appears seriously changed, with marked nuclear hypertrophy associated with clear impossibility of retraction of the nucleus.

In the area of high degree dysplasia there is one possibility: hyperplasia of the reserve cells where these cells pile up when still undifferentiated and immature. It is a rare lesion which is sometimes seen in pregnancy and it is important because it may be mistaken for a carcinoma *in situ*.

The natural evolution of high degree dysplasia cannot be foreseen. About 50% of cases of high grade dysplasia persist unchanged even for very long periods of time. A considerable proportion of cases (about 40%) become attenuated or regress through renewal of the maturation and differentiation processes which control it in low degree dysplasia. The effect of biopsy or the desquamative action of local tetracycline therapies can also contribute to the regression. The remaining 10% of high degree dysplasias progress towards cancer *in situ* or, rather more rarely, towards invasive cancer (fig. 5).

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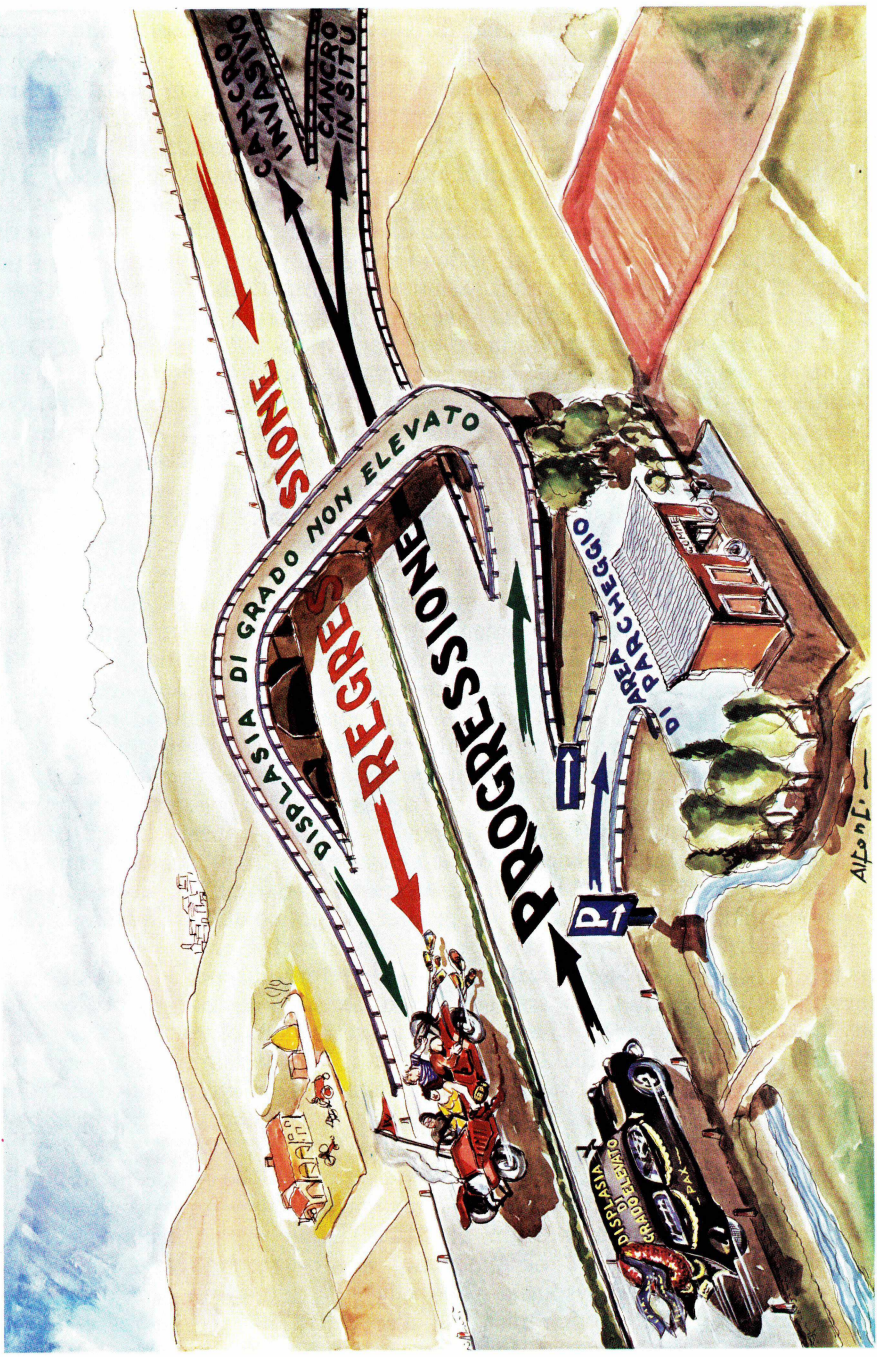

DIAGNOSIS

In studying the colposcopic pictures observed in cases of high degree dysplasia it is seen that the more marked the images of atypical epithelium with a tendency to cornification, the more readily will biopsy reveal the lesion in question. In order of frequency they are: leucoplakia in relief; mosaic in relief especially if of large tessera; base of leucoplakia of coarse pattern and with considerable distance between the capillaries; finally it is often seen in cases of atypical transformation. This last term, « atypical transformation » (or transformation which does not present the features appertaining to the normal type) is a rather vague term and therefore often used wrongly. To clarify this picture it is useful to refer to what we usually define as *functional* colposcopy. By histochemical artifices this often enables us to establish precisely the region of atypical transformation where cellular activity is greatest, and therefore the point where it will be most useful to perform the guided biopsy (Lugol solution, Toluidine blue, Acridine orange, tetracyline, Nile blue sulphate etc.).

High degree dysplasia is an epithelium with cellular growth arrested at the stage of the basal elements and with serious disturbance of maturation and differentiation. In the *smear,* therefore, practically only external basal or small intermediate markedly dyskaryotic cells are to be found. Therefore we shall find bluish cells of basal type with black nuclei derived more from superficial necrobiosis than from true and proper maturative processes. Differential diagnosis from low degree dysplasia is based on the fact that it desquamates abnormal cells belonging to all the layers. Hyperplasia of the reserve cells exfoliate into strips of loosely syncytian character composed of undifferentiated monomorph cells with slightly atypical nuclei and with a normal nucleocytoplasm ratio.

Our own experience and that of others in the matter of the cytochemistry of dysplasia has been mainly disappointing. This is true of research with succinodehydrogenase, diphosphopyridinenucleotide-diaphorase ([5]) and lipids evidences in fluorescence with 3:4-benzopyrene ([6]) and with Nile blue sulphate ([7]). Rather unsatisfactory also were the results with biochemical methods based on the assay of betaglycuronidase and oxidative enzymes in the vaginal content ([8]).

Table 1. *Colposcopy * in 235 cases of dysplasia at an high degree ***

1. Leucoplachia	34%	Flat	6%
		Raised	28%
2. Mosaic (Pavement)	24%	Flat	8%
		Raised	16%
3. Atypical transformation	24%	Simple	10%
		Papillary	14%
4. Basis of leucoplachia	24%		
5. True erosion	6%		
6. Iodo-negative transformation with clear-cut edges	5%		
7. Uncharacteristic red area	3%		

* Only those colposcopic tables are indicated where the guided biopsy has been carried out.

** In 12% of the cases the dysplasia was seated exclusively endocervically and was thus lacking in colposcopic evidence.

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Table 2. *Functional colposcopy in cervical displasia*

1. Schiller's reagent[1] (local)	Ordinary light	Iodo-negative with clear-cut edges
5. Toulidine blue[2] (local)	Ordinary light	Dark blue colorization
6. TTC[3] (local)	Ordinary light	Violet-red colorization
7. Tetracycline[4] (in a general way)	Fluorescent	Brilliant yellow fluorescence
8. Quinacrine[5] (in a general way)	Fluorescent	Palish green fluorescence
9. Acridine orange[6] (local)	Fluorescent	Brilliant yellow fluorescence
10. Nile blue sulphate[7] (local)	Fluorescent	Reddish yellow fluorescence (inconstant)

1. Metallic iodine 10 gr; potassium iodide 20 gr; distilled water to 500 gr.
2. Toluidine blue watery solution at 1%.
3. Solution of 1 per cent of 2, 3, 5 chloride of triphenyltetrazolium in phosphate buffer of pH 7, 2 containing 7 mg. methylene blue to 1000 ml and 1 mg per ml sodium succinate.
4. Tetracycline chloridrate or dimethylchlortetracycline chloridrate 250 mg. four times a day by os for 1 - 5 days.
5. Quinachrine dichloride (atebrin) in a single oral dose of 500 mg. Examine after about 24 hours.
6. Acridine orange in watery solution to 0,01 per cent in phosphate buffer at pH 4, 5.
7. Nile blue sulphate watery solution to 0,1 per cent.

TREATMENT

At the level of the uterine cervix a true and proper « *gradus ad cancrum* » ranging from absolute benignity to absolute malignity is easier to imagine than to demonstrate. No possibility exists therefore of identifying which high grade dysplasia will become a cancer and which will heal. Perhaps some high grade dysplasias are of such a high grade that they are already carcinoma *in situ*. Other high grade dysplasias are only waiting to be cured.

In view of this uncertain evolution, it is better to assume an active policy: conization when there are reproductive problems; hysterectomy where such problems do not exist and particularly if any other gynaecological abnormality is present that may make intervention advisable.

If high grade dysplasia is revealed by the smear but not confirmed by biopsy, before resorting to cone biopsy with serial examination, we carry out repeat colposcopic examination, also exploring the cervical canal. If, despite this, we are unsuccessful in explaining the cytological anomaly we resort to conization.

In pregnancy we are inclined to defer any therapeutic action until after delivery. If the persistence of the high grade dysplastic lesion is revealed, we proceed in the manner just described for patients outside the gestation period. Otherwise, periodical examination is sufficient.

SUMMARY

On the basis of 235 personal observations, the main significances of the high degree dysplasia of the uterine cervix are discussed either from the clinical or from the pathological wiewpoint.

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Plasma alpha-fetoprotein levels in normal and abnormal pregnancy

by
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A new variable has recently been added to the biochemical monitoring of pregnancy at risk; the determination of alpha-fetoprotein in the maternal plasma and in the amniotic fluid.

The chemical and physical properties of the substance have been described in a number of reports ([1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]).

The origin of alpha-fetoprotein in the maternal plasma has not been entirely explained as yet. The most likely hypothesis is that it is produced by the foetus and that it passes to the mother either through the placenta or through the amniotic fluid. As to its production site, autoradiographic tests have shown that in the human foetus it can be synthetised in the liver and in the amniotic sac, but not in the placenta ([19, 20, 21]).

The significant correlation between maternal and fetal levels and the gradient between the two compartments (300 to 600 times) favours the foetal origin ([13]). However, maternal origin, at least in part, is not excluded.

Radio-immunological studies have revealed small quantities of alpha-fetoprotein in the serum of healthy adult subjects ([14, 15, 16]).

It may be that pregnant women produce a greater quantity of alpha-fetoprotein than other women; in other words, an unknown placental factor may weaken the repression of the foetal gene responsible for alpha-fetoprotein synthesis ([17]), as occurs in primary neoplasia of the liver, severe hepatitis and cirrhosis ([19]).

Jacob and Monod ([22]) have suggested that the biosynthesis of alpha-fetoprotein in healthy adults is inhibited by a repressor agent which affects the gene responsible for its production.

The possibility that a large amount of alpha-fetoprotein is produced during pregnancy also appears to be confirmed by the high concentration found in a case of vesicular mola, where fetal production was negligible ([23]).

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