there were 52 patients and had hirsutismus. In 19% of first group, 34% of second group and 60% of third group DHEAS was found high.

When Prolactin value was compared between primary infertility and fertil hirsutic group, we find high in fertil hirsutism ($p<0.1$). This also have been shown by Lobo *et al.* with similar research in 1981 ([1]).

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EPIDEMIOLOGICAL DATA, CYTOLOGY AND COLPOSCOPY IN IUD (Intrauterine device), E-P (Estro-progestogens) AND DIAPHRAGM USERS. STUDY OF CYTOLOGICAL CHANGES OF ENDOMETRIUM IUD RELATED

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Summary: The Author compares the epidemiological, cytological and colposcopical data found in IUD users, with a control population of estro-progestogens and condom users.

The age, parity and clinical symptomatology, mainly leukorrhea, was higher in IUD users. At the colposcopic examination a normal pattern was found in condom users more frequently, but the suspect colposcopic signs were frequently associated with the use of the IUD. The oncologic evaluation of smears showed a slight dysplasia in 17.65% and 10.53% in IUD users and estro-progestogens users respectively. The only case of carcinoma *in situ* was found in the IUD users group. The bacteriological diagnosis on the smears did not reveal a quantitative difference in the three groups, while a qualitative difference was found, particularly with a high frequence of Trichomonas vaginalis and Corynebacterium vaginalis, and one case of Actynomyces in IUD users.

The cytological study of the endometrium obtained by mono-use devices, revealed an aspect of aspecific non plasmacellular endometritis in 75% of the cases; a disfunctional hormonal cytological aspect in 32.50%, and the oncological evaluation in 60% of the cases revealed atypical endometrial cells IUD related. No neoplastic lesion was found.

The Author concludes that the use of IUD must be prudent and accurate follow up must be carried out.

Key words: IUD, Estro-progestogens, Diaphragm, Cytology, Colposcopy, Endometrium.

INTRODUCTION

The IUD (intrauterine device) represents, after the pill, the most diffused contraceptive method in the world. This diffusion has stimulated a large quantity of study in order to reach an understanding of the intrinsic mechanism of the action, the side effects and the complications caused by such use.

Particular attention has been paid to inflammatory complications which are today largely accepted, and to the carcino-

genetic potentiality on which the various authors are still divided in opinion.

The mechanisms postulated by which IUD avoid pregnancy are many and not all clear.

They are the following:

1) Foreign body reaction consisting in infiltration by macrophages, plasmacytes and leukocytes, which is manifest above all at the points of contact of the device and endometrium and is associated with biochemical and enzymatic modifications ([1-9]).

2) The antibody production with the increase of Ig G and Ig M ([1, 2, 6, 10-13]). This reaction suggests that a sort of immunological mechanism is involved with the use of IUD.

3) Irritant action of the copper ([14]) above all with the alteration of the cellular ultrastructure, interesting the mitochondria with successive alteration of the carbohydrate metabolism, with subsequent alteration of the respiration and of the production of energy cells ([15, 16]).

4) Alteration of the biochemical composition of endometrial cells with reduction of the RNA/DNA ratio ([17]) and increase of calcium ions ([15]).

5) Hormonal alterations: the presence of copper which covers the IUD may have an effect on the sensitivity of the endometrial hormonal receptors with estro-progestogens disbalance which is manifest by an aspect of proliferation in the luteal phase with a delay in the glycogenic secretion and interference in the development of the blastocyst ([18]).

6) Vascular modification with an increase in vascularization owing to the inflammatory response, in addition to an alteration of a destructive type with microthrombosis of the stromal capillaries, extra-vascular thrombi, erytrocytes and fibrin deposition in the adjacent stroma ([19, 20]).

7) Mechanical modifications with excitation of the fallopian tube motility and acceleration of the descent of the oocyte; thus evoiding fecondation. If feconded it arrives in advance in the uterus and either due to insufficient evolution of oocyte or by hystological insufficiency of the endometrium it does not develop. The irritant action of the IUD operates also with an increase of peristalsis of the walls of the uterus.

8) Inflammatory modifications: the increased incidence of inflammation in the female genital tract may cause an alteration of the ambiental conditions which are unfavourable the survival of the spermatozoa.

9) Phagocytosis of the spermatozoa by action of the macrophages as an aspecific response or by a specific activation of the spermatozoa antigens on the macrophages ([6, 21]).

10) Alteration of the process of capacitation of the spermatozoa due to an increased concentration of calcium ions ([17]).

11) Change of polarity of the endometrial surface during secretory phase. In particular a decrease of fucose/sialic acid ratio takes place with an increase of the latter and a consequent change in the polarity of endometrium surface. This may be important either for the mechanism of transport of the spermatozoa or for the development of the fecunded oocyte ([17]).

12) Substances liberated by the macrophages, like prostaglandins, may exercise unfavourable action on the vitality of the spermatozoa ([6, 22]).

All these mechanisms have a repercussion on the endometrium structure, with modifications which involves the biochemical composition, the intercellular organelles and the cells themselves. Cellular modifications IUD induced appear extremely strange and atypical, and only the experience and the knowledge of their existence avoids erroneous diagnosis of dysplasia or even neoplasia with the consequent inadequate treatment of the patients ([23, 24]).

Table 1. — *Late sequelae of IUD usage (from Gupta 1982).*

SQUAMOUS CELL CHANGES
Inflammatory - Atypical forms - Reparative changes
COLUMNAR CELL CHANGES
Inflammatory - Papillary proliferation (endocervical, endometrial) - Nonpapillary proliferation (endocervical, endometrial) - Mucoid cell proliferation (endocervical) - Squamous metaplasia (endocervical, endometrial)
INDETERMINATE CHANGES
Bizarre cell forms (endometrial? histiocytic? metaplastic?) - Giant cells - multinucleate forms (endocervical? endometrial?) - Calcification and psammomabody formation

While the microbic flora modifications associated with the use of the IUD are fully accepted ([25, 26]) as a correlation with PID (Pelvic Inflammatory Disease) ([25, 27]), doubt has been expressed over the recent years on the possible carcinogenetic capacity of the IUD. This doubt is especially due to the appearance of atypical cells in the eso-endocervical and endometrial smears.

In synthesis, the cells most commonly encountered on the IUD removed after 24-72 hours or directly from the uterine cavity, are constituted essentially by macrophages and neutrophilous leukocytes; the macrophages are exceptionally active and it is possible to observe within them fragments of cells phagocytosed, also spermatozoa fragments ([2, 5, 6, 8, 35]).

After two days the macrophages completely cover the surface of the IUD and are probably mobilised by the endometrium. The presence of most cells and other connective tissue cells is notable ([1, 2, 24, 29, 30, 31]).

Bacteria and lynphocytes are also observed ([6, 32, 33]).

The observable modifications by the cytological study of IUD retained in uterus for a long time seem to be more important. Gupta defines these modifications as late sequelae of IUD usage ([34]) (table 1).

Cellular changes may be either relative to a stimulated reparatory process resulting from inflammation or infection, or specifically relative to the IUD usage ([34]). These latter consist of cylindrical cells of uncertain origin: endocervical or endometrial, perhaps hisocytes, endometrial stromal cells or metaplastic.

They generally present vacuolised cytoplasm, hyperchromatic nucleus, granular chromatina, prominent nucleoli, nuclear membrane thickened and folded as in degenerate cells.

Gupta ([34, 35]) recently suggested that the atypic glandular cells found in a Pap-smear of IUD users are of endometrial origin. Kobayashi ([36]) has also described a characteristic cellular pattern of atypical glandular cells present in uterine fluid of women wearing a IUD. These atypical aspects may appear to be endometrial adenocarcinoma. Since the atypical cells were present in a higher frequency in the uterine fluid (65%) than in cervical mucus (6%), this author concludes that their origin is endometrial.

Thus a correlation has been found between the IUD and the atypical glandular cells but no relationship has been established with the atypia of squamous cells ([37, 38]).

Now the questions in this respect are: whot relationship exists between cervical dysplasia and prolonged use of IUD? ([5, 23, 24, 37, 39, 40]). And in particular, may the constituents of the IUD exercise a carcinogenetic effect?

Experimental studies have been carried out in this respect by Hoppenhaimer ([41, 42]), Hadler ([43]), Pincus and Garcia ([44]), they reveal unanimous results in respect of the carcinogenic potentiality of the polyethilene which constitues entirely the inert IUD and partially the medicated IUD.

Ayre ([45]) has published in this respect the studies carried out on human material documenting the carcinogenetic potentiality of polyethilene (Margulies' Coil).

He reveals the rise of dysplasia in two patients whose cervical smears were cytologically normal the year before; in a second group of three patients he reveals a rapid progression of a pre-existent dysplasia.

Many clinical studies have been successively carried out, tending to confirm or to contradict the alarming conclusions of Ayre in respect of the development and progression of cervical dysplasia and cancer in women using the IUD.

None of these studies, however, demonstrated the association between IUD and the increased risk of cervical neoplasia ([46, 47]). Thus, whilst Gupta ([34]) and others ([28, 47, 48]) have not observed either an increased risk or a rapid progression of epithelial atypia between IUD users, other Authors maintain the opposite theory ([44, 45, 49]).

The problem of regression or progression of dysplastic lesions has recently been analysed by Noda ([50]), who reveals, in summarising scientific literature, a variable progression ranging from 5% to 67%. This notable difference may be due to the different criteria in selection of the cases.

It must be noted that the study of this kind is somewhot difficult to conduct through different motives: an insufficient number of patients, inadequate observation time so as to observe the results over a long period, loss of patients during the follow up period.

Luthra ([51]) carried out a cytomorphological study on 2603 IUD users and observed them for a period of 60 months maximum. The rate of dysplastic lesions in the initial smears was 2.5%. Grouping the 60 months of follow-up into five periods of one year each, the annual rate of dysplasia during the follow-up period was, for every respective year, 4.2%, 1.6%, 3.8%, 0.9% and 3%.

No dysplasia, during the study period, progressed towards a carcinoma and no differences were observed in the behaviour of the dysplastic lesions revealed during the initial period of the investigations or during the period of the use of IUD. Christopherson ([52]) effected a long term study on IUD users and gives the following rate of incidence of dysplastic lesions in successive controls: 4.68%, 5.42%, 6.22% and 4.52% taken from the initial scraping to the 4th control, respectively.

Stern ([53]) gives the incidence rate of 5.4% and 2.4% respectively at the first control of a new population, and in those in whom successive controls were effected.

Richart and Barron ([46]) did not note any influence of the IUD on the transit time of the progression of medium dysplasia towards a carcinoma in situ (86 months) and of severe dysplasia towards carcinoma in situ (18 months).

Aikat ([54]) carried out studies on 833 IUD users. His report shows that 5 cases with dysplasia (3 medium and 2 moderate) diagnosed before insertion of the IUD acquired the regression after 6 months, and in one case of medium dysplasia verified during the follow-up period occurred the regression in 6-12 months. No dysplasia progressed in a follow-up period from 6 months up to 5 years.

The scope of this study is that of comparing the results of colposcopic and cytologic (scraping to the cervix) examinations obtained on patients who utilised different methods of contraception (estro-progestogens, IUD, diaphragm) and to investigate further on the modifications induced by IUD at a level of endometrial mucosa, on material obtained by cytologic sample from the uterine cavity by use of a mono-use device (Endocyte).

MATERIAL AND METHODS

Charts of women who were treated by the Center of cervical pathology of the Clinic of Obstetrics and Gynecology of the University of Pisa, were taken into consideration relative to the 6 months period from June to December 1984.

Among these 125 women using estroprogestogens, 68 women using IUD and 13 women

Table 2. — *General epidemiological data of the three groups of patients examined.*

	Total No.	Average age	Average age menarche	Average age sexual act.	Parity No.		%	Abortions No.		%
IUD	68	30.19	12.36	18.61	0	28	41.18	0	46	67.65
					1	13	19.12	1	17	25.00
					2	27	39.71	2	5	7.35
					>2	/	/	>2	/	/
E-P	125	27.69	12.27	18.67	0	66	52.80	0	100	80.00
					1	26	20.80	1	22	17.60
					2	31	24.80	2	2	1.60
					>2	2	1.60	>2	1	0.80
DIA	13	31.62	12.69	22.25	0	7	53.84	0	7	53.84
					1	3	23.08	1	3	23.08
					2	3	23.08	2	3	23.08
					>2	/	/	>2	/	/

Note IUD: Intra Uterine Device; E-P: Estro-progestogens; DIA: Diaphragm.

using diaphragm were selected. The above were all regular submitted to examination by colposcopy and cytology of the esocervix by scraping.

In 40 cases where removal of the IUD was necessary due to termination of its use, by medical advice or by patient's personal choice, an endouterine smear, using a mono-use decive was effected to obtain endo-uterine cells (Endocyte).

This cellular material was coloured by Papanicolau technic, and a triple evaluation was effected: phlogistic, hormonal and oncologic.

RESULTS

The average age of the three groups of patients examined did not reveal any significant difference, although the lowest average age of women who assumed estroprogestogens should be noted (27.69 years) (tab. 2).

The age of menarche was approximately the same in the three groups. The average age of starting of sexual activity did not show any difference between the estroprogestogens users and the IUD users (18.67 and 18.61 years), while a delay in start of sexual activity was revelaled in women who used diaphragm (22.25 years) (tab. 2).

From comparative data it was evidenced that 39.71% of the wearers of IUD had had 2 pregnancies previously; that the users of estroprogestogens only 24.80% and the users of diaphragm 23.08% of pregnancies (tab. 2).

It must be underlined that the women who used estroprogestogens in 80% of the cases had not aborted previously as against the women of the other two groups (IUD 32.35% and diaphragm, 46.16% of previous abortions).

The symptoms experienced by patients is reassumed in tab. 3; from it, it is evident that in 40.28% of the cases the users of IUD presented leukorrhea and in 28.36% of the cases experienced electro-diatermocoagulation of the cervix previously. Xantorrhea is often experienced by patients who use diaphragm and 15.38% of them complained hematic stilicidium. Often the symptoms are noted contemporaneously, in fact the irritation is frequently associated with leukorrhea and xantorrhea.

No symptoms were present in 32.84% of IUD users, 38.40% of the women who assumed estroprogestogens and 38.46% of those using a diaphragm. The 12% of the women assuming estroprogestogens were submitted to local medical care and in

Table 3. — *Present symptoms and previous treatments in the three groups of patients examined.*

Symptoms	IUD		E-P		DIA	
	No.	%	No.	%	No.	%
Leukorrhea	29	43.28	47	37.60	3	23.08
Xanthorrhea	4	5.97	7	5.60	1	7.69
Haematic stillicidium	1	1.49	7	5.60	2	15.38
Pruritus	11	16.42	22	17.60	2	15.38
Previous vag. phlogosis	8	11.94	17	13.60	/	/
Local medical therapy	4	5.97	15	12.00	1	7.69
Electro - diat. - coagulat.	19	28.36	23	18.30	3	23.08
Conization	/	/	1	0.80	/	/

only one case had a conization been carried out in precedence.

The table 4 displays the colposcopic aspects present in the three groups, from which may be seen a high incidence of normal cervix among the users of diaphragm (38.46%); benignant modifications are more represented in the group of the women who assumed estroprogestogens (56.80%), whilst suspect modifications are more frequent among the IUD users (25%).

Cytological examination (tab. 5) expresses in percentage among the group colposcopically suspect and on the total number of each group displaying the following aspects: a more frequent arisal of some infections in IUD users (Trichomonas vaginalis, Corynebacterium vaginalis).

The group of IUD users showed a more frequent arisal of condilomatose lesions (11.76% of suspect lesions and 2.94% of the total number).

The cytological aspect of slight dysplasia in suspect colposcopic lesions was 17.65% among the IUD users and 10.53% of estroprogestogens users.

The association dysplasia and condilomatose lesions were shown in 5.26% among the group of suspect lesions among women who assumed estroprogestogens (condiloma + slight dysplasia) and 5.88% in the group of suspect lesions among IUD users (condiloma + moderate dysplasia).

The single case of carcinoma in situ was discovered in the group of IUD users.

The bacteriological study on cervicovaginal smears did not show any quantitative difference among the IUD users and the estroprogestogen group. Note that the only case of infection by Actinomyces was found among the IUD users.

The cytological study after IUD remotion by endocyte showed in 10% of the cases normal endometrial cells; in 75% specific plasmacellular endometritis and in 5% of the cases asymptomatic bacterial endometritis (tab. 6).

At the hormonal evaluation a disfunctional aspect was detected in 13 patients, equivalent to 32.50%, these alteration were characterised by the presence of endometrial cells in a proliferating phase presumably during the secretive phase of the cycle (tab. 6).

The oncological evaluation (tab. 6) did not show the rise of neoplasia, but showed that in 60% of the cases there was the presence of atypic glandular cells of a variable form, characterised by nuclei with an increased volume, with gross granular chromatina with irregular distribution, sometimes with conspicuous nucleoli. These atypic cells type are similar to those

Table 4. — *Colposcopic aspects in the three groups examined.*

	IUD		E-P		DIA	
	No.	%	No.	%	No.	%
Normal cervix	23	33.82	35	28.00	5	38.46
Benignant modifications	38	41.18	71	56.80	6	46.16
Suspect modifications	17	25.00	19	15.20	2	15.38

Table 5. — *Cytological signs of colposcopically suspect lesions and % of the total number of the three groups examined.*

	IUD			E-P			DIA		
	No.	% susp. les.	% tot.	No.	% susp. les.	% tot.	No	% susp. les.	% tot.
Negative	6	35.29	8.82	12	63.16	9.60	2	100	15.39
Trichomonas vag.	3	17.65	4.41	/	/	/	/	/	/
Corynebacterium vag.	1	5.88	1.47	3	15.79	2.40	/	/	/
Condiloma acuminata	2	11.76	2.94	1	5.26	0.80	/	/	/
Slight dysplasia	3	17.65	4.41	2	10.53	1.60	/	/	/
Condiloma + Slight dysplasia	/	/	/	1	5.26	0.80	/	/	/
Condiloma + Moderate dysplasia	1	5.88	1.47	/	/	/	/	/	/
Carcinoma *in situ*	1	5.88	1.47	/	/	/	/	/	/

of adenocarcinoma and are interpreted as specific cells induced by the presence of the IUD.

The cytologic study on cervicovaginal smears in this group of 40 patients gave the following results: normal for 18 cases (45%), phlogosis in 14 cases (35%), squamous metaplasia in 6 cases (15%) and slight dysplasia in 2 cases (5%).

DISCUSSION

The fact that the age and the parity result higher in the IUD users when compared with the estroprogestogens users, probably explains, on the basis of largely accepted epidemiological data, the major incidence of dysplastic lesions in this group (7.35% against 2.40%). One limit is represented by not having investigated also the sexual activity of these women.

Table 6. — *Endouterine cytological aspects at the moment of the IUD removal.*

Evaluation	Results	No.	%
Phlogistic	Normal endometrium	4	10.00
	Aspecific no plasmacellular endometritis	30	75.00
	Aspecific plasmacellular endometritis	4	10.00
	Bacterial endometritis	2	5.00
Hormonal	Normal	27	67.50
	Disfunctional	13	32.50
Oncological	Normal	16	40.00
	Presence of atypical cells IUD-related	24	60.00

One comment of particular interest is the single case of the carcinoma in situ: the patient was a 29 year old woman, para 2002, wearer of an IUD for 6 years. The lesion, already suspected in the colposcopic examination and successively confirmed by the cytology and by histological study on biopsy, lead the surgeon to an intervention of conization. A relationship therefore seems possible betwen the carcinoma in situ and the IUD in the case where the IUD had been for a long time in the uterine cavity, even if today the greater number of authors tend to exclude this probability ([28, 46, 48, 55-61]). This will be demonstrated in the future when the period of permanence within the uterus of the IUD has been far greater.

There is no doubt that the users of IUD are exposed to infection and in our group there was the presence of leukorrhea in 43.28% of the cases and 28.36% of the group components using IUD had undergone electro-diathermo-coagulation of the cervix, presumably due to alteration of the cervical epithelium. Note that in only 32.84% there was no mention of any

symptom, while the percentage of asymptomatic women in the other groups was quite high.

The only case of Actimomyces infection was encoutered in the IUD users and in this case the IUND was removed, as suggested by many authors ([34]).

Colposcopic examination is particularly important for women who use contraceptives to gain a early evaluation of suspected lesions; in this study 25% of IUD users presented suspect lesions. The cytology has in fact confirmed that in 17.65% of the cases there was a slight dysplasia and in 5.88% (1 case) a carcinoma in situ was diagnosed. Another case dealt with a condiloma associated with moderate dysplasia.

The major incidence of condilomatous lesions was in the IUD group and this may be due to major sexual activity of this group, but this was not investigated.

The endometrial cells obtained by Endocyte and carried out only in IUD users, confirmed the results described by other authors ([30, 31, 34, 36]). In the majority of the cases the cytological study on endometrium gave an aspect of aspecific no plasmacellular endometritis, condition through which the IUD realizes verosimilarly the principal contraceptive mechanism.

Bacterial infection and aspecific plasmacellular endometritis were rather rare; they are potentially dangerous for the development of pelvic inflammatory disease (PID).

The hormonal alteration encountered in 32.50% of the cases reflects what has been demonstrated by Electronic Microscopic study ([18]) and the study on the biochemical composition of the endometrium ([15, 16, 17]), regarding the action of the copper IUD on the sensitiveness of the hormonal receptors and especially on the progesteron receptors ([30]).

Oncologic evaluation of the action of IUDs on the endometrial mucosa showed the presence of atypic glandular cells in 60% of the cases, which is due to the contraceptive action of the IUD ([34, 36]); they are reversible lesions, well known to the cytologists.

No cases of endometrial neoplastic lesions were encountered.

CONCLUSIONS

Since there are no conclusive results in existence about the rise and progression and the regression of dysplastic lesions before and during the use of the IUDs, there remains among gynecologists a comprehensible and notable variety of views. It is therefore important to stress that the patient, user of the IUD, merits particular attention both from the oncological viewpoint and in respect of other complications, even if rare, which should not be forgotten (hematic loss with anemia, infection, PID, extra uterine conception, uterine perforations ...), since these are forms of chronic irritation provoked by foreign body within a organ such as the uterus, which in a woman and are the most frequent site of neoplastic lesions.

De Brux ([30]) in fact defines the mechanism of the action of the IUD as " a 'common' reaction by a foreign body on a tissue that is 'little banal' ".

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