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RECENT RESEARCH ON INTRAUTERINE DEVICES*

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This review would discuss research that has recently been carried out in the following areas:

(a) Intrauterine devices and bleeding,

(b) Intrauterine devices and pelvic inflammatory disease and

(c) Intrauterine devices and ectopic pregnancy.

It would also highlight the results obtained in a few clinical trials carried out with devices that were particularly developed with the hope that occurrence of the troublesome side effect of bleeding would not occur with these newer devices.

(A) *Intrauterine Devices and Bleeding*

The intermenstrual spotting and bleeding associated with the use of intrauterine devices has been identified by clinical investigators, social scientists and national family planning administrators as the one major factor largely responsible for the disappointing acceptance and continuation rates with intrauterine devices not only in India but in several countries in Asia. A concerted programme of work has, therefore, been launched by the WHO, the Indian Council of Medical Reserch and other organizations to find out why and how bleeding occurs with the use of these otherwise effective contraceptive agents. It is felt that if the cause and mechanism of IUD induced bleeding was understood it may then be possible to fashion and develop intrauterine devices that would not induce this troublesome side effect.

The work being carried out can be conveniently discussed under the following:

(a) Alteration in endometrial morphology.

(b) Alteration in endometrial fibrinolysins.

(c) Alteration in endometrial mast cell and heparin levels.

(d) Alteration in platelet uptake and turnover in the endometrium in the presence of intrauterine devices.

(e) Relationship of prostaglandins to IUD induced bleeding and the use of prostaglandin synthetase inhibiting drugs.

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(a) *Endometrial Morphology*

What could perhaps be a major breakthrough in our understanding of IUD induced bleeding has been the result of electron microscopic studies carried out by Hohman *et al* (1977) at Los Angleles on uteri obtained at hysterectomy from 22 women using intrauterine devices and 22 control women. These investigators have demonstrated gaps or openings in the lining of the small blood vessels in the endometrium obtained from women using intrauterine devices. They suggest that the combination of physical interaction between intrauterine devices and the uterus could create a pressure that is mechanically transmitted into the endometrium producing sufficient distortion to directly injure a small percentage of superficial vessels continuously throughout the cycle. It is felt by the investigators that those endothelial cells, which are subject to pressure could perhaps degenerate, eventually separate and form gaps that could be a route for blood cells and plasma to escape into extravascular tissue and later into the uterine cavity particularly as the lining at the gaps is inadequately protected by platelets and fibrin. The first part of this—the appearance of gaps in the endothelial lining—has been clearly demonstrated while the remaining ideas remain speculative. In a recent study, Shaw *et al* (1979 a) have studied, in the same hysterectomy specimens, macroscopically and with light and electron microscopy 3 portions of the endometrium. These were (a) endometrium depressed by direct contact with the device, (b) endometrium adjacent to the depressed site and (c) endometrium from a remote site. The results demonstrated very clearly that most of the changes occurred in the endometrium adjacent to the depressed site. The depressed area in the endometrium was usually blanched and did not exhibit evidence of haemorrhage. The endometrium from an area remote from the depressed area was usually healthy in appearance although occasionally it was congested and haemorrhagic. The endometrium adjacent to the IUD depressed area was usually edematous and often congested and haemorrhagic. These areas often exhibited interstitial haemorrhage. The investigators feel that the areas adjacent to the IUD depressed areas were responsible for the IUD induced bleeding and that the increase in vascular permeability, the endothelial gaps and the lack of platelets and fibrin leads to interstitial oedema and haemorrhage which eventually escapes into the uterine cavity. In another study Shaw and Macaulay (1979 b) have tried to find out how the blood cells actually escape into the uterine cavity. By studying electron microscopically the surface epithelium and basement membrane they have come to the conclusion that the red blood cells did not escape through defects in the epithelium as very rarely did they observe such defects. They have speculated that the blood cells escape into the endometrium probably by transmigration through an otherwise intact surface epithelium. It is difficult to conceptually accept this although it is true that plasma proteins and leucocytes do travel and find their way into the intraluminal fluid in the presence of intrauterine devices. The investigators suggest that endogenously circulating substances like prostaglandins could assist in this migration.

(b) *Endometrial fibrinolysins*

The involvement of endometrial fibrinolysins in bleeding induced by intrauterine devices was suggested by Larsson

and Wennergren (1974, 1975). These investigators measured histochemically fibrinolytic activity of the endometrium in 15 women before and 3 months after introduction of the copper intrauterine device (Larsson *et al* 1974). The fibrinolytic activity was increased in 10 out of 15 women. These investigators demonstrated lytic areas in the endometrium in contact with the devices that were not present in control endometrium. They extended their earlier observations by measuring fibrinolysins at 2-5 months and again 8-12 months after insertion (Larsson *et al* 1975). They obtained elevated levels of fibrinolytic activity but there was no difference between the levels at 2-5 months and 8-12 months. It is well demonstrated that the copper intrauterine device induces an increase in menstrual blood loss and it may well be possible, these investigators suggest, that the enhanced levels of fibrinolysins alter coagulation and haemostasis and induce bleeding. Another very interesting observation by Leidholm *et al* (1978) provides further support for this hypothesis. These investigators measured, again histochemically, endometrial fibrinolysins before and 3-4 months after insertion of progesterone containing intrauterine devices which are known not to induce bleeding. There was no increase in the levels of endometrial fibrinolysins. These results clearly suggest that the increased fibrinolysin levels associated with the intrauterine device that induces bleeding is more than a coincidental observation. These findings have prompted the suggestion made by Larsson *et al* (1975) and others that plasminogen activators are released by the devices and these plasminogen activators are concentrated in endometrial tissue next to the device.

Clinical evaluation of the effectiveness of antifibrinolytic agents in diminishing the bleeding induced by intrauterine devices again furnishes further information supporting the hypothesis that fibrinolysins are connected with IUD induced bleeding. As early as 1970 Westrom and Bengtsson demonstrated that the fibrinolytic inhibiting drugs epsilon aminocaproic acid and tranexamic acid were effective in reducing menstrual blood in women with intrauterine devices. This was further confirmed by Kasonde and Bonnar (1975). These investigators measured the menstrual blood loss in 28 women wearing the Lippes D device and in 28 control women allocated randomly to the 2 groups. Menstrual blood loss was measured for 1 cycle before and for 8 cycles following insertion of the device. Epsilon aminocaproic acid, an antifibrinolytic drug was administered initially 7 days after insertion of the intrauterine device and for 8 subsequent cycles. There was a clear significant decrease in the menstrual blood loss in the women administered the epsilon aminocaproic acid. In the control women the mean menstrual blood loss increased from 42.7 ml. to 121.1 ml. while in women administered the drug it was 43.0 ml. before insertion and remained below 54.1 after the device had been inserted. In another group of subjects who had come with bleeding after insertion of different types of devices—Lippes D, Saf-T-Coil, Dalkon Shield and Copper-7, epsilon aminocaproic acid significantly reduced the menstrual blood loss.

Clinical evaluation has also been carried out on the effect of another antifibrinolytic agent—ethamsylate in IUD induced bleeding. Two studies have been carried out by investigators in England using the same dose of ethamsylate but administering the drug by a different

regime. The first results published by Kasonde and Bonnar (1975) appeared to indicate that ethamsylate did not decrease menstrual blood loss in the women fitted with intrauterine devices. The later results published by Harrison and Campbell (1976) showed that the mean menstrual blood loss was significantly reduced by 19% in patients with intrauterine devices. In the first trial ethamsylate was administered at the onset of menstruation and continued till the last day of bleeding while in second trial ethamsylate was administered 5 days before the anticipated onset of menstruation and continued for 10 days. This perhaps is the explanation for the failure of ethamsylate to reduce menstrual blood loss in the trial carried out by Kasonde and Bonnar (1975). These two studies suggest that ethamsylate should be given a few days before the onset of menstruation to be effective in reducing the bleeding induced by intrauterine devices.

(c) *Endometrial Mast Cells and Heparin*

The possible relationship between bleeding induced by intrauterine devices and mast cells and heparin was first suggested by Mathur and Chaudhury (1968) when it was demonstrated that an intrauterine device increased the number of mast cells in rat urerus. Mast cells contain in their granules pharmacologically active substances such as histamine, 5-HT and heparin. It was subsequently demonstrated by Mehra *et al* (1970) that the endometrial mast cell count was significantly raised in women with intrauterine devices only when the endometrial sample was obtained at the bleeding phase. When the sample was obtained at the non-bleeding phase, even in women who experienced the side effect of bleeding with an intrauterine device, there was no increase in the mast cell count. It was possible that the intrauterine device induced bleeding by releasing either histamine or heparin from the mast cell granules. A study was, therefore, carried out to clinically evaluate a long acting antihistaminic substance, buclizine hydrochloride on IUD induced bleeding in humans by Bedi *et al* (1968). They observed that buclizine hydrochloride could counteract the IUD induced bleeding. A similar study in the subhuman primate was also carried out by Kar and Chandra (1969). They demonstrated that in the subhuman primate also buclizine hydrochloride reduced the IUD induced bleeding. In a further study Bhattacharjee (1971) has shown that while the antihistaminic, buclizine hydrochloride administered orally induced a clinical improvement in about 75% of cases, the endometrial mast cell count was reduced in only 50%. In 20% women there was no alteration in the endometrial mast cell count while in 30% there was an increase in the count. Chaudhury *et al* (1967) suggested that antiheparin drugs should be considered for control of bleeding in women with intrauterine devices as it was felt that the device could be inducing bleeding by releasing heparin. Nothing very much happened till 3 years ago when the WHO Special Programme for Research in Reproduction felt that this should form one of the major thrusts in the effort to elucidate the mechanism of IUD induced bleeding. Endometrial heparin and heparin content in the endometrial fluid is being measured at Leeds by Professor McNicol (Personal Communication). The analysis of menstrual and intermenstrual uterine fluids have shown the presence of heparin like activity. This

heparin like activity was increased in some women with intrauterine devices.

(d) *Platelet Uptake and Turnover Studies in the Presence of Intrauterine Devices in Human*

Platelet aggregation appears to be altered in the endothelial lining of the small blood vessels in women with intrauterine devices. It is possible that the platelet uptake and turnover is altered in the presence of intrauterine devices. Studies are being carried out at the present time to determine whether the intrauterine devices alter platelet aggregation or turnover in the endometrial vessels. Studies are also underway to observe whether fibrin deposition occurs normally over injured blood vessels in contact with intrauterine devices. Preliminary results obtained by McNicol and his associates (Personal Communication) have shown that platelet survival and turnover in the endometrial vessels in control women and in women with intrauterine devices were not different during or between menstruation.

(e) *Prostaglandin Synthetase Inhibitors and IUD Induced Bleeding*

The possible role of prostaglandins in the bleeding induced by intrauterine devices began with a chance observation when an investigator in Holland treated 4 women with pain after insertion of intrauterine devices with compound K-4277 which had been shown to inhibit the synthesis of prostaglandins. The investigator felt that the IUD induced pain may be induced by release of prostaglandins and that a compound which inhibits synthesis of prostaglandins may relieve the pain. He administered K-4277 by the intrauterine route and found, to his surprise, that normal menstruation stopped in 3 of the 4 women.

Anderson *et al* (1976) treated 6 women with menorrhagia due to dysfunctional uterine bleeding and 1 patient with IUD induced menorrhagia with the prostaglandin synthetase inhibitors, mefenamic acid or flufenamic acid. They observed that these drugs significantly reduced the excessive blood loss in these women. Mefenamic acid was administered at a dose of 500 mgm. three times a day for 7-10 days starting on the first day of established menstrual bleeding. The menstrual blood loss decreased from 162 and 128 ml. in the 2 pre-drug cycles to 49 ml. and 80 ml. in the 2 cycles immediately following the drug. After the drug was stopped the blood loss returned to levels of 100 ml. and 130 ml. and fell again when the drug was administered in the next 2 cycles. In a subsequent study, Guillebaud *et al* (1978) administered mefenamic acid-500 mgm. 3 times a day to 25 women using intrauterine devices during 2 menstrual periods. A highly significant reduction in the mean total blood loss was observed during the treatment period. This reduction was observed in users of both inert and copper containing devices.

There are several drugs which inhibit the synthesis of prostaglandins. Some of these are aspirin, indomethacin, flufenamic acid, mefenamic acid, ibuprofen and tolfenamic acid. In addition to the results just described after administration of mefenamic acid, there is information also about the effectiveness of indomethacin and tolfenamic acid in reducing menstrual blood loss. Damarawy and Toppazada (1976) demonstrated that indomethacin exerted a beneficial effect in women with bleeding induced by intrauterine devices. Ylikorkala *et al* (1978) have shown clearly, in a double blind trial carried