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EFFECT OF IRRADIATION ON THE FETO-PLACENTAL TISSUES

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Intra-uterine death due to irradiation may theoretically either be caused by a direct irradiation effect on the fetus or indirectly through an impaired uteroplacental circulation. Damage to the fetus caused by ionizing radiation has been reported by several authors (MAYER et coll. 1936, BRENT 1960, RUGH 1973, SWEET & KINZIE 1976). However, the biologic effect of irradiation upon the human placental tissue appears to be unknown.

Genital malignant disease detected during pregnancy represents a special problem. If the disease is diagnosed during the last trimester, it may be possible to save both the mother and the child. During the first two trimesters it is usually necessary to sacrifice the fetus. In some cases external irradiation will be the treatment of choice, either alone or in combination with surgery.

The aim of the present report is to discuss the effect of high voltage irradiation on the uterus, placenta and fetus during the first two trimesters.

Material and Methods

The series consisted of 7 pregnant patients with genital carcinoma admitted to this hospital during the years 1966–1977 (Table).

Initial treatment was in all cases external photon irradiation, which was delivered either by a betatron (33 MeV), a linear accelerator (8 MeV) or a Co machine through

Submitted for publication 16 October 1978.

Table

Type of genital carcinoma, patient age and gestational age in 7 pregnant patients treated by high voltage irradiation

Type of carcinoma	Age (years)	Gestation (weeks)
Adenocarcinoma of the ovary stage I	20	11
Adenocarcinoma of the ovary stage I	19	16
Squamous cell carcinoma of the cervix stage I	37	16
Adenocarcinoma of the ovary stage III	28	20
Squamous cell carcinoma of the cervix stage I	31	20
Squamous cell carcinoma of the cervix stage I	23	25
Squamous cell carcinoma of the cervix stage I	36	27

opposed anterior and posterior portals on alternative days to a pelvic field. The calculated mid-pelvic dose was in 6 patients 30 Gy, in one patient 34 Gy. In 4 patients the placenta was completely within the irradiated volume. In the other 3 approximately one half of the placenta was irradiated. The further treatment was operation and post-operative irradiation.

Before, during and after irradiation, angiography was performed in all the patients to demonstrate the uteroplacental circulation and the placental size. A polyethylene catheter No. 205 was introduced percutaneously into the upper femoral artery with the tip just above the common iliac arteries. Thirty ml of Urografin 76% was injected with a rate of 10 to 12 ml per second. Films were exposed during the arterial, parenchymatous and venous phases.

The specimens of the uteroplacental and fetal tissues after spontaneous abortion or operation, were fixed in 4% formaldehyde and processed for light microscopy. The slides were stained with hematoxylin-eosin and examined by one of the authors. (Only the fetus of 27 weeks was autopsied.)

During the irradiation oestriol, human chorionic gonadotrophin and pregnanediol excretion in the urine were examined. In two patients treated in 1977 serum levels of progesterone and human chorionic somatomammotrophin were also measured. (All analyses were performed at The Hormone Laboratory, Aker Hospital, Oslo.)

Results

One of the patients treated for carcinoma of the cervix died 6 months after the operation from renal failure due to bilateral stenosis of the ureters. No recurrence of the cervical tumor was found at autopsy. Another patient, also treated for cervical carcinoma, died 5 months after operation from a pelvic recurrence. Five patients are alive and without evidence of malignant disease 5 to 11 years after treatment.

The uterus grew normally in all patients throughout the treatment period. Five

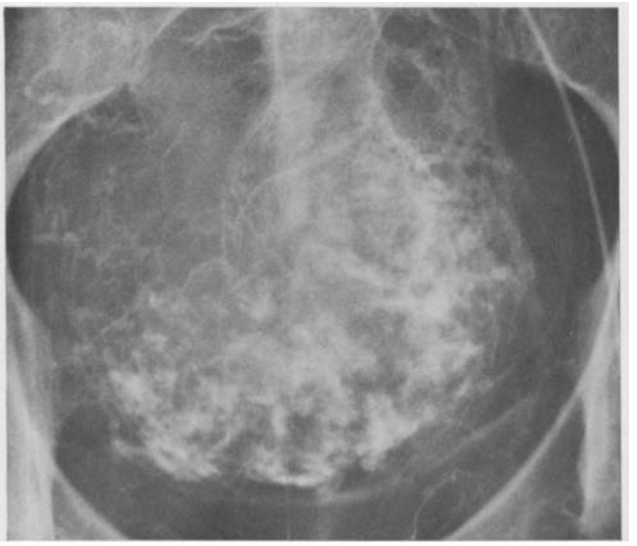

Fig. 1. Normal angiography with the placenta in the left side of the uterus before treatment (20th week of gestation).

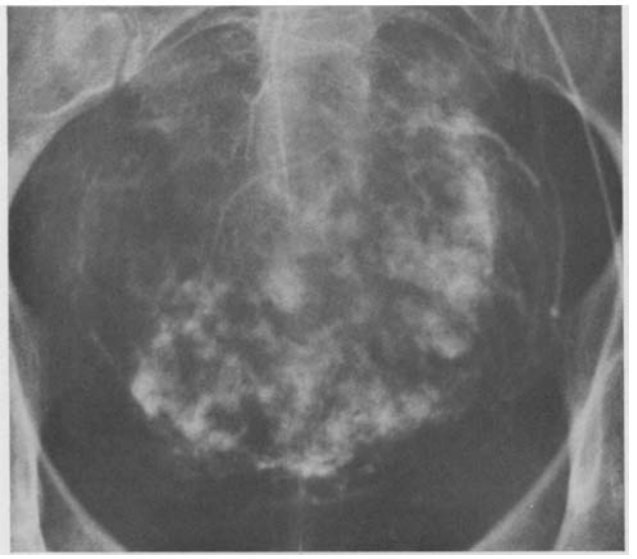

Fig. 2. Same patient. Angiography after 30 Gy high voltage irradiation. Decrease in the size of the placenta, but no change in the maternal circulation.

patients aborted spontaneously after completed irradiation and 2 were operated upon within two weeks after the cessation of irradiation.

The films exposed after 10 and 30 Gy did not show any significant changes in the uterine circulation (Figs 1, 2).

At the end of completed radiation therapy radiography demonstrated deformation of the fetal skull in 3 of the patients (Fig. 3), and an unnatural position of the head and neck in a fourth. In the other patients the fetus appeared normal.

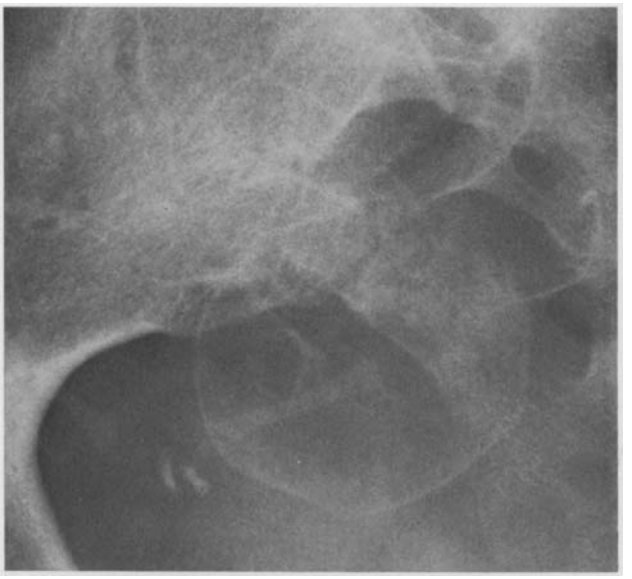

Fig. 3. Same patient. Overlapping of the cranial vaults in the fetus after 30 Gy.

The microscopy showed in all cases dilated vessels in the uterine wall, without obliterative process, intimal fibrosis or thrombosis. The sinusoids in the decidua basalis and the basal plate of the placenta were dilated with slight regressive changes in 4 specimens. Three cases had fresh fibrin thrombi, congestion of the sinusoids and necrosis in the surrounding decidua. In all cases the placenta was severely degenerated with obliteration of the villous vessels, particularly in the terminal villi, generalized fibrosis, focal calcification and syncytial degeneration. Microscopy of the fetal tissues in the one case examined showed hyperemia in all organs, but no parenchymatous degeneration or specific abnormalities in large or small vessels. (The brain was not examined due to a general autolysis.)

Oestriol and chorionic gonadotrophin excretion in the urine and serum levels of progesterone and chorionic somatomammotrophin during treatment are shown in Fig. 4 (the twentieth week of gestation). Oestriol and progesterone decreased after 20 Gy in all patients. No change in somatomammotrophin was observed (2 patients).

Discussion

The maternal circulation of the placenta as demonstrated at angiography was not reduced during high voltage irradiation in 6 of the 7 patients. This may be due to the fact that larger vessels are rather resistant to radiation (DUNCAN & NIAS 1977). The placental margins were not visible in the seventh patient examined in the eleventh week of gestation, and no conclusion could be drawn concerning the placental circulation in this patient. This last observation corresponds with the statement of BORELL

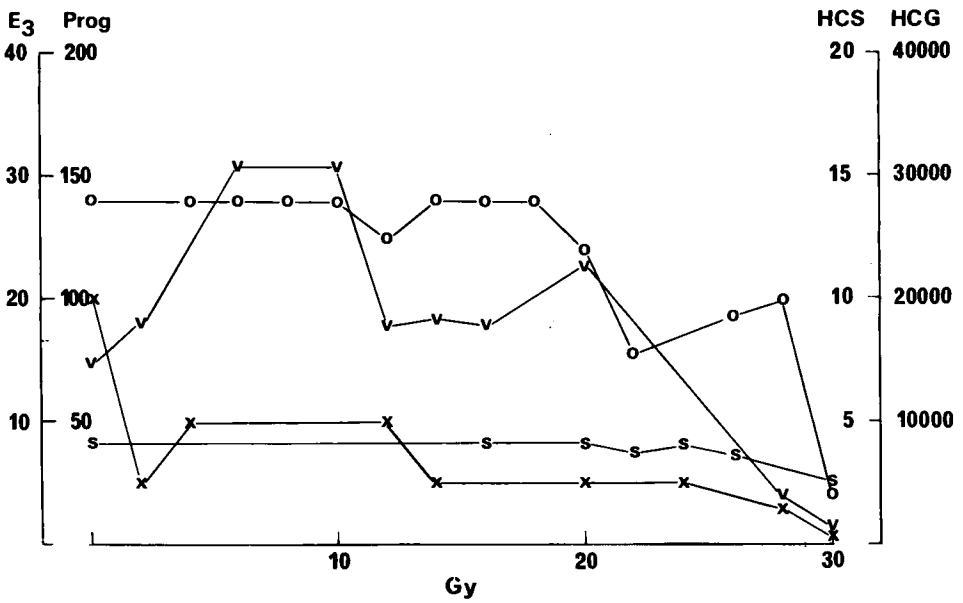

Fig. 4. Same patient. Excretion of oestriol and human chorionic gonadotrophin (HCG) in the urine and progesterone and human chorionic somatomammotrophin (HCS) in the serum during irradiation. Oestriol (E_3), μmol/l = v. HCG, IU/l = x. Progesterone, nmol/l = o. HCS, μg/ml = s.

et coll. (1952), who found that contrast medium in the decidual sinusoids indicates the site of the placenta only from the third month of gestation.

The microscopy showed no intimal thickening or obliterative process in the vessels in the myometrium and decidua. The decidual abnormalities were moderate and of a kind sometimes found in normal pregnancies at term. Fetal death is therefore probably not induced by radiation effects on the maternal tissues.

The fetal part of the placental circulation cannot be examined by angiography. At microscopy the placenta showed marked degenerative abnormalities with obliteration of villous vessels. Furthermore fibrosis and calcification of the stroma of the villi were found and in one case chorionitis. Such abnormalities are characteristically found after intra-uterine fetal death. Therefore no reason exists to relate them to irradiation. These observations are in full agreement with the experimental results of BRENT (1960), who found that the placenta was relatively insensitive to radiation.

Fetal malformations are not induced after the sixteenth week of gestation, but immediate radiation injury to the parenchymal cells may occur. The central nervous system is specially vulnerable, and it is therefore reasonable to be of the opinion that fetal death following irradiation is due to damage to the brain. RUGH (1973) mentioned that the neuroblasts may be destroyed by only 0.25 Gy. MAYER et coll. (1936) performed therapeutic abortions by a total radiation dose of 6 Gy with a clinical success in 96 per cent. The abortions occurred about 33 days after the irradiation. It is not

possible to draw any conclusion from the present material regarding the radiation dose necessary to kill the fetus. All the patients were given 30 to 34 Gy within a treatment period of about three weeks before abortion. Spontaneous abortion might also have occurred if e.g. 3 Gy had been given as a single fraction followed by a pause of two to three weeks.

Acknowledgements

The authors are grateful to Drs Per Kolstad and Per Marton of the Norwegian Radium Hospital, Oslo, who gave advice in preparation of the report of the investigation.

SUMMARY

Seven pregnant patients with genital carcinoma were treated with high voltage irradiation in combination with operation. Five patients aborted spontaneously after a dose of 30 to 34 Gy. Two were operated within 2 weeks after completed irradiation. Angiography, microscopy and hormone analyses indicate that damage of the fetal central nervous system and not placental insufficiency is responsible for the intrauterine fetal death.

ZUSAMMENFASSUNG

Sieben gravide Patienten mit Genital-Karzinom wurden mit Hochvolt-Bestrahlung in Kombination mit Operation behandelt. Fünf Patienten abortierten spontan nach einer Dosis von 30 bis 34 Gy. Zwei wurden innerhalb von zwei Wochen nach abgeschlossener Bestrahlung operiert. Angiographie, Mikroskopie und Hormonanalysen zeigten, dass ein Schaden des Zentralnervensystems des Fötus und nicht eine placentare Insuffizienz verantwortlich für den intrauterinen fötalen Tot ist.

RÉSUMÉ

Sept malades enceintes atteintes de carcinome génital ont été traitées par irradiation de haut voltage associée à une opération. Cinq malades ont avorté spontanément après une dose de 30 à 34 Gy. Deux ont été opérées dans les deux semaines après la fin de l'irradiation. L'angiographie, l'examen microscopique et les analyses hormonales montrent que les lésions du système nerveux du fœtus sont responsables de la mort fœtale intra-utérine, et non l'insuffisance placentaire.

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