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Radiotherapy in Benign Uterine Bleeding Disorders

The Radiumhemmet metropathia cohort 1912–1977. Short and long term results

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ABSTRACT

Radiotherapy was earlier a method of choice for treatment of benign bleeding disorders (metropathia), especially in women of high surgical risk. During the period 1912 to 1977 933 women with benign bleeding disorders were treated at Radiumhemmet with intracavitary brachytherapy or external irradiation or a combination of both. The result with regard to cure of the uterine bleedings was good (48%). Hormonal withdrawal symptoms after treatment were noted in 45% of the patients. In the long term follow up an increased risk of cardiovascular death was found in women treated before menopause. Malignant tumours occurred in 107 cases versus 90.2 expected (RR 1.19). The estimated ovarian dose of ionizing radiation varied from 3.5 Gy to 6.0 Gy for the three standard techniques. Two women gave birth to a healthy child 4 and 5 years after intracavitary radium treatment. The estimated absorbed dose to the ovaries in these two women were 1 Gy and 4 Gy, respectively.

INTRODUCTION

Benign uterine bleeding disorders caused by e.g. endometrial hyperplasia or fibromyomas today create a minor problem as compared to the situation during previous decades. Improved knowledge with regard to hormonal regulation of the endometrial growth gave new tools for treatment. Women earlier looked upon as great anesthetic or surgical risk are now handled much safer, and a hysterectomy is mostly performed without any complication. Curettage, often repeated, earlier used to be not only the diagnostic procedure but also the only treatment method for benign uterine bleeding disorders.

Hysterectomy, intrauterine brachytherapy or external irradiation have been used to stop the bleeding if menopause was near. The last two methods initiate a menopause secondary to the arrest of the ovarian function. Hysterectomy,

on the other hand, permits preservation of ovarian activity.

Heyman (1922) (9) described a radiotherapy method used at Radiumhemmet for treatment of benign bleeding disorders and reported the early results with regard to control of bleeding. Three different regimes were used - intracavitary brachytherapy, external radiotherapy or a combination of both. Thirty years later Hundley and Kottmeier (10,16) stated that radiotherapy should be considered for patients above the age of 40, where conservative methods as curettage or hormonal therapy had failed. They also stated that patients, who were mentally unbalanced or those who had had pelvic infections should not be irradiated. Fibroids were not considered as a contraindication for radiotherapy.

As many of the women treated for metropathia still are alive and will appear at departments of obstetrics and gynaecology for other reasons e.g. a malignant tumour it seemed important to spread more information about this somewhat historical mode of treatment. The present study, based on the Radiumhemmet material of this type of treatment, represents one of the largest single series in the world.

MATERIAL

During the period 1912 to 1977 933 women were treated at Radiumhemmet for metropathia with ionizing irradiation. In the following discussion 145 women were excluded due to different reasons (Table 1).

Table 1.

THE RADIUMHEMMET METROPATHIA SERIES. CASES EXCLUDED.

	No.	%
Previously treated for malignant tumour	28	3
Suspicion of malignant tumour in uterus at time of admission	9	1
Records missing	10	1
Incomplete follow up	98	11
Total	145	16

All the hospital records were reviewed and bleeding history, number of children, age of menarche, age at admittance to Radiumhemmet, and residence were registered. The treatment results were recorded according to the bleedings (no, mild, moderate and severe remaining bleedings, continuous regular menstruation

and data missing) and according to the frequency of hormonal withdrawal symptoms (no, mild, moderate and severe withdrawal symptoms and data missing). All women were followed up in the population registers for vital status and if death had occurred the cause was registered.

CHARACTERISTICS OF THE STUDY POPULATION

The length of the bleeding history varied from one month up to more than 88 months. The average time was 20.8 months (Table 2). The mean age at menarche was 14.1 years (Table 2).

The women had on average given birth to 2.3 children. Eighteen per cent (143/788) of the women were nullipara (Table 2).

The age at admittance to Radiumhemmet varied from 14 to 85 years (mean 46.8 years) (Table 3).

All women were followed up until death, or at most to middle of February 1986. The mean age at the last follow up date was 73.7 years (range 15 - 99 years) (Table 3).

At the last follow up date 577 (73%) of the women were reported dead. The most common cause of death was cardiovascular disease (39%) and the second most common cause was malignant tumours (15%) (Table 4).

The majority of the women - 65 per cent - lived in the Stockholm area, whereas 17% of the women lived in small towns. Eighteen per cent of the women lived in the country side.

Table 2.
THE RADIUMHEMMET METROPATHIA SERIES. BLEEDING HISTORY, MENARCHE AND PARITY.

	mean	range
Bleeding history months	20.8	0 - ≥88
Not known %	2	
Age at menarche (years)	14.1	7 - 20
Not known %	64	
Parity	2.3	0 - 13
Not known %	5	
Nullipara %	18	

Table 3.
THE RADIUMHEMMET METROPATHIA SERIES. AGE AT ADMITTANCE AND FOLLOW UP.

Median year of birth		1895
Age at admittance to Radiumhemmet, mean, range (years)	46.8	14 - 85
Age at follow up mean, range (years)	73.7	15 - 99
Median age at follow up (years)	76	

Table 4.
THE RADIUMHEMMET METROPATHIA SERIES. CAUSES OF DEATH.

	No. of cases	%
Cardiovascular disease	308	39
Malignant tumour	121	15
Lung disease	49	6
All other causes	99	13
Total	577	73

STANDARD TREATMENTS

When treatment of metropathia started during the 1910's, brachytherapy techniques were mostly used (Heyman 1922) (9). Small Dominici-tubes filled with about 6.3 mg radium-226 were applied into capsules. The filtering properties were equal to 1 mm of lead. Three of these capsules (19 mg Ra-226) were applied into a rubber tube, which was inserted into uterus. The treatment time varied from 16 to 20 hours (about 350 mgh). From 1921 and onwards, 4 capsules (each containing 9.5 mg Ra-226) were used in the same manner (Fig. 1) and the treatment time was reduced to 16 hours (about 600 mgh). A small number of patients were treated only with vaginal applicators. For the latter, about 75 mg radium-226 was divided into two metal alloy capsules. The filtering property of the capsules was equal to 3-4 mm of lead. These capsules were applied to the vaults of vagina with a "spacer" in between and secured by tampons (Fig. 2). The treatment time was usually 25 hours (about 1900 mgh). The estimated absorbed dose to the ovaries from the intrauterine radium treatment (40 mg, 16 h) was 4 Gy and 3.5 Gy from the vaginal treatment (75 mg, 25 h). The distance from the uterine cavity to the midpoint of the ovary has been estimated to 3.5 cm.

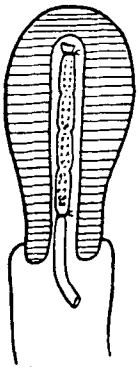

Fig. 1. Intrauterine radium treatment. A rubber tube with four capsules inserted in the cavity. Schematic drawing. (From Lärobok i gynekologi by C D Josephson, Alb Bonniers boktryckeri, 1922).

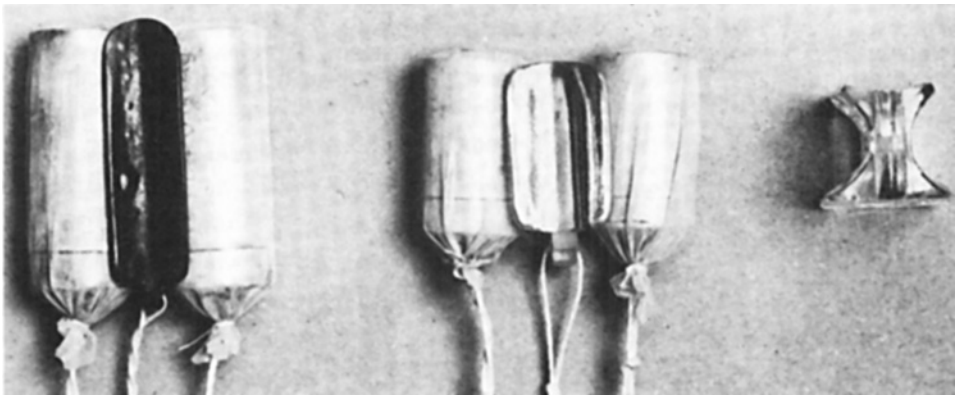

Fig. 2. Intravaginal radium treatment. Pair of Capsules with spacer in between. (From J. Heyman, Acta Radiol 16: 129, 1935 by permission)

Women who were found not suitable for the brachytherapy were treated with orthovoltage X rays (175 kVP, HVL 1 mm Cu). The treatment was administered by two anterior and one posterior portal (field sizes 75 cm^2 and 175 cm^2, respectively). The anterior portals were given over the ovaries and with compression. The absorbed dose to the ovaries was about 6 Gy per treatment session. This treatment could be repeated after an interval of at least one menstrual cycle. Most women were treated with one of the three standard techniques. Some women, however, received a smaller or greater absorbed dose to the ovaries.

RESULTS

657 women were treated with radium application, of whom 33 needed more than one application. External radiotherapy was given to 115 women. Nineteen had more than one treatment course. A combination of intracavitary brachyradiumtherapy and external irradiation was given to 16 patients.

Almost half of the women (48 per cent) had no bleedings after treatment. A few women still had severe bleedings (5 per cent) and 8 per cent had continuous regular menstruation (Table 5).

The estimated absorbed doses to the ovaries in the three groups no bleeding, severe bleedings and regular menstruation were on an average 4 Gy, 5 Gy and 4 Gy, respectively. The ranges were 1 - 24 Gy, 1 - 15 Gy and 1-12 Gy.

Table 5.
THE RADIUMHEMMET METROPATHIA SERIES. TREATMENT RESULTS.

	cases	%
No remaining bleeding	376	48
Mild remaining bleeding disorders	180	23
Moderate remaining bleeding disorders	41	5
Severe remaining bleeding disorders	39	5
Continuous menstruation	60	8
Not known	92	12

Table 6.
THE RADIUMHEMMET METROPATHIA SERIES. HORMONAL WITHDRAWAL SYMPTOMS FOLLOWING TREATMENT.

	cases	%
No symptoms	281	36
Mild symptoms	170	22
Moderate symptoms	133	17
Severe symptoms	51	6
Not known	153	19

Two patients gave birth to a child at 31 and 46 years of age, respectively, 5 and 4 years after the intracavitary treatment. The estimated absorbed dose to the ovaries was 1 Gy and 4 Gy, respectively.

The most common cause of death was cardiovascular disease. The risk for cardiovascular death compared to the National death rates of the female Swedish population was 0.92. The risk among women treated before versus after age 50 compared to the risk in the population was 1.02 and 0.76, respectively. The second most common cause of death was malignant tumours. Among the irradiated women 107 malignant tumours were observed during the period 1958 to 1982 compared to the expected number 90.2 calculated from the cancer incidence of Sweden for the corresponding period, which gave a risk ratio of 1.19.

DISCUSSION

Information on what radiation dose that impairs the human ovarian function permanently or temporarily is rare in the literature. Doll and Smith (7) estimated that an ovarian dose of 360 to 720 rads gave permanent stop of menstruation in nearly all patients. Lushbaugh and Ricks (17) estimated the 50% probability level for permanent sterility to be around 2,000 rads over a 6 week regimen. With increasing number of fractions the probability for temporary sterility increases. Kaplan (14) reported that a skin dose of 50 to 75 R, given twice to an anterior pelvic field and once or twice to a posterior pelvic field did not result in permanent ovarian impairment. International Commission on Radiological Protection (ICRP) (12) stated that a brief single dose of 2.5 to 6.0 Sv or a highly fractionated or protracted exposure of 6.0 Sv to the ovary results in sterility.

The curative effect of radiotherapy on bleeding disorders (48%) in the present study was in the same level as the results (48.6%) reported by Barr (2). The women in Barr's study received intracavitary radium 50 mg for 30 hours. The calculated dose rate was 406 rad per hour and the ovarian dose was estimated to be less than 200 rads. Hundley et al (10) reported immediate stop of bleeding in 67% after one intracavitary radium application of 100 mg for 20 hours. Hunter et al (11) described a failure rate of only 3.9% after intracavitary radium applications. The amount of milligram hours (mgh) delivered to the uterine cavity varied from few to 3,500. Kottmeier (16) determined that the ovarian dose was 350 - 400 R when the metropathia treatment was given through one anterior pelvic field. With the intracavitary radium applications the ovarian dose measured in phantom was 150 - 250 R. The varying results may be explained by different position of the uterus causing varying ovarian doses. Kaplan (15) reported a series of women irradiated because of sterility. The average dose given to the ovaries was 65 rads with a range of 50 to 90 rads. Some 55% of the women conceived after irradiation.

Moderate or severe menopausal symptoms occurred after therapy in 23% in the present series as compared to 46.5% moderate and severe flushing reported by Turnbull (22,23). Thirty six % were free of postmenopausal symptoms in our series. An increased risk of cardiovascular disease after radiotherapy is reported by Brinkley, Darby and Smith et al (3,6,20,21). Surgically induced menopause is reported to be followed by an increased risk of cardiovascular disease (4,13,19,25).

The relative risk of 1.19 in this report to develop a malignant tumour after irradiation for metropathia is in the same order as the risk reported by Wagoner (1.3) (24). The reported relative risk of malignant tumours secondary to radiotherapy for benign bleeding disorders varies from 1.0 to 2.1 (1,3,5, 7,21).

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