

Menstruation and Pregnancy in Hodgkin's Disease (Lymphadenoma).

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THE incidence of Hodgkin's disease in pregnancy in a patient who came under my observation in 1919, has led to this further investigation of the clinical records and literature of the disease, on account of its rarity, its gravity and the obscurity of the ætiology.

As to its rarity : it is a remarkable fact that in a very extensive search through the literature of the subject one other case only has been found fully recorded.¹

The patient referred to in the opening sentence is a married lady, Mrs. W. A., æt. 23 (Case 1), i-para, and living in comfortable circumstances.

In July, 1919, she gave a history of having missed one menstrual period and complained of a "stiff neck" and a slight hæmorrhage per vaginam.

Her previous history was that she had been perfectly healthy, her menses had been regular and her first child was born in August, 1918, at full time, a normal but precipitate labour with a normal puerperium and a healthy child.

Examination showed that there were enlarged, discrete glands in the left anterior triangle of her neck of a soft consistence, and also that she was suffering from a threatened abortion. By rest in bed the abortion was averted. At this time it was thought that the glands were tubercular, and in view of the threatened abortion and the fact that she was on a holiday in a very healthy part of the country, no treatment of them was undertaken.

The pregnancy continued and the glands increased in size but remained discrete and soft without showing any signs of inflammation or of breaking down. This aroused the suspicion that the condition was Hodgkin's disease.

In November, 1919, the patient being then four and a half months pregnant, it was decided to remove the glands, as this

would probably effect a cure if they were tubercular and in any case pathological examination would show the exact nature of the lesion.

The micro-photograph here reproduced shows the appearances seen in these sections, which demonstrates that the lesion is that of Hodgkin's disease—proliferation of the endothelial cells and the appearance of multinucleated cells irregularly placed.

The recovery from the operation was without incident. Subsequently the patient was treated with arsenic and extract of lymphatic gland internally and X-rays were applied over the area from which the glands had been removed.

The pregnancy continued to term when a healthy male child was born. The labour and puerperium were normal.

For several months after delivery the above treatment was continued and all traces of glandular involvement disappeared. The patient appeared to be cured.

In 1920 the third pregnancy commenced, and at the eighth week glands began to appear in the old site and enlarged rapidly.

The advisability of terminating the gestation was considered, as the previous glandular enlargement had been coincident with conception and had grown with gestation. It was decided that this should be done, but, in the meantime, the patient was attacked by influenza with a temperature ranging from 101.8 to 103 and aborted spontaneously. Further treatment on the above lines again restored her to health in a few weeks.

A fourth pregnancy commenced in the spring of 1922, and when she was seen in September her uterus was the size of a 20 weeks' gestation, and there were some small masses in the left anterior triangle, which, she said, she had first noticed about the 21st of August.

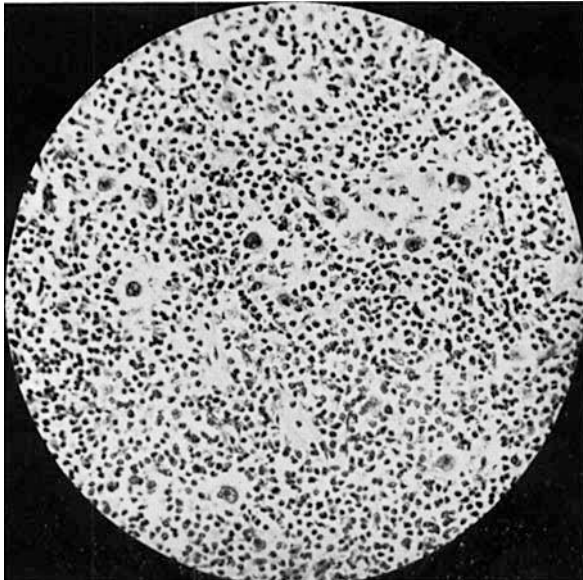
Treatment as before was immediately recommenced and the neck improved. On January 25th, 1923, she was delivered of a healthy male child, the labour and puerperium being normal. No glands can now be felt.

It is a noteworthy fact that in this case, throughout, no other superficial lymphatic glands have been involved and there have been no signs or symptoms of involvement of the deep groups of glands.

It was the study of the best course to adopt in the treatment of these cases, with reference to the intercurrent pregnancy, which was the inspiration of this paper.

An examination of the literature revealed only the following generalizations:—

Professor George Murray, writing in Allbutt and Rolleston's "System of Medicine"² states: "The disease rarely occurs during



pregnancy, but several cases have occurred shortly after childbirth and have run a very acute course—ending fatally in a few weeks. Parturition has thus an unfavourable influence upon the progress of the disease.”

Sir William Gowers in Reynolds' "System of Medicine,"³ states: "In one case only" (out of 25 fatal female cases) "did the disease apparently commence during pregnancy. The progress of the disease was, in another, distinctly checked during pregnancy, and it advanced rapidly after delivery. In several cases the first symptoms of the disease were observed soon after childbirth, and in one of these recorded by Trousseau⁴ there had been a large post-partum hæmorrhage."

The following facts are based on a study of 57 cases of Hodgkin's disease in the female. Eight of these cases were treated in the Liverpool hospitals during the past seven years. These are all cases whose history I have been able to ascertain personally. The remaining cases are collected from the literature.

The age of incidence of the disease is set out in the following table, and it will be noted that it corresponds fairly closely with that prepared by Sir Wm. Gowers in the article already quoted, except that the percentage of cases under ten years of age is smaller in this collection. It also bears out the statement of James H. Hutchinson⁵: "The liability to the disease would, therefore, appear to increase up to 30, and after that to diminish."

TABLE I.

up to 5 years	3	20-30 years	18
5-10 "	2	30-40 "	12
10-15 "	5	40-45 "	1
15-20 "	8	over 45 "	8

This gives 39 cases during the normal period of menstrual activity, or 69.64 per cent., and 30 cases between 20 and 40, which may be taken as the normal child-bearing period, *i.e.*, 53.5 per cent.; while eight cases (12.2 per cent.) occurred after the normal menopause.

In those cases, 39 in number, in which it has been possible to ascertain the civil state of the patients, 16 are found to be married and 23 single.

In 17 cases only, all between puberty and the menopause, was the menstrual history obtained, and of these 14 patients show varying degrees of oligomenorrhœa, even as far as complete amenorrhœa in some cases. In the other three cases the menses do not appear to have been disturbed by the disease (see Table 2).

TABLE II.

Menstrual history of 17 cases of Hodgkin's Diseases.

Case Number.	Age.	Menstrual History since onset of disease.
1. W. A.	23	Regular
3. F. J.	27	Irregular with dysmenorrhœa
4. M. H.	32	Complete amenorrhœa
5. M. G.	25	Complete amenorrhœa
7. L. H.	25	Irregular and scanty with dysmenorrhœa
11. A. B.	32	Regular ¹
14.	17	Amenorrhœa ⁶
17. W. A. B.	40	Regular, but scanty, with dysmenorrhœa ⁷
18. G. G.	28	Regular ⁷
19. I. H.	22	Regular, but scanty ⁷
20. J. P.	27	Regular 28—35 day type; scanty flow ⁷
21. M. K.	28	Suppressed ⁸
48.	32	Nil; abnormal before onset ⁹
49.	36	Scanty, intervals of 4—6 weeks ⁹
51.	19	Suppressed ⁹
52.	23	Considerable irregularity with scanty flow ⁹
53. N. B.	35	Amenorrhœa ¹⁰

Of the 16 married women, six dated the onset of their disease from some pregnancy, while in six other cases it is not stated whether they had had any children or not. Thus in ten definitely parous women six dated their disease from a pregnancy (see Table 3).

TABLE III.

Time of onset of disease in six parous women.

Case Number.	Age.	Parity.	Date of onset of disease.
1. W. A.	23	2	2nd month of 2nd pregnancy
11. A. B.	32	5	3rd month of 5th pregnancy
16. X.	23	2	3rd or 4th month of 2nd pregnancy
18. G. G.	28	6	Just after birth of 6th child
48.	32	1	3rd month of pregnancy
49.	36	7	Early in 6th pregnancy

It is realized that 57 cases is a very small number from which to draw any conclusions, but Hodgkin's disease in the female is not common.

The following facts which emerge from a study of the foregoing tables are worthy of notice,

69.64 per cent. of the cases occur during the period of normal menstrual activity, and 53.5 per cent. occur during the normal child-bearing period, which may be considered as the period of maximum activity of the female sexual organs. But, on the other hand, if those cases are considered in which the disease first appeared during physiological amenorrhœa one finds (*a*) before puberty, 10; (*b*) after menopause, 8; (*c*) during pregnancy, 5; (*d*) during lactation, 2; a total of 25 cases, or 45.85 per cent., which is a surprisingly high figure.

Two facts issue from the foregoing :—

- (1) The disease is frequently accompanied by diminution in the menstrual flow.
- (2) Nearly half of the cases in this series had their onset during periods of physiological amenorrhœa.

Further, it is an established fact that the disease is more common in males than in females (4 to 1—Osler).

A consideration of these facts with a view to their possible correlation has led me to the following conclusions.

The female is, in some measure, protected against this disease to a greater extent than the male; to explain this on an anatomical or physiological basis one must look to the female sexual organs and female endocrine system as being the main points of difference between the sexes. The only organ which plays a part in both systems is the ovary.

If there is a hypo-function of the ovary oligomenorrhœa will occur in varying degree, depending on the amount of ovarian involvement.

Prior to puberty and after the menopause there is no ovarian hormone poured out. The question of what becomes of this hormone during pregnancy is a very difficult one, and there is little information in the literature, but opinion appears to point to its being used up locally in the nutrition of the rapidly growing uterus and fœtus, while most authors favour the view that during the first three months of pregnancy the true ovarian hormone is replaced by that of the corpus luteum whose function is concerned almost entirely with implantation of the ovum. It is important, in this connexion, to recall that, in those cases in Table 3, in which the onset of the disease is related to pregnancy, five out of the six cases occurred in the early months.

Therefore it may be that as long as there is sufficient ovarian hormone in the general circulation the individual can resist the disease; should, however, this amount be reduced by any cause, Hodgkin's disease may occur, and once this has happened the function of the ovary is inhibited, both by the disease itself and by

the anæmia which is a part of it, although often only very mild in degree.

The obvious inference from this suggestion is that in addition to treatment on the present well recognized lines of arsenic and X-rays, ovarian extract should be given to the patients to prevent the spread of the disease and give the individual the opportunity of dealing with it.

Post mortem examination notes of the sexual organs are available in only four cases (Table 4), but these are of great interest in support of the above suggestion.

TABLE IV.
Post Mortem Notes.

Case Number.	Age.	P.M. Notes on Sexual Organs.
11. A. B.	32	Uterus and ovaries normal
40. D. R.	55	Uterus and appendages normal ¹¹
41.	24	The Fallopian tubes showed evidence of tubercular disease ¹²
56.	31	"The body was more of the male than of the female type. ¹³ The uterus is small, measuring but 6 cms. from cervix to fundus. Cervix presents scars of old stellate lacerations. The arbor vitæ of the cervical canal is indistinct. The mucous membrane of the uterine cavity is anæmic and atrophic. The vagina is atrophic. The ovaries are small and atrophic and recently ruptured follicles are not to be seen."

In Case 11 the ovaries are reported as normal macroscopically, but it does not necessarily follow that its hormonal activity was normal. A normal ovary of a patient of 55, as in Case 40, must, necessarily, be atrophic, and this is supported by the history of the case which states that the disease commenced seven years after the menopause.

Case 56 presents very important evidence, for here are found small atrophic ovaries without trace of recently ruptured follicles—a proof of diminished hormone production—and the result of this on the patient is shown by the general form of the body being more male than female. Unfortunately it has not been possible to ascertain if this woman suffered from amenorrhœa before the onset of the disease.

Table 5 gives the course of the labours and puerperia of those who were known to be suffering from the disease prior to their confinements.

TABLE V.

Case Number.	Labour.	Puerperium.
1. W. A.	Normal	Normal
11. A. B.	Normal	Temperature varied from 102°—105°. Died on 190th day
12. E. H.	Severe P. P. H. (had had floodings after previous labours, but this was the worst).	Normal ⁶
16. X.	Normal	Normal at first; died some months later.
48.	Normal	Normal
49.	Normal, rapid	Normal; left hospital on 12th day

Abortions occurred in only three cases and a premature labour at the seventh month in one case.

In two other cases, Nos. 18 and 50,⁹ pregnancy occurred during the disease. Nothing is known of the labour or puerperium in either of these cases. The after history of Case 50 is also unknown, but letters addressed to patient No. 18 having been returned unclaimed, death may be presumed. This gives three deaths in eight cases, but in case No. 11 the condition of the patient was so bad before delivery, owing to implication of the spinal cord, that it is exceptional. Even excluding this the mortality is 25 per cent., which is very high.

All the six reported labours were normal, but that in Case 12 was complicated by severe post-partum hæmorrhage. This complication should always be anticipated on account of the liability to hæmorrhages in this disease.

No conclusions can be drawn from the three cases of abortion, for in only one did it occur definitely during the presence of Hodgkin's disease, and in this case took place during an inter-current infection by influenza.

The outlook for the labour itself, then, in these cases is good, but the ultimate prognosis is poor.

But in such a case as No. 1, in which the disease is apparently not very advanced, and the treatment with arsenic and X-rays is keeping its progress in check, it appears that in the intervals between child bearing, while the ovary is functioning normally, the patient is in good health. As soon as the hormonal activity of the ovary is checked by pregnancy, the disease progresses again.

Arguing from this, it would appear that when Hodgkin's disease is diagnosed in its early stages and in the early months

of a pregnancy, it is advisable to empty the uterus, to allow the ovary to return to its proper function and to employ the means already stated to treat the existing disease. This statement is supported by the facts stated in connexion with the natural abortion in Case 1 in 1920, after which the glandular involvement disappeared in a few weeks. Further, the woman should be warned of the dangers of future pregnancies.

If Hodgkin's disease is advanced the termination of the pregnancy would probably be too late, and if the pregnancy is far advanced it is likely that the outlook in an artificially produced puerperium would be no better than if the patient were allowed to go to term.

CONCLUSIONS.

1. Oligomenorrhœa is a symptom of Hodgkin's disease and is not produced only by the anæmia present.
2. When early Hodgkin's disease and early pregnancy occur together the pregnancy should be terminated.
3. Possibly Hodgkin's disease occurs, in the female, chiefly when there is a hypo-function of the ovary.

I thank most gratefully Dr. J. E. Gemmell for his kindness in bringing Case No. 1 to my notice, and the following gentlemen for allowing me to investigate their cases:—Prof. Hill Abram, Drs. R. J. M. Buchanan, John Hay, Murray Bligh, and Pemberton, Mr. K. W. Monserrat, all of Liverpool, and Dr. Henry M. Bowing of the Mayo Clinic.

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