

it be considered a specific in bringing about recovery.

Observations on the group of cases having a hæmorrhagic diathesis unrelated to a deficiency in prothrombin corroborates observations of others that there is no reason or rationale for the administration of vitamin K or synthetic compounds to patients who show normal prothrombin times.

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RÉSUMÉ

Les substituts synthétiques de la vitamine K ont été employés, 1° dans des cas d'ictère par obstruction avec troubles dans le rythme de la prothrombine; 2° dans des cas de troubles prothrombiniques avec lésions hépatiques, et 3° dans des cas de diathèse hémorrhagique sans ictère et sans troubles de la régulation de la prothrombine. Les premiers ont répondu de façon satisfaisante à la thérapeutique par la vitamine K synthétique. Les seconds ont répondu de façon moins constante. Les troisièmes n'ont été aucunement influencés. Les composés synthétiques peuvent agir aussi bien par la bouche que par les voies intraveineuses et intramusculaires. Le voie parentérale a cependant l'avantage d'être efficace sans sels biliaires ajoutés et elle ne provoque pas de nausées.

JEAN SAUCIER

THE INFLUENCE OF MENSTRUATION ON CARBOHYDRATE TOLERANCE IN DIABETES MELLITUS*

By H. I. CRAMER

Montreal

DIABETES mellitus has long been known to exert a marked influence on menstruation and sexual function. Formerly amenorrhœa was quite common in diabetics and was frequently associated with an impairment of libido and sterility.¹ Similarly, in the male diabetic impotence and sterility were frequent findings. Anatomically, in female diabetics an atrophy of the uterus and ovaries has been reported,² which has been regarded as secondary to the diabetic condition. However, since the discovery of insulin and the resulting improvement in treatment such anatomical and physiological sexual abnormalities in diabetics have become infrequent.

Also, during the past 15 years a great deal of information regarding the relationship of the anterior pituitary gland to carbohydrate metabolism and diabetes mellitus has been accumulated. This work began with the important contributions of Houssay and his collaborators,^{3, 4}

who demonstrated that, in an animal made diabetic by pancreatectomy, hypophysectomy ameliorated the diabetic state, while, on the other hand, treatment with anterior pituitary extract aggravated it. Later it was shown that a normal animal with an intact pancreas became diabetic when treated with anterior pituitary extract. Furthermore, it has been demonstrated recently by Young,⁵ Campbell and Best,⁶ and Dohan and Lukens⁷ that prolonged treatment of normal animals with anterior pituitary extract induces a diabetic state which persists even after discontinuation of the extract and remains permanent.

During the same period the relationship between the anterior pituitary and sexual function and menstruation has also been worked out in considerable detail. It has been satisfactorily shown that normal menstruation occurs only after oestrogen and corpus luteum hormones have acted upon the endometrium and that the elaboration of these hormones by the ovary is in turn controlled by gonadotropic hormones secreted by the anterior pituitary. Failure of

* From the Department of Metabolism, Royal Victoria Hospital and the McGill University Clinic, Montreal.

the secretion of these gonadotropic hormones by the pituitary is followed by the cessation of the formation of oestrogens and progesterone by the ovary, resulting in amenorrhœa. It is also known that maturation of the ovum and ovulation, and therefore fertility, are controlled by the anterior pituitary.

In view of the above facts a study was undertaken to show whether menstruation had any effect on the carbohydrate tolerance of the diabetic female. A review of the literature suggests the probability of a moderate lowering of carbohydrate tolerance with menstruation. Von Noorden⁸ made this observation years ago; he claimed that 20 per cent of diabetic females manifest a tendency to decreased carbohydrate tolerance during menstruation. In 1918 Harrop and Mosenthal⁹ reported the case of a female in diabetic acidosis who, after showing some improvement, became much worse with the onset of menstruation and later died in diabetic coma during a menstrual period. Rosenbloom¹⁰ observed a daily glycosuria of 10 to 22 gm. during menstruation in two females who ordinarily were free from glycosuria. Recently Peperkorn¹¹ reported two cases of diabetic acidosis occurring during menstruation. Although both of his patients improved, their condition became aggravated again at the following menstrual period. This author states that he has observed 14 cases in which the diabetes became worse during menstruation.

A similar, though less marked lowering of carbohydrate tolerance has also been noted in normal, non-diabetic women during menstruation. Heilig¹² investigated the glucose tolerance of a number of normal females during menstruation and in the intermenstruum. He found that in a large proportion of cases there was a marked impairment of carbohydrate tolerance on the first or second day of menstruation. His figures indicate that during the menstrual period the peak of the venous glucose curve was in some cases as much as 100 to 150 mg. per cent above the fasting level, that the drop to normal occurred in four to five hours, and that glycosuria was present. The fasting blood-sugar levels were investigated in a number of cases by Bloch and Bergel.¹³ They found that the curve of the fasting blood sugar in sexually mature females reaches its lowest level in the intermenstruum, rises gradually with the beginning of the premenstruum, gains its maximum on the first day of bleeding, and then

returns to the intermenstrual level at the end of menstruation. Similar findings have also been reported by Pucher and others¹⁴ on this continent. A number of Italian workers^{15, 16, 17} also studied this problem. They all agree that at menstruation there occurs a rise in the blood sugar, some claiming that in spite of this the blood sugar remains within normal limits and others claiming that an actual hyperglycæmia results. Garafi and Ruggeri performed as many as 1,000 glucose tolerance tests on 93 healthy females at different parts of the menstrual cycle. Their lowest blood sugar values were found at about the time of ovulation; a rise occurred during the premenstruum and reached its maximum with the onset of menstruation. Then the values gradually dropped again to reach a minimum level within 12 days.

The influence of menstruation on the course of diabetes was investigated by the two following methods: (a) A statistical review of cases of diabetic acidosis in females who were menstruating regularly, to observe the incidence of acidosis at the time of menstruation. (b) An investigation of blood sugars before, during, and after menstruation.

REVIEW OF CASES OF DIABETIC ACIDOSIS

An examination was carried out of the hospital records of all female diabetics between the ages of 14 and 45 years who were admitted in acidosis to the Royal Victoria Hospital from 1922 (date of beginning of insulin therapy) to 1940. This age-group covers the period of sexual activity and extends from puberty to the menopause. The records were searched as to whether the patient was menstruating at the time of admission to the hospital. The case history occasionally indicated when the patient's last menstrual period had occurred, and a few instances yielded the information that the patient was menstruating when the symptoms of acidosis were developing, even though she was not menstruating at the time of entrance into the hospital. These sources of information are naturally imperfect. The error however, is more likely to be one of failing to record menstruation when this was occurring.

Our purpose was to observe what percentage of the cases menstruated on admission to the hospital or just before or after. Those cases were therefore omitted whose records indicated that they were amenorrhœic, or where puberty had not yet occurred. Furthermore, since the

aim of the investigation was to observe if menstruation could disturb a case of presumably controlled diabetes, those cases were also omitted that had entered the hospital for the first time and had not had any previous diabetic treatment, as well as those cases that were complicated by infection. The latter had temperatures ranging from 100° F. to 105.8° F., and infections alone are known to upset cases of well-controlled diabetes.

TABLE I.

ANALYSIS OF CASES OF FEMALE DIABETICS, AGE 14 TO 45 YEARS, ADMITTED IN ACIDOSIS FROM 1922 TO 1940

<i>Type of cases</i>	<i>No. of cases</i>
Cases before puberty	7
Cases with amenorrhœa	5
Cases with infection	5
Cases admitted to hospital for first time. (Not treated before)	17
Treated cases, without infection, not menstruating on admission	19
Treated cases, without infection, menstruating on admission	17
Total	70

RESULTS

Table I shows an analysis of all the cases. Of a total of 70 female patients in diabetic acidosis between the ages of 14 and 45 years there were 36 who were menstruating regularly, who had been treated for diabetes previously, and who did not manifest any infection on admission to the hospital. Of these 36 cases 17 were menstruating on admission or two days before or after admission. That is, in 47.2 per cent of the cases of acidosis in which the precipitating cause was neither infection nor lack of treatment, menstruation occurred at or about the time that the acidosis developed. These figures indicate the number of hospital admissions. The number of patients in this series of admissions was smaller. The 36 admissions were composed of only 14 patients and of this number 6, or 42.8 per cent, were admitted in acidosis at the menstrual period or just before or after on one or more occasions. There were also some cases who were admitted in acidosis during the menstrual period at one time and who at another time developed acidosis during the interval between two periods.

In looking through our series of cases of diabetic acidosis one was also impressed by the small number of males as compared with females. Therefore a search was made of the number of male cases of acidosis between the ages of 14 and 45 years irrespective of the cause. This

number consisted of only 26 admissions as compared with 70 female admissions in the same age period. That is, of a group of 96 cases of acidosis in patients of ages 14 to 45 years, 27 per cent were males and 73 per cent were females. The difference becomes noteworthy when one realizes that in this age-period the incidence of diabetes is greater in the male than in the female.¹

BLOOD SUGAR INVESTIGATION AT MENSTRUAL PERIOD

In a series of eleven menstruating diabetic females the blood sugar was determined before, during, and in some cases after the menstrual periods. During the time of investigation each patient was following a constant diet and taking a constant dose of insulin. Eight of these were Out-Door clinic patients. In these the blood sugar was examined on every occasion at about 2½ hours after breakfast. The blood sugar was generally estimated every second day before, during, and, in some cases, after the menstrual period. The remaining three were ward patients. In two of these the blood sugar was examined under fasting conditions and at four hours after the morning insulin, while in the third case (F.D.) it was examined at these periods as well as at 1½ hours after lunch and at 9 p.m. In the latter case as well as in one of the other two ward cases, the CO₂ combining power was determined at the same time. The blood sugars were estimated by the Folin-Wu method and the CO₂ combining power by the volumetric Van Slyke technique.

RESULTS

The findings, on the whole, did not substantiate the results obtained in the first part of the investigation. Most of the patients failed to show any noteworthy disturbance of the carbohydrate metabolism at the menstrual period. Quite a number did manifest some rise of the blood sugar values during menstruation, but this rise was generally small. In comparing the mean sugar values (Table II) during menstruation with those before and after it was found that 2 of the 11 cases showed a lower mean during menstruation, while the remaining 9 showed a higher mean value during the period. In these 9 cases the difference between the menstrual and premenstrual blood sugar values varied between 8 and 115 mgm. per cent, while that between the menstrual and postmenstrual values varied between 3 and 170 mgm. per cent.

TABLE II.
COMPARISON BETWEEN MEAN BLOOD SUGAR VALUES
BEFORE, DURING AND AFTER MENSTRUATION

Case	Blood sugar—mgm. per cent		
	Premen- strual	Men- strual	Postmen- strual
A.N. 2½ hours after breakfast	108	101	...
B.L. " " " "	137	118	...
G.N. " " " "	114	132	...
M.W. " " " "	187	202	176
C.D. " " " "	208	312	260
D.L. " " " "	172	209	172
R.B. " " " "	...	370	150
M.N. " " " "	107	165	128
E.D. (a) fasting	93	132	117
(b) 4 hours after morning insulin	96	104	101
A.L. (a) fasting	314	324	220
(b) 4 hours after morning insulin	188	231	186
F.D. (a) fasting	399	440	344
(b) 4 hours after morning insulin	241	356	242
(c) 1½ hours after lunch	374	401	335
(d) 9 p.m.	218	143	162

It should be noted here that in a few cases the blood sugar rise began to appear just before menstruation and, as in case F.D. (Fig. 1), may have reached its peak immediately before the onset of menstrual bleeding. The most striking findings were in Case F.D. (Fig. 1), who was admitted to the ward purposely for this investigation and who was studied quite thoroughly. This patient manifested a marked rise of the blood sugar four days premenstrually. This

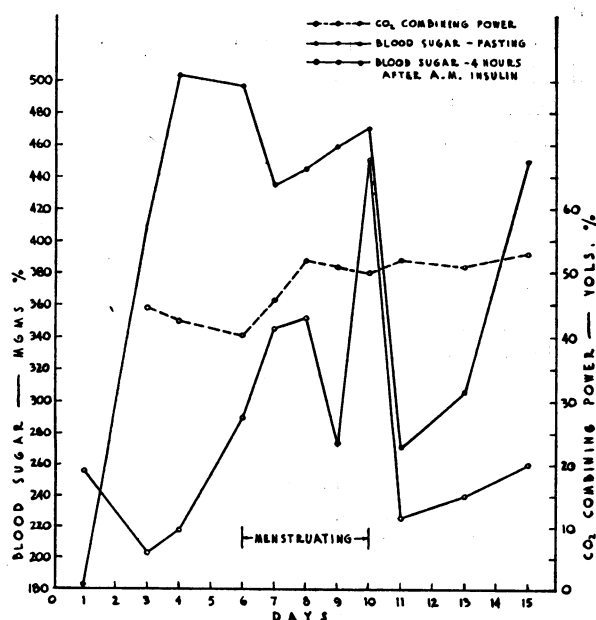


Fig. 1.—Case F.D., juvenile diabetic. Diet: 70 gm. protein, 50 gm. fat, and 200 gm. carbohydrate. Taking 24 units crystalline zinc insulin before breakfast and before supper. CO₂ combining power was not estimated before the third day after admission. Daily urinalysis showed acetone for first time only on third day.

rise persisted during the period. The drop postmenstrually, however, was comparatively slow and never reached the initial level. The CO₂ combining power was also studied in this case. Four days prior to menstruation it was 44.5 vols. per cent, dropping to 40 vols. per cent one day premenstrually. It rose again, reaching 52 vols. per cent on the second day of menstruation, and remained normal thereafter. During this entire investigation both diet and insulin remained constant. Unfortunately, the CO₂ combining power was not estimated prior to the fourth day premenstrually but acetone and diacetic acid were found in the urine for the first time on that day. The CO₂ combining power was also studied in Case A.L., in whom it remained normal. This patient did not exhibit a pronounced rise of blood sugar values.

DISCUSSION

The results obtained in the first part of our investigation were striking. After excluding the cases of diabetic acidosis associated with the two most common causes of this condition, namely, infection and non-treatment of the diabetes, we were left with a group of 36 cases of which 17, or 47.2 per cent, were menstruating at about the time the acidosis developed. Such a high incidence of the association between menstruation and acidosis cannot be regarded as a mere coincidence. Furthermore, since infection and lack of treatment of the diabetes are not causes of the disturbed carbohydrate metabolism in this series it appears likely that menstruation was the precipitating cause of the acidosis in this group.

It should be noted here that among the 17 cases of acidosis not included in the group of 36, because the diabetes was not treated before admission to the hospital, two were menstruating at the time of admission. Indeed, in one case the history suggested very strongly that the diabetic state started at the menstrual period.

The results of the second part of the investigation are not so convincing. However, most of the patients did show some rise of the blood sugar values at the menstrual period, and in a few this rise was quite marked. In one patient the CO₂ combining power fell to 40 vols. per cent. This was a case of juvenile diabetes which was admitted to the ward merely for investigation and had no complaints whatever. The diabetes appeared to be fairly well controlled before admission. Furthermore, no change in diet or insulin was instituted after admission to

the hospital. On the whole, therefore, the findings in this group of cases do confirm in some degree the conclusions drawn from the first part of the investigation that there is a lowering of carbohydrate tolerance at menstruation. The failure to obtain more striking results may be interpreted as meaning that not all diabetic females show a disturbance of carbohydrate tolerance during menstruation, and that in some cases there may occur such a disturbance at one menstrual period and not at another. This latter phenomenon was illustrated in our statistical study.

E. H. Mason¹⁹ has also observed the case of a middle-aged female whose menstrual periods were frequently delayed by 8 to 12 days. Whenever this delay occurred, the insulin requirement rose from 8 units regular insulin twice daily to 32 units twice daily. When menstrual bleeding set in the insulin requirement gradually returned to its previous level. During the period the diet remained constant. If, on the other hand, the period occurred normally the insulin requirement remained unchanged.

The difference in the incidence of diabetic acidosis in males and females is also striking. There were practically three times as many cases of acidosis in females as in males in the age period in which the normal woman menstruates. This is particularly remarkable when one remembers that the incidence of diabetes is greater in the male than in the female before the age of 45 years.¹ In view of the frequency of diabetic acidosis at menstruation one wonders if the greater incidence of acidosis in young women is not at least partly due to the disturbance in carbohydrate tolerance that occurs in some diabetic females at the menstrual period.

SUMMARY AND CONCLUSIONS

There occurs in some diabetics an impairment of carbohydrate tolerance at the menstrual period. This may be severe enough to precipi-

tate diabetic acidosis and coma. This disturbance in carbohydrate metabolism at menstruation does not occur in all diabetic women. Furthermore, in the same patient this upset may take place at one menstrual period and not at another.

There is also a much smaller incidence of diabetic acidosis in males than in females below the age of 45 years, although in this period the incidence of diabetes mellitus is greater in the male than in the female. This higher incidence of acidosis in the female may be associated with the frequent occurrence of acidosis at the menstrual period.

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PRECEPTS OF EPICETUS

"Difficulties are the things that show what men are."

"A soul conversant with virtue resembles a perpetual fountain; for it is clear, and gentle, and potable, and sweet, and communicative, and rich, and harmless, and innocent."

"Nothing is meaner than the love of pleasure, the love of gain, and insolence. Nothing is nobler than magnanimity, meekness, and good-nature."

"In every affair consider what precedes and follows, and then undertake it."

"Consider carefully, know thyself, consult the divinity, attempt nothing without God."