Seven Cases of Jaundice in Women Taking an Oral Contraceptive, Anovlar

K. E. THULIN,* M.D.; JERKER NERMARK,† M.B.

Brit. med. J., 1966, 1, 584-586

There have been several reports recently of the possibility of liver damage following the use of oral-contraceptive pills. Cullberg *et al.* (1965) made a survey of 16 reports of investigations of liver function in patients on oral contraceptives. These reports included general clinical trials and solitary cases of jaundice published during the last three years. The reports were in part contradictory but it was possible to distinguish certain common features. In several large-scale long-term investigations of women in the reproductive years taking contraceptive pills serum-transaminase levels were found to be normal, with only solitary exceptions in some of the series. However, in two studies pathological bromsulphalein (B.S.P.) retention occurred in 4-20% of cases, while a number of smaller studies of menopausal women showed increase of transaminase values up to 100% and also occasional elevation of the serum bilirubin. But a recent report from Bakke (1965), who had treated 36 menopausal women with mestranol¹ or Enavid,² gave no evidence of significant changes in the liver-function tests.

Stoll *et al.* (1965) administered Lyndiol³ at six times the normal dosage to four menopausal women and reported two cases of jaundice, and elevated bilirubin values in the others. Liver biopsy showed centrilobular parenchymal-cell necrosis in all four cases and cholestasis in the two with jaundice. In addition, three recent reports have been published in which a total of about 400 young women had been treated with various oral-contraceptive pills. Two of these studies (Larsson-Cohn, 1965, and Eisalo *et al.*, 1965) reported slightly increased transaminase values in 4-18% and increased B.S.P. retention in 19-48%, but also elevated values of thymol turbidity in 3-11%. Swyer and Little (1965) found one case of increased bilirubin value in twelve women who had taken oral-contraceptive pills continuously for three to six years, but no other abnormal values in liver-function tests. Solitary cases of clinical jaundice in young women taking oral-contraceptive pills have also been reported by Adlercreutz (1964), Ikonen (1964), Sotaniemi *et al.* (1964) and Cullberg *et al.* (above).

Material

During a period of two months (December 1964 and January 1965) six women with clinical jaundice were admitted to the Department of Infectious Diseases, University Hospital, Lund, all of whom had been taking Anovlar⁴ for periods of time ranging from twenty days to six months. Four cases were under treatment for dysmenorrhoea or endometriosis; the other two had used Anovlar for contraceptive purpose only. The dosage was in all cases one tablet a day.

Case Reports

Case 1.—A gravida-0 aged 37 had complained of premenstrual tension and dysmenorrhoea, which often kept her in bed on the first day of menstruation. She had been under gynaecological observation for one year with suspected endometriosis in the pouch of Douglas.

Case 2.—A gravida-2 aged 29 gave a history of urticaria in childhood and a tendency for allergic eczema. One month before admission she had been operated on for pelvic endometriosis.

Case 3.—A gravida-0 aged 21 had suffered from severe dysmenorrhoea since puberty. In 1961 she had an illness with tonsillitis and painful joints.

Case 4.—A gravida-0 aged 19 complained of premenstrual tension and dysmenorrhoea. She gave a history of developing an allergic exanthematous rash after eating apples.

Case 5.—A gravida-3 aged 32 gave a history of eclampsia in 1953 and pre-eclampsia in 1963. At 16 she had had an illness described as "rheumatic fever and chorea." Since then she had been subject to recurrent painful swelling of the joints of the hands. She developed gall-bladder dyspepsia after eating eggs.

Case 6.—A gravida-2 aged 34 gave a history of premature delivery at the 33rd and 34th week respectively in 1949 and 1951. Jaundice had developed four days before her last delivery (incompatible Rh-group). Severe itching had occurred late in both pregnancies.

Investigation

All women were jaundiced on admission and afebrile with no other abnormal physical signs. No drug suspected of producing jaundice had been taken at the same time as the Anovlar medication in any of these cases. The patients gave no history of jaundice, and denied exposure to hepatitis. There was no explanation of the fact that so many cases of clinical jaundice associated with the use of oral contraceptives were collected in such a short period at one clinic. At the Department of Gynaecology, Lund, Anovlar was prescribed for about 500 women in 1964, and a number of private practitioners within the area also prescribed the drug.

The laboratory findings of interest are shown in Table I. Elevated bilirubin values and significantly raised transaminase levels were found in all six cases, but the thymol turbidity values were normal and in five of the six cases the alkaline phosphatase values were practically normal. Lactate-dehydrogenase values were normal. These results pointed to liver dysfunction in an acute stage, and differed from those in drug-induced jaundice in that the alkaline phosphatase level was not raised.

Electrophoresis of the plasma proteins was performed in four cases. The tests were carried out in the week following the onset of jaundice; all showed a similar distribution of the protein fractions with clear elevation of α_2 - and β -fractions. The γ -globulin fractions were within normal limits in three cases, but in Case 4 there was a slight increase. This pattern is similar to that seen in obstructive jaundice; normal γ -globulin values usually exclude infectious hepatitis or cirrhosis.

Liver Biopsy

Liver biopsy with a Vim-Silvermann needle was performed in the department of gynaecology. All six

* Head of the Department of Infectious Diseases, University Hospital, Lund.

† Now Senior Medical Officer of Health, Lund.

¹ Mestranol.—1 pill contains: 0.15 mg. mestranol (3 methoxy-17-ethinyloestradiol).

² Enavid.—1 pill contains: mestranol 0.075 mg. + norethynodrel 5 mg.

³ Lyndiol.—1 pill contains: mestranol 0.15 mg. + lynoesrenol 5 mg.

⁴ Anovlar.—1 pill contains: ethinyloestradiol 0.05 mg. + norethisterone acetate 4 mg.

performed in six of the cases with histological changes very similar to those seen in chlorpromazine-induced jaundice. The laboratory findings were a normal or only slightly raised alkaline phosphatase value and high transaminase levels. Certain features in the history were present in several cases: two had suffered from icterus and pruritus gravidarum, and this should be regarded as a contraindication to the use of contraceptive pills. The widespread use of oral contraceptives leads us to the supposition that this cause for jaundice is sometimes overlooked.

REFERENCES

- Adlercreutz, H. (1964). *Nord. med.*, **72**, 1004.
 Bakke, J. L. (1965). *Brit. med. J.*, **1**, 631.
 Cullberg, G., Lundström, R., and Stenram, U. (1965). *Ibid.*, **1**, 695.
 Eisalo, A., Järvinen, P. A., and Luukkainen, T. (1964). *Ibid.*, **2**, 426.
 ——— (1965). *Ibid.*, **1**, 1416.
 Ikonen, E. (1964). *Acta obstet. gynec. scand.*, **43**, Suppl. No. 5.
 Larsson-Cohn, U. (1965). *Brit. med. J.*, **1**, 1414.
 Sotaniemi, E., Kreus, K. E., and Scheinin, T. M. (1964). *Ibid.*, **2**, 1264.
 Stoll, B. A., Andrews, J. T., Motteram, R., and Upfall, J. (1965). *Ibid.*, **1**, 723.
 Swyer, G. I. M., and Little, V. (1965). *Ibid.*, **1**, 1412.
 Zimmerman, H. J. (1963). *Ann. N.Y. Acad. Sci.*, **104**, 954.

Thirst Fever, with a Characteristic Temperature Pattern in Infants in Kuwait

YEHIA SHAKER,* M.D., D.C.H.

Brit. med. J., 1966, **1**, 586–588

The importance of water metabolism in infancy and childhood is well recognized. The high metabolic rate of infants as compared with that of adults, the relative excess of their body-water with a greater daily turnover, as well as the immaturity of their renal function, explain the increased need for water in this age-group and the marked intolerance to water-deprivation. A slight change in the fluid intake, though negligible in an adult, may be serious in a little child with a small total fluid volume and a fairly narrow limit of variability (Hill, 1954).

Fever due to water-deprivation is well known in the newborn. In older infants it is rather rare but sometimes creates diagnostic problems. It may, however, occur in hot climates. In Greece, Choremis *et al.* (1959) described cases in which infants had an irregular prolonged fever as the only symptom

the infant or when its food is too rich in calories or in proteins and it is not getting any extra water. Holliday and Segar (1957) have estimated that for every gramme of protein given in excess of the minimum requirement 20 ml. of extra water is needed to excrete the products of protein catabolism in a larger volume of urine. Increased salt intake has also been described as a cause of fever (Finkelstein, 1938; Levesque and Bastin, 1949).

The diagnosis of fever due to water-deprivation is not always easy. It should be based on a careful history, the lack of any other abnormal clinical or laboratory findings, the failure of the infant to respond to any kind of drug treatment, and finally the subsidence of the fever after administration of extra water alone.

This paper presents a clinical variety of thirst fever with a characteristic temperature pattern.

Material and Results

During the past few years some cases have been referred to the paediatric consultation clinic because of a prolonged pyrexia of unknown origin, most of the patients having already received various kinds of medical treatment without improvement.

Seventeen such patients (10 males and 7 females) were studied (see Table). Fifteen were followed up as out-patients; the other two were admitted to hospital. Their ages ranged from 3 to 10 months with one exception, a male infant aged 13 months. Only one infant was a Kuwaiti; the rest were of other nationalities. All the cases presented during the hot humid season. The main presenting feature was a pyrexia of long duration, varying between 12 and 68 days. All the infants except one showed a similar unusual pattern of fever—high (ranging from 39 to 40.8° C. per rectum) in the morning and gradually falling during the day, to become normal or almost normal in the evening (Fig. 2).

Apart from the fever, no significant abnormal findings could be detected on clinical examination. Three cases, however, showed early rickets, manifested by craniotabes and/or increased head-sweating (see Table). All the infants were active well-fed babies of average normal weight for their age. Their appetite was good. Only two patients (Cases 6 and 17) were exclusively breast-fed; the rest were having either artificial or mixed feeding, with or without some solid food. The exact

FIG. 1.—Experimentally induced thirst fever and its correction by rehydration (after Choremis *et al.*, 1959). Reproduced by permission, from *Helvetica paediatrica acta*.

of inadequate water intake, occurring particularly during summer. They also produced such a fever experimentally in infants (Fig. 1).

Thirst fever is due to a relative or an absolute lack of water, resulting in an inadequate reduction of heat. It can therefore occur when the water intake is not sufficient for the needs of

* From the Paediatric Department, Al Sabah Hospital, Kuwait.