

HYPOTHYROIDISM AND PREGNANCY

(Report of Three Cases and Review of Literature†)

by

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The state of thyroid activity exerts a significant influence on the function of the reproductive system. Disorders of thyroid function in women may affect ovulation, and produce consequent menstrual irregularities and infertility. However, neither hypothyroidism nor hyperthyroidism is totally incompatible with the occurrence of pregnancy. The occurrence of pregnancy is influenced more in hypothyroidism than in hyperthyroidism. A survey of the world literature showed reports of only 46 cases of pregnancy occurring in hypothyroidism. In the present communication pregnancy in two untreated cases and in one inadequately treated case of hypothyroidism is reported and the world literature on this subject is reviewed.

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Case 1: S.D., a 26 years old woman, born in West Pakistan and a resident of Delhi for the past 19 years, came to the hospital for the first time on April 12, 1965, with a history of 6 months amenorrhoea.

She was born at term, but was rather small. All her milestones were delayed and she could not be sent to school before the age of 10 years. She reached the third standard in 5 years after which she could not progress further. She experienced intolerance to cold and was never noticed to have any sweating. She was lethargic and had excessive somnolence. Her voice was husky and speech slurring. She had poor appetite.

Menarche started at 15 years of age. The menstrual cycles were irregular and the bleeding occurred at the interval of 37 to 70 days with excessive flow lasting for 6 to 7 days. She was married for 7 years and had two abortions, one 6½ years ago after four months of gestation and the other 3 years ago at the third month.

On examination, the patient looked very dull and pale. Her height was 132.5 cm. and weight 47.8 kg. She was found to have a prolonged latent period in responding to any question. The speech was slurred and the voice husky. The face was puffy and expressionless. The lips were thick and everted, and the tongue appeared too large for her mouth. She had pitting oedema on the feet and the legs. The skin was cold and very coarse, and the hair sparse and coarse. The pulse rate was 80 per min. and the blood pressure 120/80 mm. of Hg. A

soft systolic murmur was heard along the left parasternal border. The deep reflexes were prompt, but the relaxation phase was markedly prolonged. The fundi were normal. The uterus was of the size of 24 weeks of gestation.

Laboratory Investigations: Haemoglobin 9.2 gm.%, P.C.V. 29%, and the erythrocytes were normocytic and hypochromic. Haemoglobin level improved to 11.6 gm% after therapy with thyroid hormone. The serological tests for syphilis were negative. Blood group was 'AB' and Rh positive. The serum cholesterol was 220 mgm.% prior to therapy and 175 mgm.% after one month of therapy. The basal metabolic rate (BMR) was minus 48 per cent and the plasma protein bound iodine (PBI) was 2.4 μ g.%. Urinary 17-ketosteroids were 9.3 mg. and 10.0 mg. per 24 hours on two consecutive days. An X-ray of the skull showed that the sutures were wide open.

The patient was initially put on thyroid extract 30 mgm. daily, which was gradually increased to 195 mgm. Within one week of therapy she showed improvement in her appearance and skin condition, and started feeling more active. She manifested no evidence of thyrotoxicosis during this therapy. At full term she was delivered of a normal male baby weighing 2.65 Kg. The dose of thyroid extract was gradually decreased to a maintenance dose of 120 mg. daily during the postpartum period. The patient did not have normal lactation. The child last seen at the age of five and a half years was doing well. The mother had one more full-term normal delivery with no complications during pregnancy, when she received adequate thyroid therapy.

Case 2: G.D., a 32 years old female born in Punjab and a resident of Delhi for the past 11 years, first visited the hospital in January, 1966, with the complaints of 6 months of amenorrhoea and generalized swelling for 2 months. Menarche started at 16 years of age and the menstrual cycles were regular, with the duration of flow of 5 to 6 days. She had three normal full term deliveries and she was keeping well until 2½ years ago, when she had her fourth pregnancy. At that time she started feeling very weak, and lethargic and looked pale and ill. She had no interest in her activities

and had excessive somnolence. She also developed cold intolerance, puffiness of the face, swelling of the feet, loss of appetite and constipation. This pregnancy terminated in a spontaneous abortion at 6th month. Following this she started having irregular periods after 2 to 3 months, lasting 6 to 8 days with excessive blood loss. All these complaints persisted and became worse during the fifth pregnancy with which she presented herself to this hospital. Her voice became hoarse and the speech somewhat slurring.

On examination, her face was puffy and she looked very pale and dull. The lips were thick and everted, and the tongue large. The skin was cold and coarse with few sparse hair. The hair on the eyebrows were scanty. She had oedema of the feet and legs. Thyroid was not palpable. Her body weight was 40 Kg., the height 145 cm. and the pulse rate 72 per min. She had a para-umbilical hernia and the uterine size was consistent with 24 weeks of pregnancy. Her speech was slow and slurring. The deep reflexes were brisk with prolonged relaxation phase.

Laboratory Investigations: Haemoglobin was 6.5 gm.%, P.C.V. 21% and the erythrocytes were normocytic and hypochromic. The bone marrow smear was compatible with normoblastic erythropoiesis with mild iron deficiency. Total serum protein was 5.6 gm.% with albumin 3.1 gm.% and globulin 2.5 gm.%. Serum cholesterol was 300 mgm. % and BMR was minus 38 per cent. The serum PBI was 3.3 μ g.%. Electrocardiogram showed low voltage with T wave changes.

Therapy with iron and hematinics for two weeks did not improve her anaemia significantly. She was put on a daily dose of 30 mg. thyroid extract, which was gradually increased to 150 mgm. over a period of two and a half months and this was maintained till delivery. She showed rapid improvement. She was delivered of a normal live male baby weighing 3.15 Kg. at term. The child did not have any stigma of thyroid disorder at birth or later on. Following delivery, her thyroid dose was decreased to 120 mgm. daily and she was doing well.

Case 3: S.S., a 27 years old female born at Madras and a resident of Delhi for 10

years visited the hospital on August 25, 1965 with a history of amenorrhoea of 13 weeks.

She had menarche at 14 years of age. The cycles were irregular and their length varied from 30 to 50 days. She had ovarian cystectomy in October, 1958. During her stay in the hospital at that time she was diagnosed to have myxoedema and was put on 30 mgm. of thyroid extract daily which was increased to 60 mgm. daily from April, 1960. Her mother also had hypothyroidism. She got married in June, 1956. In March, 1957, she had a spontaneous abortion after 3 months of amenorrhoea. During a subsequent pregnancy she had been receiving thyroid extract 60 mg. daily, and in January, 1961, she gave birth at term to a normal female child, who is alive and healthy. In June, 1964, she had a premature delivery of a stillborn baby at 8 months of pregnancy which was associated with hydramnios.

Physical Examination: She had an average built with a height of 145 cm. and weight of 49 Kg. The patient appeared rather dull and showed minimal change of expression. She looked pale and had puffiness of the face and oedema of the feet. The skin was cold and coarse and the hair scanty. The eyebrows had less hair and the scalp hair were coarse. The pulse rate was 68 per min. and the blood pressure 115/70 mm. of Hg. The thyroid was not palpable. There was a small umbilical hernia. The height of the fundus corresponded with 22 weeks of gestation. Deep reflexes showed prolonged relaxation phase.

Laboratory Investigations: Haemoglobin was 11 gm.% and P.C.V. 34%. The fasting blood sugar was 92 mg.%, blood urea 33 mg.% and serum cholesterol 400 mgm%. Serological tests for syphilis were negative. The blood group was 'A' and Rh positive. The total serum protein was 6.2 gm.% albumin 3.2 gm.%, globulin 3.0 gm.% and PBI was 5.9 μ g. per cent.

The thyroid dose was immediately raised from 30 mg. to 60 mg., which in a period of 4 weeks was increased to 120 mg. daily, and from the 28 weeks of gestation she was receiving 180 mg. daily. She did not develop any symptoms or signs of thyrotoxicosis during this therapy. Her expression

changed to normal within a period of about 4 weeks. Unfortunately, she developed hydramnios and had a premature delivery at 32 weeks. The baby was small, stillborn and weighed 1.6 Kg. with no gross congenital malformation. The dose of thyroid extract was reduced to 120 mgm. after delivery. She was doing well. Subsequently, she became pregnant again and the thyroid dosage was appropriately increased. She was delivered of a normal female baby at term in March, 1967, and the child, now five years old, is doing well.

Discussion

In the present communication three cases of pregnancy occurring in association with hypothyroidism are reported. The first case was a cretin, and in the second case hypothyroidism apparently developed during a previous pregnancy about two and a half years ago which ended in a stillbirth at 6 months of gestation. The presently reported pregnancy occurred in both these patients while they were still in untreated myxoedematous state. The third patient, a diagnosed case of hypothyroidism, was receiving only 30 mgm. of thyroid extract daily when she conceived. Obviously, this dose was inadequate. With the occurrence of pregnancy the sign and symptoms of hypothyroidism became overt and exacerbated.

In 1963, Echt and Doss reviewed the world literature and could collect only 29 cases of myxoedema in pregnancy, in addition to the three cases of their own. Subsequently, reports of three more cases have appeared in the literature (Chatfield, 1966; Anderson and Beales, 1970 and Lachelin, 1970). Chatfield (1966) has independently reviewed the literature and collected 26 cases. He apparently has missed the report of Echt and Doss (1963). Nevertheless, Chatfield has cited some additional cases which are not mentioned in the report of Echt and Doss. In Table I are presented all the available

TABLE I
Pregnancy in Hypothyroidism—A Survey of Literature

Author	Year	No. Cases		Method of Diagnosis
		Adult	Cretin Juvenile	
1. Townsend	1897		1	Clinical
2. Mac-Ilewaine	1902	1		Clinical
3. Herrgot	1902		1	Clinical
4. Howard	1907	3		Clinical
5. Welz	1919		1	Clinical
6. Audebert and Claverie	1921		1	Clinical
7. Plummer	1922	1		Clinical
8. Merquet	1922		1	Clinical
9. Wollenberg	1922		1	Clinical
10. Fruhinsholz	1925	1		Clinical
11. Zimmerman	1928	1		Clinical
12. Witts	1929		1	Clinical
13. Kirk (quoted by) Rolleston	1936	1		Clinical
14. Patton	1936		1	Clinical
15. De Garis	1941		1	Clinical
16. Parkin and Greene	1943	5	1	Clinical, BMR, serum cholesterol
17. Zondek	1944		1	Clinical (Cretin)
18. Means	1948	2		Clinical, BMR, serum cholesterol
19. Hodges et al	1952		1	Clinical, BMR, serum cholesterol PBI and I^{131} clearance postpartum
20. Bruk and Kerr	1954	1		Clinical, BMR, E.C.G.
21. Lister and Ashe	1955	1		Clinical, BMR, serum cholesterol, PBI.
22. Siegler	1956		1	Clinical, serum cholesterol and I^{131} uptake.
23. Stoffer et al	1957	1		Clinical, BMR.
24. Man et al	1958	4		Clinical, BEI.
25. Bercovici and Ehrenfeld	1959		2	Clinical, BMR, serum cholesterol, I^{131} clearance ante-partum.
26. Iverson	1959	1		Clinical, BMR, serum cholesterol.
27. Paz-Carranza et al	1959	1		Clinical, PBI, I^{131} clearance postpartum.
28. Chosson et al	1960		1	—
29. Echt and Doss	1963	3		Clinical, BMR, cholesterol/PBI/PBI/ and I^{131} .
30. Chatfield	1966	1		Clinical, PBI before and after TSH, I^{131} clearance ante-partum.
31. Anderson and Beales	1970	1		Clinical, PBI.
32. Lachelin	1970	1		Clinical, PBI.
33. Present report	1972	2	1	Clinical, BMR, PBI, serum cholesterol.
	Total	32	17	

cases, including three cases of the present report. It is noted that out of the total 49 cases, 17 had either cretinism or juvenile myxoedema and the remaining 32 developed hypothyroidism during adult age.

The paucity of reports of such cases in the literature may be due to several reasons: (a) Moderate to severe hypothyroidism causes irregularity in menstrual cycle and disturbs ovulation. Consequently, pregnancy is rare in untreated cases. (b) Mild and borderline cases are difficult to diagnose, particularly when the index of suspicion is not high. Furthermore, the diagnostic tests for thyroid function, such as the BMR and the PBI are altered during pregnancy, and the use of radioactive iodine, particularly I^{131} , is contraindicated. Since I^{132} has a very short half life, some investigators have advocated the use of this isotope test during pregnancy (Wayne, 1960; Chatfield, 1966). However, adequate information on this subject is not available. In the earlier reports, diagnosis of myxoedema was established on clinical examination only. More recently, one or more laboratory investigations have been done.

In normal non-pregnant females the serum PBI ranges from 4 to 8 $\mu\text{g.}\%$ (Heineman *et al.*, 1948 and Gulati *et al.* 1972). Different groups of investigators have reported that in pregnancy the values range from 6.2 to 11.2 $\mu\text{g.}\%$ (Heineman *et al.*, 1948) and 6.5 to 11.5 $\mu\text{g.}\%$ (Prout, 1966). It has been noted by us that the serum PBI ranges from 6 to 14 $\mu\text{g.}\%$ during pregnancy. The earliest rise in the PBI has been noted during the 5th week of gestation, but from the 10th week onwards there is a steady rise (Gulati, 1966; Gulati *et al.*, 1972a).

The high level of circulating estrogen increases the level of thyroxine binding

globulin as well as their thyroxine binding capacity (Dowling *et al.*, 1956, 1960). As a result, the bound form of hormone as measured by the serum PBI is increased and the physiologically active free form of thyroid hormone is lowered. Normally, this is compensated by some rise in the secretion of thyroid stimulating hormone (TSH) with resultant increased secretion of thyroid hormone. However, in cases with abnormal thyroid gland function, this compensation cannot occur. Consequently, the degree of hypothyroid state becomes more pronounced. This is very well illustrated in case 3, who was on inadequate dose of thyroid substitution therapy. Now a days this type of cases are more likely to be encountered. It would be appropriate to advise an increase in the dose of thyroid in case a patient on substitution therapy conceives.

Apparently, the incidence of pregnancy wastage is somewhat increased in hypothyroidism (Silver *et al.*, 1960; Steinback & Carey, 1963). Echt and Doss (1963) reviewed the literature and concluded that there was no increase in the foetal abnormality in these cases, although Greenman *et al.* (1962) drew attention to the possibility of abnormalities in mental and physical development in these children. There is evidence to suggest that the thyroid hormone is not required during the early development of the foetus, and by the 14th week of foetal life the thyroid-pituitary axis becomes physiologically active (Franchimont *et al.* 1970). Although small amount of thyroid hormone crosses from the mother to the foetus at a later stage of pregnancy, maternal TSH does not cross to the foetus (Steinbeck, 1963). It appears that normally the foetus does not depend upon any maternal supply of thyroid hormone. It may however, be pertinent to mention

that Man *et al*, (1971) have reported that 4 of the 6 progeny of hypothyroxinemic women not given adequate thyroid replacement therapy during gestation have been classified as "not normal" with low I.Q., and that more suspect or abnormal children are noted in the progeny of inadequately treated hypothyroxinemic women than in the progeny of euthyroid mothers or of hypothyroxinemic women given adequate thyroid replacement therapy. Further work is obviously needed for understanding the significance of these observations.

Summary

Three cases of pregnancy occurring in hypothyroidism are presented. Surveying the literature 46 additional cases could be collected. The pertinent subject is discussed in the light of recent development

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