MENSTRUAL PATTERN AND FERTILITY STATUS OF HYPOTHYROID WOMEN

DIPAK LAHIRI ● ANJAN DASGUPTA ● SARMILA KUNDU

SUMMARY

One hundred and twenty eight hypothyroid women were studied to find out their menstrual pattern and fertility status. As many as 91 patients (71.09%) had subclinical hypothyroidism; 46.87% had normal menstrual pattern. Menstrual aberrations included mainly oligomenorrhoea, hypomenorrhoea, menorrhagia and secondary amenorrhoea. Oligomenorrhoea was the commonest menstrual abnormality and found mainly in early age-group women. Menorrhagia was commoner in late age-group. No correlative thyroid function hormonal value was found between normally menstruating women and those with abnormal menstruation or between different varieties of abnormal menstruation. Anovulatory infertility was common. Pregnancy loss, particularly recurrent pregnancy loss, was another common observation. Thyroxine supplementation for 1 to 2 years proved to be of value in majority of cases of infertility and pregnancy loss. However, in menstrual aberrations, response to thyroxine was not notable and more than 25 percent of women had no response at all.

INTRODUCTION

It is only over past few decades that hypothyroidism has been recognised as an entity in a wide variety of gynaecologic disorders ranging from abnormal sexual development to menstrual aberrations, anovulation, infertility and reproductive wastage when pregnancy is achieved. Subclinical hypothyroidism which is equally pathogenic passes unrecognised. The studies on the subject are few.

Delayed puberty had been observed by

Dept. of Obs & Gyn I.P.G.M.E.R. & S.S.K.M. Hospital, Calcutta.

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Singh et al (1990) while few others found precocious puberty in long-standing hypothyroidism (Hemady et al, 1978; Thomas & Reid, 1987). Menorrhagia was the commonest aberration observed by Scott & Mussey (1964) and Akande (1975). Singh et al (1990), found oligomenorrhoea as the predominant menstrual abnormality. Thomas and Reid (1987) suggested hyperprolactinaemia associated with long-standing severe hypothyroidism resulting in oligomenorrhoea and amenorrhoea. Several studies (Thomas and Reid, 1987; Singh et al, 1990) suggested hypothyroidism to be associated with anovulatory cycles and infertility. Once there was pregnancy, again, various obstetric complications, were observed including abortions, preterm delivery and foetal growth retardation (Thomas & Reid, 1987; Lahiri and Mitra, 1989).

The reproductive performance of hypothyroid women has been presented in an earlier review from our centre (Lahiri and Mitra, 1989). The aim of the present study is to critically evaluate the menstrual pattern and the fertility status of hypothyroid women. The background information will particularly help to screen cases for subclinical hypothyroidism which comprise the majority of cases of hypothyroidism presenting with menstrual aberrations, infertility and subfertility.

PATIENTS & MATHODS

The study was carried out in the Dept. of Obs-Gynae, SSKM Hospital and Polyclinic, Calcutta, during the 10 years period of 1986 to 1995. 128 hypothyroid women were studied presenting with various complaints like intractible menstrual problems, infertility and recurrent pregnancy loss with or without menstrual problems. The patients were considered hypothyroid when the serum TSH value was above 5 microunits per ml. Prout (1975) and Speroff et al (1994) considered it to be the best method to detect hypothyroidism. The patients with any other specific disease/ disorder were excluded (which included 13 patients with diabetes mellitus).

The study protocol included thorough history-taking, clinical evaluation and serum T3, T4, and TSH estimation. Premenstrual dated endometrial biopsy was done in almost all patients with infertility with or without menstrual problems to detect ovulation stigma or anyother pathology. Other methods for ovulation study included, in some women, serial BBT recording for 6 normal menstrual cycles and serum progesterone value estimation on the day 20 of normal menstrual cycle. Hormonal studies were minimal in view of the cost-factor and serum prolactin was estimated in a few.

Thyroxine supplementation (2-3 mcgm/ Kg/d) was done with starting thyroxine sodium 50-100 mcgm/day and raised by 50 mcgm/day every 4 weeks to 100-300 mcgm/day - according to clinical evaluation and additional biochemical assessment in few. Recovery of hypothalamic-pituitary axis has been stated to require usually 8 weeks time (Speroff et al, 1994).

RESULTS

Table I shows how hypothyroidism was diagnosed in 128 women. The great majority (71.09%) had subclinical disease. Table I indicates that assessment of thyroid function should be a part of investigation

Table I
DETECTION OF HYPOTHYROIDISM (N = 128)

(A)	Known hypothyroid	....	....	28
(B)	Clinically hypothyroid	....	....	9
(C)	Subclinical hypothyroid	....	....	91
	i) Diagnosed during infertility evaluation		...	27
	ii) Diagnosed during evaluation of menstrual aberration with or without infertility		...	37
	iii) Diagnosed during investigation for recurrent pregnancy loss		...	27

Table II
AGE AT MENARCHE (N = 128)

Less than 12 years	....	....	....	3
12 to 14 years	....	....	....	105
Above 14 to 17 years	....	....	....	19

N.B. One had primary amenorrhoea (46 XX Karyotype).

Table III
MENSTRUAL PATTERN & AGE GROUP (N = 128)

Mens. pattern & no. of cases	12-20 yrs.	21-25 yrs.	26-30 yrs.	31-35 yrs.	Above 35 yrs.
Normal (60)	-	7	33	16	4
Oligomenorrhhoea (23)	2	10	5	3	3
Hypomenorrhoea (10)	2	2	4	2	-
Sec. amenorrhoea (11)	2	2	1	4	2
Menorrhagia (17)	-	-	6	3	8
Polymenorrhoea (1)	-	-	-	1	-
Irreg. mens (5)	-	-	1	3	1
Primary ameno. (1)	-	1	-	-	-

protocol in cases of infertility (in particular, anovulatory infertility), persistent menstrual aberrations and in recurrent pregnancy loss.

Table II depicts the age at menarche. The values observed were compared with a control group of 100 healthy women without known or suspected hypothyroidism. In the controls, the majority (87%) had menarche by 12 years of age while in the study group most of the women (96.84%) had relatively delayed menarche.

Table III illustrates the menstrual pattern in different age-groups amongst 128 hypothrooids. 60 women (46.87%) had normal menstrual pattern. Most common menstrual abnormality found was oligomenorrhoea. Menorrhagia was the second frequent disorder. Oligomenorrhoea, hypomenorrhoea and secondary amenorrhoea were commoner in early half of reproductive life while menorrhagia was most frequent in late reproductive age group.

Table IV
AGE AT ONSET OF MENSTRUAL ABNORMALITY & DETECTION OF HYPOTHYROIDISM
(n = 68)

	12-20 yrs.	21-25 yrs.	26-30 yrs.	31-35 yrs.	Above 35 yrs.
Menstrual abnormality onset	7	14	18	15	14
Hypothyroidism detected	7	14	20	15	12

Table V
SERUM TSH VALUES & THE MENSTRUAL PATTERN (n = 128)

Menstrual pattern	Serum TSH range (microunit/ml)
Normal (60)	5.1 to 12.4
Oligomenorrhoea (23)	5.8 to 31.5
Hypomenorrhoea (10)	9.2 to 12.6
Sec. amenorrhoea (11)	5.5 to 13.7
Menorrhagia (17)	5.6 to 15.6
Polymenorrhoea (1)	5.8
Irreg. mens (5)	5.2 to 9.5
Primary ameno. (1)	14.2

Table IV shows the age at onset of menstrual abnormality related to the age-group when hypothyroidism was detected. Menstrual abnormality was present in 53.13 percent. In 26-30 years age group, there were 20 hypothyroids of which 18 had menstrual problems. The remaining 2 developed menstrual abnormality subsequently.

Table V shows the serum TSH values in relation to menstrual pattern. The TSH values could not be correlated to menstrual pattern - normal or abnormal. Thyroid hormones T3 ranged between 0.6 to 1.2 ng/ml and T4 values between 30 to 64 ng/ml and could also not be correlated to menstrual pattern. Serum prolactin value was determined in 21 cases with abnormal menstruation (all cases of secondary amenorrhoea and the rest from others) and the range was within normal limits (9.8 ng/ml to 21.2 ng/ml) in 20 cases. Only one nulliparous woman with oligomenorrhoea and galctorrhoea had TSH value 31.5 microunits/ml and PRL value 32.8 ng/ml.

Table VI shows the effects of thyroxine supplementation on the menstrual pattern. 18 (26.5%) had no response even after 2 years of thyroxine supplementation. Though 50 women responded to therapy, the menstrual pattern was not completely normal in the great majority. The cases with secondary amenorrhoea were most resistant to therapy.

Table VII shows the fertility status of the hypothyroid women. The 48 infertile women had varying periods of infertility without any explainable factor apart from anovulation in great majority as shown in Table VIII.

Table VI
ABNORMAL MENSTRUATION & *RESPONSE TO THYROXINE SUPPLEMENTATION (n = 68)

Abnormal mens	Response in 6 months	Response in 1 year	Response in 2 years	No response
Oligomeno. (23)	2	13	3	5
Hypomeno. (10)	1	5	2	2
Sec. ameno. (11)	-	1	1	9
Menorrhagia (17)	-	4	12	1
Polymeno. (1)	1	-	-	-
Irreg. mens (5)	-	2	3	-
Primary ameno. (1)	-	-	-	1
Total (68)	4	25	21	18

* Response meant a change towards normality or some improvement.

Table VII
FERTILITY PATTERN (n = 48)

Duration of infertility	Primary infertility (n = 34)	Secondary infertility (n = 14)
1 to 2 years	5	2
More than 2 to 5 yrs.	15	3
More than 5 yrs.	14	9

Table VIII
STUDY FOR OVULATION IN INFERTILE WOMEN (n = 48)

Nature of study	Observation	No. of cases	Inference
A. BBT Chart : (n = 18)	i) Monophasic or irregular	14	Anovulatory
	ii) Biphasic	4	Ovulatory
B. Endometrial study in pre-menstrual phase (n=48)	i) Proliferative	35	Anovulatory
	ii) Patchy secretory	10	Ovulatory with inadequate luteal phase
	iii) Secretory	3	Ovulatory
C. Serum level of progesterone on about 20th day in ng/ml (n=15)	i) Less than 2.5	9	Corpus luteum not formed (anovulatory)
	ii) 2.5 to 5	3	Early degeneration of corpus luteum (defective ovulation)
	iii) Above 5	3	Corpus luteum formed and satisfactory.

Table VIII depicts the results on study for ovulation. Anovulation was found in the majority. Next common observation was luteal phase defect.

Table IX
INFERTILITY & SUBSEQUENT PREGNANCY FOLLOWING THYROXINE SUPPLEMENTATION (n=48)

	Successful	Pregnancy loss	No pregnancy	Lost in follow-up
A. Primary (n=34)	10	8	7	9
B. Secondary (n=14)	2	4	5	3

Table X
BOH & SUBSEQUENT PREGNANCY FOLLOWING THYROXINE SUPPLEMENTATION (n=33)

Successful pregnancy	Pregnancy loss again	No pregnancy	Lost in follow-up
21	7	2	3

Table IX shows the fertility status following thyroxine supplementation in infertile women. 20 women conceived within one year of thyroxine therapy and another 4 had pregnancy between 1 and 2 years. 12 women had no pregnancy even after 2 years of treatment.

Table X shows the outcome of subsequent pregnancy following thyroxine supplementation in women with bad obstetric history. Of the 33 cases, 6 were clinical or known hypothyroids and 27 had subclinical hypothyroidism. 14 (42.42%) were habitual aborters (4 had consecutive 5 first trimester abortions), 8 had consecutive 2 first trimester abortions and the remaining 11 had consecutive 2 or more pregnancy loss beyond first trimester. Following adequate thyroxine supplement, 21 out of 28 (75%) had successful outcome and achieved pregnancy again.

DISCUSSION

Hypothyroidism has been implicated in multitude of gynaecologic and reproductive disorders. Speroff et al (1994) suggested increased susceptibility of women to hypothyroidism "secondary to an autoimmune reaction" and "perhaps their endocrine environment". As majority of cases are subclinical, it is essential to evaluate thyroid function in all women with intractable menstrual disorders, infertility and recurrent pregnancy loss.

Comparative case-controlled study in this series revealed relatively delayed puberty. This has been suggested to be likely because of interference with gonadotrophins secretion (Larsen and Ingbar, 1992; Rosen and Kelch, 1995). Hemady et al (1978) and Kramer et al (1979) opined that there might be paradoxical precocious puberty in juvenile hypothyroidism as a result of prolactin hypersecretion.

46.87% women in this series had normal menstrual pattern. Oligomenorrhoea was the commonest menstrual abnormality and next common was menorrhagia. Singh et al (1990) from a similar study of Indian women in 9 hypothyroids found oligomenorrhoea in 4, menorrhagia in 3 and normal menstruation in 1 only (11.1%). Scott and Mussey (1964) in a very early study of 50 patients found normal menstruation in 22 (44%) and menorrhagia in 10 (20%). They found menorrhagia the most common and oligomenorrhoea the rarest abnormality. Akande (1975) found menorrhagia in 4 out of 5 women studied and suggested persistent estrogen level at "threshold" the likely explanation. Thomas and Reid (1987) observed menorrhagia in "less severe" hypothyroidism and amenorrhoea in "severe or long-standing" hypothyroidism particularly accompanied by hyperprolactinaemia. Kramer et al (1979) had 2 patients with secondary amenorrhoea and euprolactinaemia and suggested interfered ovarian response to gonadotrophins in hypothyroidism. In the present study, secondary amenorrhoea was the third common menstrual aberration with 11 cases and all were euprolactinaemic. Kirkland et al (1981), from animal experimental study, concluded that hypothyroidism reduces oestrogen-induced cell division in all uterine cell-types - myometrium, endometrial stroma and luminal epithelium. Poor uterine growth, as such, might also be a factor for hypomenorrhoea or even amenorrhoea.

Singh et al (1990) found 77.8% of hypothyroid women anovulatory. In our study too, anovulation was the commonest ovulatory dysfunction.

Of the 128 women studied, 48 had infertility. Decreased fertility has also been suggested and chronic anovulation held responsible by Thomas and Reid (1987), Larsen et al (1992) and Rebar (1995). Adequate thyroxine supplementation resulted in pregnancy in 24 women out of 36 on follow-up.

Reproductive performace of the hypothyroid women has been shown by our earlier review (Lahiri and Mitra, 1989). However, study in interval period, in women with past reproductive wastage, showed hypothyrodisism as an important contributing factor and as many as 27 out of 33 such women had subclinical hypothyroidism. Adequate thyroxine supplementation resulted in successful pregnancy in 21 such women. Innerfield and Hollander (1977), have doubted whether thyroxine is necessary for foetal development. But physiologists have amply shown that thyroxine is necessary for protein synthesis, increase in the number and activity of mitochondria, cell growth and development (Guyton and Hall, 1996). As such, deficiency might lead to abnormal conceptus, pregnancy loss and foetal growth retardation.

COMMENTS

1. Hypothyroidism is responsible for

a wide variety of menstrual disorders, anovulation infertility and pregnancy loss.

2. Again, normally menstruating, ovulatory, fertile women may have hypothyroidism.

3. Subclinical hypothyroidism is a common entity responsible for similar disorders and one must be on lookout for this endocrinopathy in susceptible women.

4. Thyroid function evaluation should be made part of investigation protocol in any case of intractable menstrual aberration, infertility particularly anovulatory infertility and repeated pregnancy loss. This will particularly help detection of subclinical hypothyroids.

5. Adequate thyroxine supplementation for 1 to 2 years helps in great majority of women with ovulatory dysfunction and infertility. Response is satisfactory in menorrhagia and hypomenorrhoea, fair in oligomenorrhoea but poor in secondary amenorrhoea.

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