Role of reproductive wastage and thyroid hormones in the birth of Down syndrome

V. Babu Rao • M.D. Sadhanani • G. S. Isaac
Inst. Of Genetics & Hospital for Genetic Diseases, Osmania University, Begumpet, Hyderabad-500016, A.P.

Summary: **The study consists of forty subjects, mothers of pure trisomy 21 children (Down syndrome) and forty-five mothers who gave birth to normal children. Reproductive history and thyroid hormone (triiodothyronine, thyroxin, thyroid stimulating hormone) levels of mothers of Down syndrome children were studied and compared with the control group. The frequency of reproductive wastage and thyroid hormone (thyroxin, thyroid stimulating hormone) levels of the study group was found to be elevated significantly ($P<0.05$). We propose that the reproductive potential and physiological (hormonal) changes have a prominent aetiological significance in the birth of Down syndrome child.**

Introduction

Recent studies on aetiology of reproductive wastage demonstrated chromosomal abnormalities, luteal phase defect, metabolic and endocrinological problems, infective causes, immunological factors, anatomic defects, iatrogenic causes and male factors (Gupta and Chakravarty, 1995). Numerous studies have shown that approximately 50% or more spontaneously aborted foetus have major chromosomal abnormalities, the most common types being 45,X,triploidy and trisomy 16 (Zhou et al 1989). In case of Down syndrome (DS) or trisomy 21 it was estimated that 50% of all conceptuses get aborted spontaneously. In view of the high frequency of DS births due to maternal non-dysjunction (Sherman et al 1991, Rao et al 1996), various hypotheses have been put forward to explain the cause of trisomy 21. However, the mechanism has not yet been understood (Hook & Fabia 1978, Henderson & Edwards 1968, Crowley et al 1979). In the present study we attempted to study the role of reproductive wastage and thyroid hormones in the birth of DS offspring.

Materials and methods

Parents of 40 subjects with DS attending the Institute of Genetics for cytogenetic confirmation of their children, have formed the material for the study. The parental history regarding parental age, reproductive history, and consanguinity etc., were recorded in the case sheet. 45 mothers who had given birth to normal children were interviewed and their reproductive history was recorded. Blood samples from all the subjects and their parents and controls were taken for cytogenetic studies. Whole blood cultures set up according to a modified method of Moorhead et al (1960), were harvested after arresting at metaphase by adding colchicine and the chromosome preparations, thus obtained were stained for G-bands according to Seabright (1971). At least 30 well spread and banded metaphases were analysed visually and two were photographed for karyotyping.

Blood collected without any anticoagulant was allowed to settle for the separation of the serum and the same was used for hormonal estimation. The hormonal evaluation was conducted by the Radio Immuno Assay (RIA) method using the kits supplied by BARC, Mumbai. The data were subjected to statistical analysis with the help of χ_1^2 test for testing the significance of various observations and students t-test to test the significance of means of different observations in the study as well as control group.

Results and discussion

Chromosomal analysis of subjects revealed pure trisomy 21 and all parents of DS and controls found to have normal chromosome complements. The reproductive history of mothers of DS was not much emphasized in earlier studies. It could be presumed significant if nondysjunctional error of chromosome 21 is considered as an articulate of a physiological artefact. In the present study a significantly high ($p<0.05$) number of mothers of DS have history of spontaneous reproductive wastage (Table I). The reproductive wastage rate was found to be increased with increase in age. Interestingly, all miscarriages were found to occur before the birth of DS child. In above 30 years age group mothers, the number of abortions found to be more when compared to age matched controls who gave birth to normal children.

Table I

Frequency of reproductive wastage in mothers of DS and controls

S. No.	Age group	No. of subjects	Subjects with No. of reproductive wastage						Total no. of reproductive wastage
			1	2	3	4	5		
1	15-19	12	3	-	-	-	-		3
	15-19	(15)	(2)	-	-	-	-		(2)
2.	20-29	15	1	3	1	-	-		10
	20-29	(15)	(2)	(1)	-	-	-		(4)
3.	> 30 23	13	-	2	2	2	1		
	> 30	(15)	-	(2)	(1)	-	-		(7)
		40	4	5	3	2	1	= 1537.5%*	36*
		(45)	(4)	(3)	(1)	-	-	= (8)(17.8%)	(13)

$p^* < 0.05$, as compared with controls

Controls within brackets.

Though it was not possible to pinpoint the reasons from the reproductive wastage in the study and control subjects, it could be presumed that the chromosomal abnormality could cause a statistically significant rate of abortions in DS mothers. However, 50% of all trisomy 21 conceptuses get aborted spontaneously. Thus we can extrapolate by assuming that, besides the causes of spontaneous pregnancy loss (Gupta and Chakravarty 1995), the higher frequency of habitual abortions in the mothers of DS and others could be due to mainly chromosomal abnormality (monosomies or trisomies). These monosomies and trisomies occur due to non-dysjunction during gametogenesis in one of the parents. Crowley et al (1979) proposed "chiasma hormonal hypothesis" wherein relationship between the hormonally governed rate of meiosis and chiasma terminalisation has been established. If the changing hormonal signals lengthen the meiotic cycle chiasmata could be lost generating univalents, their might be constituting of a source of aneuploids. In view of the fact, an attempt has been made to study thyroid hormone (triiodothyronine, thyroxin, thyroid stimulating hormone) levels in mothers of DS and age matched controls. The thyroxine (except below 20 years age group) and thyroid stimulating hormone levels found to be significantly high ($p<0.05$) in mothers of DS compared to controls. The hormone levels found to be high in advanced age group, where the abortion rate was

Table II

Reproductive wastage and thyroid hormone levels in mothers of Down syndrome and controls

S. No.	Age group	No. of subjects	No. of subjects with reproductive wastage	Thyroid hormones : mean + SD		
				T3 (ng/dl)	T4 (µg/dl)	TSH (MIU/dl)
1	15-19	12	3	147.5 + 35.15	9.98 + 3.27	3.36 + 6.90*
	15-19	(15)	(2)	(134.0 + 18.18)	(9.46 + 2.03)	(3.10 + 0.31)
2.	20-29	15	5	144.4 + 24.74	11.02 + 1.86*	5.64 + 0.73*
	20-29	(15)	(3)	(141.5 + 14.79)	99.89 + 1.46)	(3.75 + 1.02)
3.	>30	13	7	150.8 + 19.40	14.52 + 1.64*	5.19 + 1.09*
	>30	(15)	(3)	(145.3 + 16.28)	(10.3 + 2.76)	(4.60 + 1.32

$p < 0.05$, as compared with controls

Controls within brackets.

more (Table II). In vitro studies have shown that thyroxine induce the satellite association frequency, and the high frequency of satellite association increase the risk of non-dysjunction (Merz et al 1966). The DS child also reported mother with hyperthyroidism (Wijk van et al 1961). Coppen and Cowie (1960) suggested that an endocrinological imbalance may cause miscarriages and further suggested that age related changes in hormone levels could bring about disturbances in meiotic chromosomal segregation.

The most direct evidence that endocrine function can cause chromosome abnormalities in human germ cell or zygote comes from the studies of Carr (1970) and Alberman (1976). Both showed an increase in frequency of severe chromosome abnormalities among abortuses from women who had been taking contraceptives. Carr (1970) suggested that these chromosome abnormalities were the results of residual hormone imbalance from oral contraceptive therapy. Fetuses with hormone induced chromosome abnormalities are apparently unlikely to survive until term, for neither prospective nor retrospective. Epidemiological studies have found a higher frequency of DS births among women who had used contraceptives before pregnancy. The study also indicates that hormones used at or before conception can cause chromosome damage in the ovum, but those same hormones do not appear to affect the maternal mechanism which rejects these aberrant products of conception. Available evidence suggests that chromosome division is sensitive to preconception hormonal action, whereas the inherent maternal rejection mechanism is not. Jenerich (1977) suggested that seasonal fluctuation of hormones at conception may lead to the birth of DS. The causes of abortions in the present study are not known. However, it could be presumed that the reproductive history and physiological status may warrant the birth of chromosomally defective child. Hence, cytogenetic investigations of the fetuses and appropriate genetic counselling may reduce the risk of chromosomally abnormal child.

Acknowledgements

The authors thank Prof. P. P. Reddy, Director, Institute of Genetics, Osmania University, for his support and encouragement throughout the study. Thanks also due to

Mr. S. Latheef for technical assistance and Ms. Mary Louella Pereira for typing the manuscript.

References

1. Alberman E, Creasy M, Elliot M, Spicer C. Br J Obst Gyn 83:621;1976.
2. Carr DH. Can Med Ass J 103:343;1970.
3. Coppen A, Cowie V. Br Med J 18:1843;1960.
4. Crowley PH, Hayden TL, Lopez P, Dyed R. Nature 280:417; 1979.
5. Gupta NJ, Chakravarty BN. J I M A 93:71;1995.
6. Henderson SA, Edwards RG. Nature 218:22;1968.
7. Hook EB, Fabia JJ. Teratology 17:223;1978.
8. Jenerich DT. Lancet 5:515;1977.
9. Merz T, Prempree, Barbara R, Miggo M Nature 209:1198; 1966.
10. Moorhead PS, Nowell PC, Mellman WJ, Battips DM, Hungerford DA. Exp Cell Res 20:613;1960.
11. Rao BV, Jyothy A, Isaac GS. J Basic & Appl Biomed 4:13; 1996.
12. Seabright M. Lancet 11:971;1971.
13. Sheman SL, Takaesu N, Freeman SB, Grantham M, Philips C, Blackston RD, Jacobs. Am J Hum Genet 49:608;1991.
14. Wijk van JAM, Stolte LAM, Kessel van HIAM, Tijdink GA. Lancet 22:887;1961.
15. Zhou XT, Tong HS, Wong SG, Shen QE, Fu XW, Cui YQ. Hum Genet 83:277;1989.