found that experienced nursing sisters function ideally in this situation, but it is essential that, at all times, an experienced medical team be on hand.

It is concluded that continuous-flow procedures for plasma and red cell exchange have an important role to play in clinical practice. To accommodate the ever-increasing indications for these procedures and to avoid their misuse, it is important that patients be evaluated by an experienced study group and then treated on protocol, so that valuable data can be collected and analysed. In this way the optimum cost-effectiveness will be ensured and isolated procedures, which may bring the technique into disrepute, be avoided.

This study was supported by the University of Cape Town Leukaemia Centre, the South African Medical Research Council and the Harry Crossley Foundation at the University of Cape Town. We thank Dr Alec Ferguson for referring the myasthenic patient, Jeanne Walker for illustrations, Sheila Katcher for bibliographic assistance, Jackie Davies for typing, Dr Jeane Hester for helpful criticism of the manuscript and Dr Jon Lindstrom of the Salk Institute for performing acetylcholine receptor antibody assays. The technical excellence of nursing staff from our cell support section is gratefully acknowledged.

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Premature gonadal failure

J. V. VAN DER MERWE

Summary

Fifty patients with premature gonadal failure were subdivided into primary and secondary failure groups. Karyotyping in the primary and ovarian histological examination in the secondary group are preferred diagnostic procedures. Several rare clinical syndromes are mentioned. Possible aetiological factors are identified, and a plea is made for the accurate diagnosis of this condition. Diagnostic pitfalls are also presented.

S. Afr. med. J., **59**, 104 (1981).

Premature gonadal failure is a relatively rare cause of amenorrhoea, with an approximate incidence of 4,8%.[1] Apart from intense psychological, sociological, and practical implications of this condition, health-threatening associations are also well known. The association with other endocrinopathies is well documented.[2,3] A higher incidence of ischaemic heart disease and severe osteoporosis is also associated with premature ovarian failure.[4,5] Patients with premature gonadal failure are very often subjected to unnecessary and extensive examinations for infertility. Furthermore, not much is known as regards the aetiology of this condition. This study was undertaken to illuminate the diagnostic procedures important in the management of these patients, as well as the aetiology of the condition.

Department of Gynaecological Endocrinology and Infertility, Tygerberg Hospital, Parowvallei, CP

J. V. VAN DER MERWE, M.B. CH.B., M.MED. (O. & G.), F.C.O.G. (S.A.), *Head*

Date received: 11 June 1980.

Patients and methods

Fifty patients with hypergonadotrophic amenorrhoea under the age of 40 years were studied. Obvious cases of intersex or gonadal dysgenesis were excluded.

Depending on whether normal sexual characteristics were present, these patients were divided arbitrarily into a primary and secondary gonadal failure group, a classification of which is seen in Table I.

TABLE I. CLASSIFICATION OF PATIENTS WITH HYPERGONADOTROPHIC AMENORRHOEA

Primary gonadal failure group	
Pure gonadal dysgenesis	6
Ovotesticular dysgenesis	1
45,XO dysgenesis without Turner stigmata	1
45,X/46,XX mosaic with Turner stigmata	1
X-chromosome deletions	2
X-chromosome translocations	2
Bilateral absent adnexa	1
	14
Secondary gonadal failure group	
Irradiational gonadal failure	2
Post-surgical gonadal failure	4
Cytostatic-associated failure	1
Auto-immune oöphoritis	7
Temporary ovarian failure	2
Idiopathic premature menopause	20
	36

All patients had a chromosome analysis; ovarian biopsies by laparotomy were performed on 34 patients, and all had serum gonadotrophin determinations. Other tests included tests for antithyroid antibodies, antiparietal cell antibodies, antinuclear factor antibodies, effective thyroid index, plasma protein electrophoresis, and full blood counts.

Results

Details of the 14 patients in the primary failure group are presented in Table II. Ten patients (71,4%) presented with primary amenorrhoea. The average age of this group was 24 years (SD 4,4 years). Chromosomal abnormalities were present in half of these patients. In 13 of these patients morphologically typical dysgenetic gonads were found. Histologically the classic picture of ovarian stroma without any primordial follicles was present. In 3 patients islands of hyperplastic interstitial cells with Reinke's crystalloids were present. The histological picture of patient 13's gonads is seen in Fig. 1. This picture of a crescent area of typical (ovarian) stromal tissue, in close approximation to an area consisting of primitive seminiferous tubes lined with Sertoli cells is suggestive of the dysgenetic gonad found in a 46,XY hermaphrodite. Patient 14 had no sign of either adnexum, despite a well-developed uterus (Fig. 2).

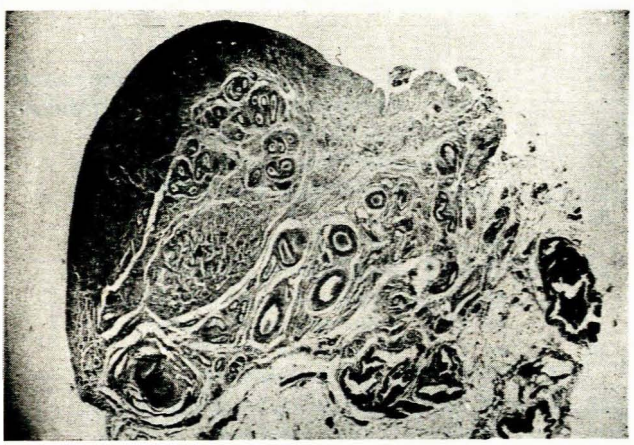

Fig. 1. Morphological appearance of the gonad in a case of ovotesticular dysgenesis. A crescentic area of ovarian stromal tissue in close approximation to an area of primitive testicular tissue can be seen.

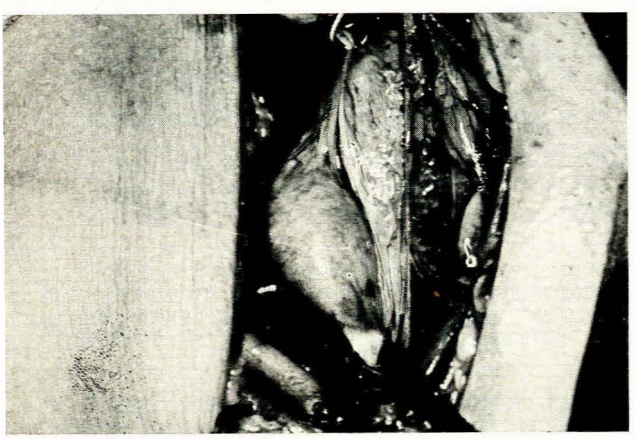

Fig. 2. Absence of adnexa in a patient with a normally developed uterus and presenting with hypergonadotrophic amenorrhoea.

TABLE II. THE PRIMARY GONADAL FAILURE GROUP

No.	Age (yrs)	G	Gonadotrophins						Karyotype	Diagnosis
			FSH			LH				
1	31	0	60	55	62	48	32	92	46,XX	Pure gonadal dysgenesis
2	26	0	70	58	180	84	80	100	46,XX	Pure gonadal dysgenesis
3	18	0	52	68		33	48		46,XX	Pure gonadal dysgenesis
4	28	0	130	90		130	186		46,XX	Pure gonadal dysgenesis
5	30	0	68	56		50	66		46,XX	Pure gonadal dysgenesis
6	25	0	120	100	132	158	115	115	46,XX	Pure gonadal dysgenesis
7	25	0	27	48		31	45		45,XO	45,XO dysgenesis without Turner stigmata
8	24	0	38	46		36	58		Mos 45XO/46,X, I(Xq)	Mosaic Turner with stigmata
9	20	0	97	80		65	55		46,X,del (X) (q24)	Gonadal dysgenesis
10	25	0	79			60			46,X,del (X) (q22)	Gonadal dysgenesis
11	21	0	96			50			46,X,t(X;7) (q24;q36)	Gonadal dysgenesis
12	27	0	84	78		50	50		46,X,t(X;2;15) (qter;p13 and 23;p12)	Gonadal dysgenesis
13	17	0	100	96		90	60		46,XY	Ovotesticular dysgenesis
14	19	0	68	48		70	65		46,XX	Absent adnexa

The details of the 36 patients in the secondary failure group are presented in Table III. The average age of these patients was 29,5 years (SD 5,76 years). Fifty-two pregnancies had occurred in 23 of these patients. All had a normal chromosome complement and all presented with secondary amenorrhoea after a normal menarche and previous regular periods.

The 2 patients categorized as post-irradiation gonadal failure had had pelvic radiotherapy 4 and 6 years previously for non-gynaecological tumours. Patient 21 developed hypergonadotrophic amenorrhoea after a complete course of busulphan (2 mg/d) for chronic myeloid leukaemia.

The development of amenorrhoea immediately after some form of gynaecological surgery could be coincidence, but the onset of the amenorrhoea dated from the surgical procedure. Patient 17 had undergone an Estes procedure, and patients 18 and 19 had been operated upon for acute ectopic pregnancy in the presence of severe adhesions of both adnexa. Patient 20 developed amenorrhoea after wedge resections had been performed to restore fertility. Follow-up ovarian biopsies revealed small ovaries with histologically normal ovarian stroma but without any follicles.

Of the 7 patients categorized as having had probable auto-immune oöphoritis, patients 22, 23 and 24 had no other detectable immunological conditions. These patients with macroscopically normal ovaries had, however, histological signs of an auto-immune tissue reaction in the ovarian substance (Figs 3 and 4). A monocellular infiltration of the ovarian tissue with lymphocytes and plasma cells was also present in areas of the blood vessel walls. In 1 patient normal well-developed follicles were present with a coarse monocellular infiltrate in the follicular wall (Fig. 4). The blood vessels showed signs of endarteritis obliterans, and a subcapsular fibrinoid reaction was present. Immunological tests on these patients were negative and all other endocrine function tests were negative.

In patient 27 the hypergonadotrophic hypogonadism was accompanied by a raised gammaglobulin fraction, the IgG fraction and the IgM fraction also being increased. Patient 25 had rheumatoid arthritis, patient 26 glomerulonephritis and patient 28 antithyroid antibodies, as well as antiparietal cell antibodies. Although in these patients no

TABLE III. SECONDARY GONADAL FAILURE GROUP

No.	Age (yrs)	G	Gonadotrophins FSH			LH			Karyotype	Diagnosis
15	27	0	38	88	92	58	24	26	46 XX	Gonadal failure due to irradiation
16	24	0	151			75			46 XX	Gonadal failure due to irradiation
17	33	3	207	124	139	36	38	48	46 XX	PS: Estes procedure
18	26	1	74	64		24	43		46 XX	PS: ectopic pregnancy
19	28	2	53	52	60	150	136	150	46 XX	PS: ectopic pregnancy
20	27	0	65	52	87	95	48	50	46 XX	PS: wedge resection
21	38	2	80			50			46 XX	Post-cytostatic failure
22	33	0	86	79	73	50	38	43	46 XX	Auto-immune oöphoritis
23	32	2	50	90		89	27		46 XX	Auto-immune oöphoritis
24	29	0	51	79		58	54		46 XX	Auto-immune oöphoritis
25	28	1	102	65	39	19	34	29	46 XX	Rheumatoid arthritis
26	30	0	80	70		130	110		46 XX	Glomerulonephritis
27	36	1	31	53	67	27	31	48	46 XX	Globulin (IgG) raised
28	26	1	27	50	44	34	44	33	46 XX	Thyroid antibodies
29	19	0	56	23	5,3	27	15	7,3	46 XX	Temporary gonadal failure
30	18	0	33	19	6,7	35	12	12	46 XX	Temporary gonadal failure
31	23	0	60	83	100	50	124	130	46 XX	IPM
32	18	0	39	43	69	50	200	28	46 XX	IPM
33	33	2	75	67	65	116	114	90	46 XX	IPM
34	20	1	102	65	39	20	34	29	46 XX	IPM
35	34	2	154	59	67	50	23	20	46 XX	IPM
36	35	4	86	70		24	56		46 XX	IPM
37	19	0	81	27	36	29	16	46	46 XX	IPM
38	32	0	18	38	34	32	20	40	46 XX	IPM
39	33	1	40	34	20	60	43	60	46 XX	IPM
40	34	1	66	140	284	50	120	32	46 XX	IPM
41	32	4	29	25	27	70	90	70	46 XX	IPM
42	27	0	32	106	87	17	66	125	46 XX	IPM
43	36	6	109	80	76	40	56	42	46 XX	IPM
44	37	3	29	14	66	70	29	80	46 XX	IPM
45	32	2	55	12	35	50	36	34	46 XX	IPM
46	29	3	80	70		120	90		46 XX	IPM
47	30	3	54	66		24	70		46 XX	IPM
48	33	4	83	100	140	100	140	90	46 XX	IPM
49	36	2	70	52	64	80	80	22	46 XX	IPM
50	37	2	36	60	54	54	92	80	46 XX	IPM

PS = post-surgery; IPM = idiopathic premature menopause.

ovarian biopsies were performed, this association with other disorders of a probable auto-immune origin has been reported.

Patients 29 and 30, with hypergonadotrophic amenorrhoea, spontaneously resumed menstruation; results of follow-up gonadotrophin determinations were within normal limits. The time lapse between the rise in gonadotrophin levels and the resumption of menstruation was so long, however, that a normal mid-cycle peak of gonadotrophins could be eliminated.

The last group (patients 31 - 50), could best be categorized as cases of idiopathic premature menopause. On 17 of these patients ovarian biopsies were performed. Morphologically the ovarian appearance varied from the typical postmenopausal shrunken appearance to macroscopically normal ovaries (Fig. 5). A stereotyped histological picture was seen, namely an ovarian stroma with no follicles and several corpora albicantes and corpora atretica.

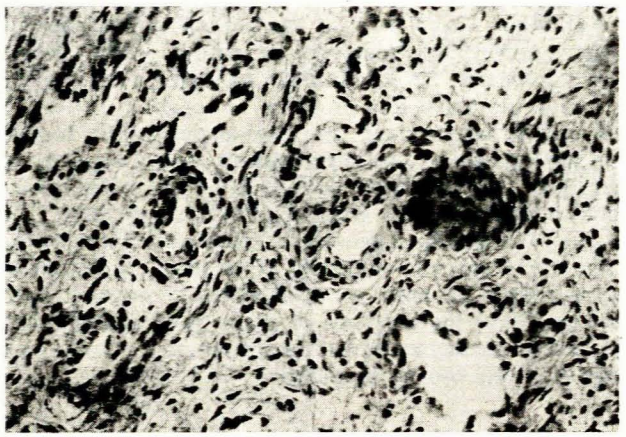

Fig. 3. Endarteritis obliterans and monocellular infiltration in the ovarian stroma as well as the blood vessel walls. From a patient with auto-immune oöphoritis.

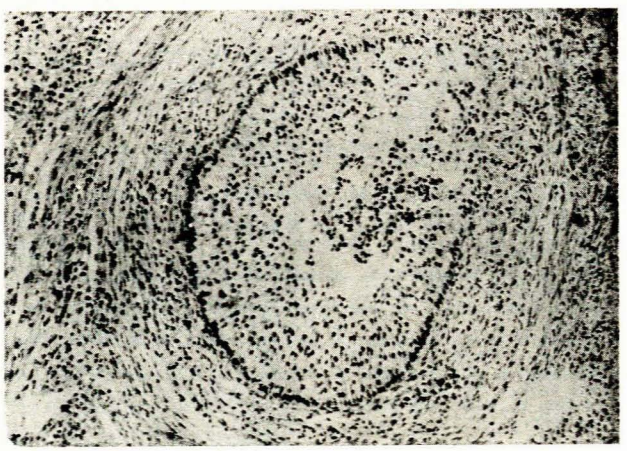

Fig. 4. A well-developed follicle with a coarse monocellular infiltration in the follicular wall extending into the granulosa cell layer. The patient had premature gonadal failure due to auto-immune oöphoritis.

Patient 44 had an interesting chromosomal abnormality, despite normal blood findings, normal left ovarian chromosomes and 3 healthy children. Fibroblasts from the right ovary showed a mosaic, namely mos 46,XX/46,XX, t(7;21)(qll;qter).

Patients 31 and 32 had a histological picture which differed from the others in this group. Their ovaries were small and 1 - 2 primordial follicles per high-power field could be seen (Fig. 6). The ovarian stroma was normal, with no signs of monocellular infiltration.

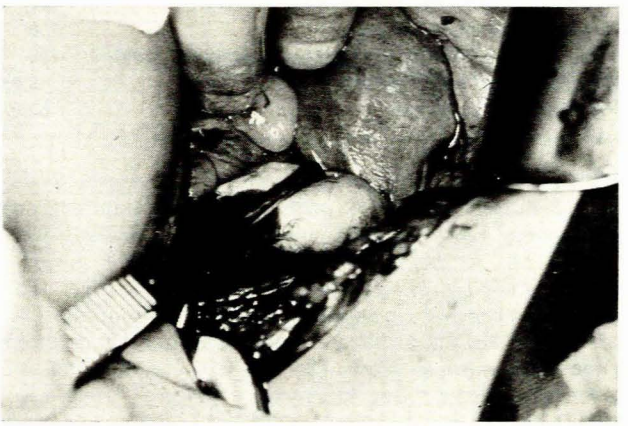

Fig. 5. Macroscopic normal appearance of ovaries in a patient with premature gonadal failure.

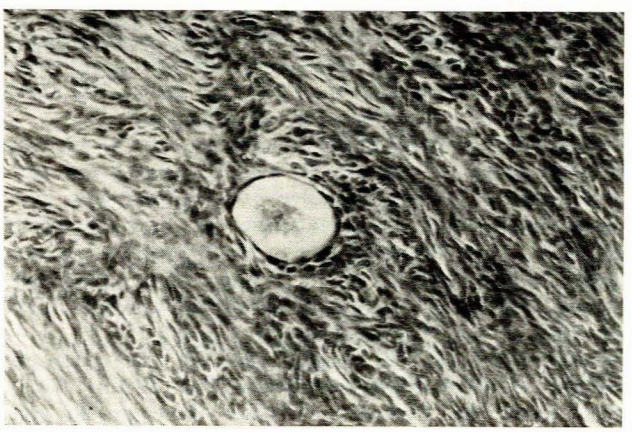

Fig. 6. A single follicle embedded in dense ovarian stroma in a case of premature gonadal failure.

Discussion

In the presence of hypergonadotrophic amenorrhoea, patients can be categorized according to their secondary sexual characteristics into a primary and a secondary gonadal failure group. The characteristics of these two groups are shown in Tables IV and V.

TABLE IV. CHARACTERISTICS OF THE PRIMARY GONADAL FAILURE GROUP

Characteristics	%
Average age 24 yrs (SD 4,4 yrs)	
Underdeveloped secondary sexual characteristics	100
Primary amenorrhoea	71,4
Dysgenetic gonads	92,8
Chromosomal abnormalities	50
Previous pregnancies	0

TABLE V. CHARACTERISTICS OF THE SECONDARY GONADAL FAILURE GROUP

Characteristics	%
Average age 29,5 yrs (SD 5,76 yrs)	
Normal secondary sexual characteristics	**100**
Secondary amenorrhoea	**100**
Ovaries macroscopically normal, absent oöcytes	**100**
Chromosomal abnormalities	**2,8**
Previous pregnancies	**63,8**

This distinction is important, since it suggests a different pathogenesis. In the primary gonadal failure group chromosomal abnormalities and dysgenetic gonads were often found, whereas in the secondary failure group a follicle-destroying process probably played a role. This could be iatrogenic (irradiation) or an auto-immune process, but in the majority a cause could not be detected. In the auto-immune group (20%) there could be an isolated organ lesion,[3,6] but the ovarian lesion is often associated with other auto-immune diseases.[2,7,8] It is therefore very important to evaluate these patients for the presence of other endocrinopathies; long-term follow-up is also essential, because these associated endocrinopathies could develop in time.[2,7] There is a known association between rheumatoid arthritis, auto-immune thyroiditis[2,8,9] and auto-immune oöphoritis, which was the case in patients 25 and 26. However, an association between glomerulonephritis and hypogonadism has not previously been reported; this may have existed in patient 36.

In the primary gonadal failure group there are 2 very interesting cases, to the best of our knowledge not previously reported in the literature. In a patient with ovotesticular dysgenesis, the gonadal morphology resembled that found in a dysgenetic true hermaphroditic gonad. Because of the high incidence of malignancies in this type of gonad,[10] they were removed. The bilateral absence of adnexa (Fig. 2) with a normal uterus is difficult to explain. Bilateral torsion of the adnexa could be a possible explanation, although the patient had no such history. Bearing in mind the absence of breast development, the ovarian tissue could have been absent from before puberty. A possible defect in the blood supply to the adnexa which could have developed *in utero,* as in congenital atresia of the gut, might explain the pathogenesis. This would then represent a form of congenital absence of adnexa.

In the secondary gonadal failure group, 52,7% of the patients had an unidentified aetiological factor. The absence of follicles in this group of previously fertile patients suggests a premature ageing process and disappearance of the oöcytes, rather than the presence of possible gonadotrophin receptor antibodies.[11,12] Although an auto-immune process is not excluded, there were no histological signs of this tissue reaction, as was the case in some of the other patients.

A chromosomal factor could be implicated in this syndrome, as was possibly the case in patient 44 with a mosaic cell line in one of her gonads. The 2 patients with idiopathic premature menopause and a few primordial follicles had normal secondary sexual characteristics. This suggests normal sex steroid production at puberty. These patients, on the younger side of the age spectrum (18 and 23 years), might have had a morphological picture resembling that present in the early stages of the oöcyte disappearance process found in cases of idiopathic premature gonadal failure.

The 2 patients with temporary hypergonadotrophic amenorrhoea demonstrate the potential pitfall in making a categorical diagnosis of permanent gonadal failure. This condition could possibly explain the few pregnancies reported in patients with previous hypergonadotrophic premature gonadal failure.[13,14]

Gonadotrophin values in the same patient with hypergonadotrophic amenorrhoea, may vary a lot (Table III). A single determination of one of the two gonadotrophins in this series could lead to the erroneous diagnosis of normogonadotrophic amenorrhoea, with a completely different prognosis. Repeated single gonadotrophin determinations could solve this problem, although in patient 35 this method would have complicated the matter further. This method would also imply making several single gonadotrophin determinations in all cases of amenorrhoea, since in the secondary gonadal failure group there were no clinical stigmata suggestive of gonadal failure. In this series the diagnostic accuracy of a single simultaneous determination of both gonadotrophins was much more accurate. Since the diagnosis of premature gonadal failure has serious consequences for the patient, an accurate diagnosis is of the utmost importance.

This is an abstract from the thesis: 'Die etiologie en diagnose van hipergonadotropiese amenoree' for the M.D. degree at the University of Stellenbosch, with promotor Professor W. A. van Niekerk.

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