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Male and Female Hypogonadisms: Etiological, Metabolic and Osteodensitometric Aspects

Nestor Ghislain Andzouana Mbamognoua[1,2], Ikram Damoune[3], Sana Doubi[3], Asmae Lahlou[3], Farida Ajdi[3]

[1]Department of Metabolic and Endocrine Diseases, Brazzaville University Hospital, Brazzaville, Republic of the Congo
[2]Faculty of Health Sciences, Marien Ngouabi University, Brazzaville, Republic of Congo
[3]Department of Endocrinology, Metabolic Diseases, Hassan II University Hospital of Fez, Fez, Morocco
Email: *andzouananestor@yahoo.fr

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Abstract

Introduction: Studies showed a high prevalence of metabolic abnormalities including dyslipidemia, type 2 diabetes in cases of low testosterone in men and which are associated with increased cardiovascular risk. Hypogonadism represents the second cause of endocrine osteoporosis. **Objectives:** The objectives of our work were: to determine the main causes of hypogonadism in women and men; to assess the frequency of metabolic and osteosdensitometric abnormalities in the hypogonadal population. **Patients and methods:** A retrospective descriptive study was carried out over 7 years on 120 patients, hospitalized in the Endocrinology department of the Hassan II University Hospital of Fez-Morocco for hypogonadism. The patients selected were those who had symptoms of hypogonadism confirmed in men by: low total testosterone for Tanner stage in adolescents, <3 ng/ml or lower limit of normal for adults; in women, hypoestrogenia < 30 pg/l. Gonadotropin dosage, karyotype, pelvic or testicular ultrasound and pituitary MRI, for etiological diagnosis, were performed. Bone densitometry was performed for bone impact and lipid profile for metabolic profile. **Results:** Out of 120 patients, there were 77 women and 43 men. The average age was 31.51 years. In men, the main causes were central hypogonadism in 67.4% and primary testicular failure in 32.6%. In women, central hypogonadism was also the most common cause noted in 63.7% and premature ovarian failure was observed in 36.4%. HypoHDL was significantly more frequent p (0.005) in women, osteopenia and osteoporosis were significantly more frequent in women than in men p (0.046). **Conclusion:** Central causes represent the most common etiology of hypogonadism in both sexes; abnormalities of bone mineralization and me-

tabolic disorders were predominant in women.

Keywords

Hypogonadism, Etiological, Metabolic, Osteodensitometric, Fez

1. Introduction

Hypogonadism is defined by a reduction in the production of testosterone in men and estradiol in women, causing abnormalities in pubertal development and a reduction in bone mineralization. Numerous studies have shown a high prevalence of metabolic abnormalities including dyslipidemia and type 2 diabetes in the event of a drop in testosterone in men and which are associated with an increased cardiovascular risk [1] [2] [3]. In Morocco, type 2 diabetes constitutes a real public health problem. The prevalence of diabetes in Morocco reaches 9% of the adult population over 20 years old, 50% of whom remain undiagnosed [4]. Due to its degenerative complications, it constitutes an economic and social burden.

Sex steroids have a crucial role in the acquisition of peak bone mass; their deficiency has clinical consequences on bone tissues which are well known, such as osteopenia and osteoporosis [5] [6].

Osteoporosis represents a public health problem, with the prevalence of osteoporotic fractures worldwide estimated in 2000 at more than 56 million with a female:male (F:M) ratio of 1.6 [7].

Although the number of fractures is higher in women, mortality linked to osteoporotic fracture is greater in men [7].

Hypogonadism represents the second cause of endocrine osteoporosis [8]. Apart from the obvious negative impact on fertility of hypogonadism, the occurrence of metabolic, bone and cardiovascular complications justifies adequate and complete care aimed at reducing the morbidity and mortality inherent to this condition within the Moroccan population, also affected by the resurgence of type 2 diabetes and cardiovascular diseases.

The objectives of our work were to:

1) Determine the main causes of hypogonadism in women and men.

2) To assess the frequency of metabolic and osteodensitometric abnormalities in the hypogonadal population.

2. Patients and Methods

This was a retrospective descriptive study carried out over a period from 2009 to 2015 involving 120 patients, hospitalized in the Endocrinology department of the Hassan II University Hospital in Fez for hypogonadism. The group of women had a larger number, consisting of 77 women compared to 43 among the men.

The patients included in our series were those who had symptoms suggestive of hypogonadism; a history and physical examination were carried out in all patients using an investigation form (Appendix I). The clinical variables were the assessment of the pubertal stage, the anomalies of the external genitalia, the anthropometric parameters, the signs pointing towards a particular etiology of hypogonadism.

For biological variables, in particular to confirm the diagnosis of hypogonadism in the female population, a determination of estradiol, FSH and LH was carried out by radioimmunological method. The standards considered were those of the follicular phase for patients who were in amenorrhea. Low oestradiol levels < 30 pg/l confirmed the diagnosis of hypogonadism [9] [10].

In cases of peripheral hypogonadism (hypergonadotropic), a karyotype was systematically carried out by the medical genetics team at the Hassan II University Hospital in Fez and a pelvic ultrasound. A hypothalamic-pituitary MRI was performed in cases of central hypogonadism (hypogonadotropic).

In men, hypogonadism was confirmed by a total serum testosterone value ≤ 3 ng/ml by radioimmunological method, or by a low serum testosterone value according to Tanner stage in adolescents [9]. FSH and LH measurements made it possible to identify the origin of hypogonadism. The gonadotropic assessment was informative in the adolescents included in our study because the bone age was greater than 13 years. Karyotype and hypothalamic-pituitary MRI were performed depending on whether the involvement was peripheral or central.

In central attacks, in both sexes, an exploration of the other endocrine axes was carried out by an 8-hour measurement of TSH, LT4, prolactin, cortisol and an autoimmunity assessment with measurement of anti-peroxidase antibodies (anti TPO) indicated in etiological research.

The impact of hypogonadism was assessed on a biological level by carrying out a lipid profile (total cholesterol, triglycerides, HDL and LDL cholesterol), a fasting blood sugar level, a vitamin D dosage and a phosphocalcic balance at the researches the factors aggravating the bone impact of hypogonadism; for the imaging variables, on the radiological level a osteodensitometric was carried out after correction of hypovitaminosis D, from the age of 18; the bone was considered normal: T score > −1, Osteopenia: −1 ≥ T score > −2.5 and Osteoporosis: T score ≤ −2.5, according to the definition of osteoporosis based on of the population established by the WHO in 1994 [11].

Cardiac exploration made possible by performing a cardiac Doppler ultrasound (DTE), in the context of the impact of hypogonadism. Renal ultrasound and DTE looking for cardiac and renal malformations are common in certain congenital gonadal insufficiencies.

We excluded from our study all patients who had a normal gonadotropin test, and those whose files were incomplete or unusable.

The statistical analysis was carried out in the Epidemiology laboratory at the

Faculty of Pharmacy and Medicine of Fez. Statistical analysis was carried out using SPSS version 20 software. Descriptive and comparative analyzes were carried out based on classic parametric tests.

Thus there is a correlation between two variables, when the p-value was less than or equal to 0.05.

3. Results

Our study population consisted of 120 patients with hypogonadism, mainly composed of women 77 (64%) compared to 43 men (36%) with a sex ratio of 1.79.

Demographically, the average age was 31.51 years with extremes of 13 and 70 years for men. The analysis of the history in search of risk factors for hypogonadism made it possible to incriminate autoimmunity as the antecedent most frequently found in particular in 12 patients, followed by medication use (influencing gonadotropic functioning) in 5 patients. Chronic diseases were only found in 2 patients (Figure 1).

Clinically, the most common reason for consultation in women was amenorrhea, observed in 67 patients, compared to 10 patients who consulted for spaniomenorrhea. This amenorrhea was isolated in 49 patients, and more frequently associated with signs of hyperandrogenism in 6 patients, followed by galactorrhea in 5 patients (Table 1).

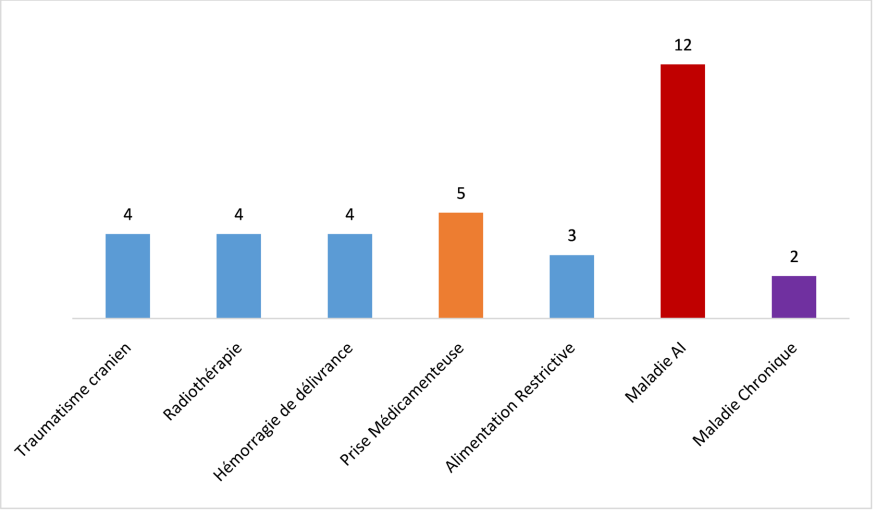

Figure 1. Distribution of risk factors for hypogonadism.

Table 1. Distribution of clinical manifestations of hypogonadism in the female population.

Amenorrhea						Effective
Spaniomenorrhea	Signs of hyperandrogenism	Hot flashes	Galactorrhea	Intracranial hypertension	isolated	
10	6	3	5	4	49	77

In the male population, infertility was the most frequent reason for consultation as it was noted in 20 patients, followed by micropenis in 12 patients, gynecomastia in 10 patients and impuberism in 10 patients. We only noted 2 patients with cryptorchidism in our series. The symptoms described were associated in most cases in these patients (Figure 2).

Regarding the causes of hypogonadism, anterior pituitary insufficiency was the most common cause of hypogonadism in both sexes. In women it was found in 41 women, followed by premature ovarian failure in 28 women; in men, anterior pituitary insufficiency was noted in 17 men and primary testicular insufficiency in 14 men.

Anterior pituitary insufficiency was more common in women than in men, approximately 41 women versus 17 men with a statistically significant difference p (0.00) (Table 2).

On the biological hormonal level, the lowest values of testosterone < 1 ng/ml were noted in patients with central hypogonadism, 15 patients compared to 6 patients with peripheral hypogonadism with p (0.045); central hypogonadism was also more numerous for patients with a serum testosterone value between 1 and 3ng/ml, however this difference was not statistically significant (Table 3).

Metabolically, the most frequently encountered abnormalities were hypoHDLemia, hypertriglyceridemia and moderate fasting hyperglycemia. HypoHDLemia was significantly more frequent p (0.005) in women, as was obesity with p (0.031) than in men. The female preponderance of hypertriglyceridemia, moderate fasting hyperglycemia and diabetes mellitus, compared to the male hypogonadal population was not statistically significant (Table 4).

On the osteodensitometric level, osteopenia and osteoporosis were significantly more frequent in women than in men with p (0.046) (Table 5).

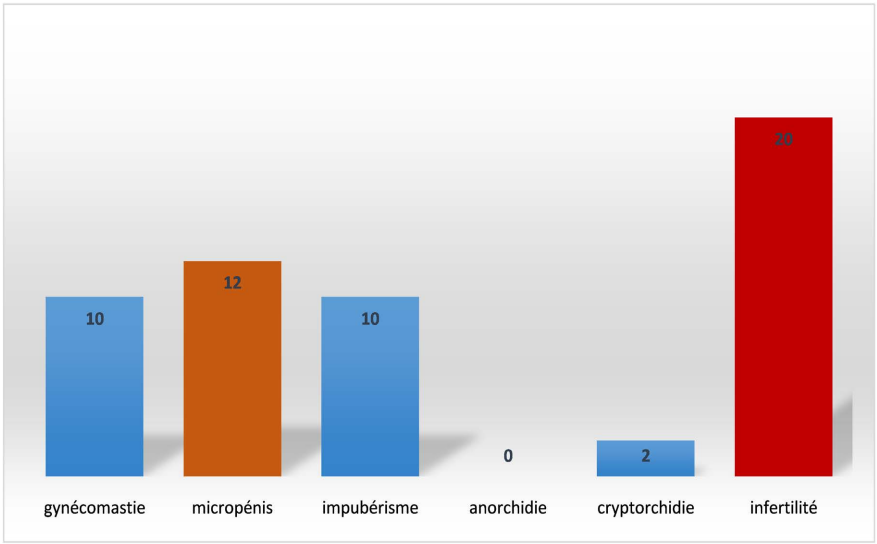

Figure 2. Distribution of clinical manifestations of hypogonadism in the male population.

Table 2. Distribution of causes of hypogonadism in both sexes.

	Anterior pituitary insufficiency		Hypogonadism Hypogonadotropic isolated		Premature Ovarian Failure	Insufficiency Primary testicular	Effective
	NOT	%	NOT	%	NOT	NOT	
Man	17	29%	12	60%	0	14	43
Women	41	71%	8	40%	28	0	77
Total	58	100%	20	100%	28	15	120
	P: 0.00 (<0.05)						

Table 3. Relationship between testosterone levels/etiologies of hypogonadism in men.

	Plasma testosterone			
	Less than 1 ng/ml		1 - 3 ng/ml	
Central hypogonadism	NOT 15	% 71	NOT 14	% 64
Peripheral hypogonadism	NOT 6	% 29	NOT 8	% 36
P	0.045 (p < 0.05)		0.7 (p < 0.05)	

Table 4. Summary of metabolic abnormalities and obesity in hypogonadal patients according to sex.

	HypoHDL		Hypertriglyceridemia		Hyperglycemia Moderate on an empty stomach		Diabetic sugar		Obesity	
	NOT	%	NOT	%	NOT	%	NOT	%	NOT	%
Man	16	24.6%	12	29.3%	14	38.9%	1	14.3%	3	14.3%
Women	49	75.4%	29	70.7%	22	61.1%	6	85.7%	18	85.7%
Total	65	100%	41	100%	36	100%	7	100%	21	100%
	P: 0.005 (<0.05)		P: 0.280 (<0.05)		P: 0.648 (<0.05)		P: 0.717 (<0.05)		P:0.031 (<0.05)	

Table 5. Osteodensitometric profile of hypogonadal patients according to sex.

	Bone Mineral Density (BMD)						Effective
	Normal		Osteopenia		Osteoporosis		
	NOT	%	NOT	%	NOT	%	
Man	28	45.2%	6	20.7%	1	16.7%	35
Women	34	54.8%	23	79.3%	5	83.3%	62
Total	62	100%	29	100%	6	100%	97
	P: 0.046 (<0.05)						

4. Discussion

In our study, the female sex was much more represented, more than half of the cases (64%, with a sex ratio of 1.79) due to its high demographic prevalence. The average age of our patients was 31.51 years with extremes of 13 and 70 years. This young average age is explained by the fact that hypogonadism mainly concerns the young population during periods of genital activity in women, who are the most frequent to consult in our study, as well as in men or steroidogenesis testicular continues until old age which explains the extreme age of 70 years in our study.

The analysis of the antecedents made it possible to incriminate autoimmunity as the antecedent most frequently found in particular in 12 patients, this is explained by the presence of premature ovarian failure in 28 patients, in which the involvement autoimmunity is common.

The most common reason for consultation among women was amenorrhea, observed in 67 patients; amenorrhea represents the most frequent manifestation of female hypogonadism [12]. Within the male population, the symptoms were associated in an intricate manner, however infertility was the most frequent reason for consultation as it was noted in 20 patients, followed by micropenis in 12 patients; this preponderance was justified by the fact that the majority of our patients were in a period of genital activity with serious social and family consequences, a considerable psychological impact in the face of the loss of masculine identity pushing these patients to consult in the face of infertility and the micropenis [13] [14].

Anterior pituitary insufficiencies represented the most common group of etiologies in both men and women. In women it was found in 41 women (63.6%), followed by premature ovarian failure in 28 women (36.4%); in men, anterior pituitary insufficiency was noted in 17 men and primary testicular insufficiency in 14 men. This trend is explained by the fact that these anterior pituitary insufficiencies are mainly acquired from tumoral, hemorrhagic and autoimmune causes.

Karavitaki N. and allies [15] report that acquired central hypogonadism dominated by tumors is the most common cause of hypogonadism. In the literature, pituitary adenomas have been described as an important cause of partial antero-pituitary insufficiency affecting rather the gonadotropic gonadotropic line [16] [17] [18], which is consistent with the results of our study.

In our female population, hypothalamic-pituitary tumors were found in 29 patients, SHEEHAN syndrome in 6 patients, autoimmune hypophysitis was the cause in 4 patients, post-radiation anterior pituitary insufficiency in 2 patients.

All these disorders were accompanied by a partial or global anterior pituitary deficiency, which explains the predominance of anterior pituitary insufficiency among the causes of hypogonadism in women.

Premature ovarian failure was the second etiological group, observed in 28 patients, the first of which included idiopathic premature ovarian failure in 19

patients, Turner syndrome in 5 patients and autoimmune origin in 4 patients.

Isolated central hypogonadism, the last etiological group in both sexes, is explained because they are due to congenital causes which are generally rare [16] notably central hypogonadism with normal MRI, Morsier's Kallmann in a woman and 2 men.

Among the 17 men with anterior pituitary insufficiency, 13 of them had a pituitary adenoma, and 4 had post-radiation anterior pituitary insufficiency.

Antepituitary insufficiency was more common in women than in men, approximately 41 women or 71% compared to 17 men or 29% with a statistically significant difference p (0.00). This difference is justified by the occurrence in women of autoimmune pituitary disorders [19], and pituitary infarctions due to SHEEHAN syndrome, thus significantly increasing the number of cases of anterior pituitary insufficiency in addition to those caused by pituitary adenomas. These autoimmune and vascular causes were not found in men in our study population. In fact, autoimmune hypophysitis preferentially affects women as reported by Trabelsi and allies in Tunisia [20].

The lowest values of serum testosterone < 1 ng/ml were noted in patients with central hypogonadism 15 patients versus 6 patients with peripheral hypogonadism with p (0.045); these peripheral hypogonadisms mainly consisted of Klinefelter syndrome. Our results agree with those reported by Eulry F. and allies [21], testosterone levels are at the lower limit of normal, therefore between 1 and 3 ng/ml and much less lowered than in other etiologies of hypogonadism (hypogonadism acquired primary, idiopathic hypogonadotrophic hypogonadism, acquired secondary hypogonadism). Indeed, hypogonadism during Klinefelter syndrome is more often partial, often discovered in adulthood due to infertility or micropenis.

The most frequently encountered metabolic abnormalities were hypoHDLemia, hypertriglyceridemia and moderate fasting hyperglycemia. HypoHDLemia was significantly more frequent p (0.005) in women, as was obesity with p (0.031) than in men. However, the female preponderance of hypertriglyceridemia, moderate fasting hyperglycemia and diabetes mellitus, compared to the male hypogonadal population was not statistically significant.

Our results agree with those reported by N. Rekkik and allies in Tunisia [22] who reported a significant drop in HDL in hypogonadal subjects compared to controls (0.96 +/− 0.25 mmol/l VS 1.08 +/− 0.27 mmol/l), as well as moderate fasting hyperglycemia predominant in hypogonadal patients compared to controls (27.5% VS 6.25 with p = 0.001).

These metabolic abnormalities found in men are undeniably linked to hypotestosteronemia, because testosterone deficiency is accompanied by a change in body composition associated with a tendency to gain weight. Fat mass, particularly visceral, is increased while lean mass, particularly muscle, is reduced [23]. Likewise, insulin resistance is induced by testosterone deficiency and both contribute to the genesis of vascular risk factors: dyslipidemia, type 2 diabetes and

hypertension [24].

In women, the significantly high frequency of obesity was more explained by a context of significant female obesity in the general population.

Bone mineralization disorders were more common in women than in men. Osteopenia was noted in 26 women (30%).

Osteoporosis is primarily a disease of women; however, this entity is a reality in men. Although the mechanisms of action of sex steroids are still poorly understood, the clinical consequences of their deficiency on bone tissue have now been known for more than 50 years. In adults, bone remodeling is modulated by sex steroids. Estrogens are primarily agents that inhibit osteoclast resorption [25]. Likewise, although their mechanisms of action are even less well known than those of estrogens, androgens seem involved in the regulation of bone volume: reduction in bone mass and increased incidence of osteoporotic fractures in hypogonadal patients, increased bone mass in women with hyperandrogenism. Estrogens are essential in both sexes. Estrogens act on the growth of the boy's bone through local aromatization of androgens, hence the particularly important role of estrogens. Due to their greater involvement in bone structure, osteoporosis in women is better described and more serious than in men; The positive effects of SDHEA supplementation in postmenopausal women are explained by peripheral conversion rather than by direct action via the androgen receptor [26], further justifying the important role of estrogens in bone structuring; which corroborates with the results observed in our population of hypogonadal men and women. Metabolic disorders are of definite therapeutic interest.

Some authors suggest that a drop in plasma testosterone levels is a predictive predictive marker for the onset of diabetes [2]. On the contrary, men, obese or not, with a higher level of plasma testosterone would be at less risk less likely to develop diabetes [3]. Substitution of in hypogonadal men has the opposite effect on body composition, reducing body composition: reduction in visceral fat and increase in lean body mass with a concomitant increase in muscle strength [27], but without any significant change in total body weight [28]. Androgen replacement in these patients is therefore essential to correct metabolic disorders and prevent cardiovascular disease.

5. Conclusion

In practice, the aspects of fertility and normal development of secondary sexual characteristics, normal sexual life constitute a priority for patients because of their impact on the social level. The consequences of hypogonadism including increased fat mass and decreased lean mass, metabolic syndrome, risk of type 2 diabetes and decreased bone mineral density are important aspects of the management of hypogonadism. hypogonadism in men and women. In addition to the etiological management of hypogonadism, the most frequent causes of which were pituitary adenomas in both sexes, screening for type 2 diabetes, dyslipide-

mia and abnormalities of bone mineralization must occupy an important place in the overall care of the patient because of their effective cardiovascular morbidity and mortality, the fracture risk linked to endocrine osteoporosis. In the light of our work, screening for hypogonadism can be suggested in type 2 diabetic patients, since a drop in testosterone is a risk factor, the search for hypo HDL in hypogonadal women, allowing a better assessment of cardiovascular risk.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix I: Survey sheet

Survey sheet for male and female hypogonadism

File number:IP:

First and last name:

Age:

Gender:

Origin: urban/__/ rural/__/

Mutual: yes/__/ no/__/

Socio-economic level: low/__/ medium/__/ high/__/

Reason for hospitalization:

ATCD:

*personal:

-Head or pelvic trauma; no/__/ yes/__/, specify……

-cranial or pelvic radiotherapy: no/__/ yes/__/ specify…….

-infiltrative disease: yes/__/ no/__/ autoimmunity: yes/__/ no/__/

-corticosteroid therapy: yes/__/ no/__/

-anosmia: yes /__/ no/__/

-general illnesses: no/__/ yes/__/ specify……

*family:

-infertility: no/__/ yes/__/ specify……...

-sexual ambiguity: yes/__/ no/__/

History of the disease:

Duration of progression of the disease:

Pituitary tumor syndrome: yes/__/ no/__/

Other associated signs:

Physical examination:

Weight= height= BMI= TT= PA=

Dysmorphic syndrome: no/__/ yes/__/ specify…….

Other somatic abnormalities:

-Tanner (dimensions or stage): testicles…… Pubic hair……..

Breasts……..…. pubic hair……..….

-micropenis: yes/__/ no/__/

-gynecomastia: yes/__/ no/__/ nipple discharge: yes/__/ no/__/

Other pituitary endocrine axes: …….

Paraclinical examinations:

-testosterone= ……. estradiol=……. FSH=……. LH=……

-prolactin=……. TSH= LT4=……. Cortisol 8h=…….

-IGF1=…… Anti TPO: positive/__/ negative /__/

-karyotype=……. MRI HH……

-pelvic or testicular ultrasound……...
-spermogram: ……
-osteodensitometric: ……...
-CT= HDL= TG= LDL= GAJ=

Diagnostic:
Hypergonadotropic hypogonadism: no /__/ yes/__/ specify……
Hypogonadotropic hypogonadism: no/__/ yes/__/ specify……..

Treatment: hormonal replacement: no/__/ yes/__/ specify…….
Etiological treatment: yes /__/ no/__/
Assisted medical procreation monitoring: yes/__/ no/__/