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Primary Amenorrhea: Contribution of Cytogenetics to Etiological Diagnosis: A Report of 19 Cases

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Abstract

Background: Primary amenorrhea is a source of concern for both the adolescent and her parents, with a diverse range of underlying etiologies. Objective: To determine the etiologies of primary amenorrhea, its frequency, and the type of chromosomal abnormalities present in Senegalese women, in order to enrich the scientific data on the etiologies of this condition and to raise further awareness among healthcare professionals of the importance of early diagnosis and prompt, appropriate management. **Methods:** A retrospective, descriptive cross-sectional study of the records of 19 adolescents and women presenting with primary amenorrhea, recorded over a 2-year and four months period (February 2024 to June 2026) at the Laboratory of Histology, Embryology and Cytogenetics of Cheikh Anta Diop University, Dakar. **Results:** The mean age of the patients was 23.7 ± 6.7 years. The karyotype was normal in 47.4% of cases and abnormal in 52.6%. The causes of primary amenorrhea were gonadal dysgenesis (57.9%), Müllerian agenesis (36.8%) and outflow tract anomalies (5.3%). Turner syndrome and its variants were the most frequent chromosomal abnormality (47.3%). There was one case of Swyer syndrome (1/19) and one case of 46,XX pure gonadal dysgenesis (1/19). **Conclusion:** Chromosomal abnormalities remain the predominant etiologies of primary amenorrhea. Cytogenetic study constitutes an important examination in the evaluation of these patients. The most frequently observed condition is Turner syndrome and its variants.

Keywords

Primary Amenorrhea, Chromosomal Abnormalities, Turner Syndrome, Senegal

1. Introduction

Puberty is the transitional period between childhood and adulthood; it is a defining event in the life of adolescent girls, and the onset of menstruation is regarded as a sign of femininity and fertility. Any delay in the appearance of menstruation causes anxiety in patients and their parents.

Primary amenorrhea is defined as the absence of menarche in girls aged 15 years or older, with or without secondary sexual characteristics, despite normal growth [1]. In dark-skinned girls, according to the third National Survey on Health and Nutrition (NHANES III), the mean age at menarche was 12.1 years [2]. The diagnostic work-up in a patient presenting with primary amenorrhea must be thorough and meticulous, ranging from clinical examination to cytogenetic study [3]. This work-up should be undertaken if menarche has not occurred within 3 years of the onset of breast development (thelarche), or within 5 years of thelarche if it occurred before the age of 10 years.

Menstruation is regulated by the hypothalamic-pituitary-ovarian (HPO) axis. Any disruption of this axis or its signaling pathways can result in the absence of menstruation [4].

Several studies on the etiologies of primary amenorrhea, published in Asia and, for the most part, in Western countries, show that the most frequent underlying causes are Müllerian duct anomalies and gonadal dysgenesis [5] [6].

Given that few studies have focused on the causes of primary amenorrhea in African women, the objective of the present study was to determine the etiologies of primary amenorrhea, its frequency, and the type of chromosomal abnormalities present in Senegalese women, in order to enrich the scientific data on the etiologies of this condition and to raise further awareness among healthcare professionals of the importance of early diagnosis and prompt, appropriate management.

2. Patients and Methods

2.1. Type of Study and Data Collection

This was a retrospective descriptive cross-sectional study. Data were extracted from the records of patients referred for karyotyping to the Laboratory of Histology, Embryology and Cytogenetics of Cheikh Anta Diop University, Dakar, between February 2024 and June 2026.

A comprehensive, pre-printed form was used to record sociodemographic data (age, height, weight, marital status). Other data were also recorded on the form, including clinical findings (evaluation of secondary sexual characteristics according to the Tanner classification), pelvic ultrasound findings, Magnetic Resonance Imaging (MRI) and karyotype. Informed consent was obtained from the patients or their guardians on the day of sampling. All complete records with primary amenorrhea as the indication were included; records without consent were excluded from the study. Etiological classification took into account secondary sexual characteristics and imaging findings, combined with cytogenetics. Swyer syndrome was diagnosed according to the criteria of King TF *et al.* (2014) (absent or

streak gonads, with the uterus and fallopian tubes usually absent or hypoplastic, in an individual with a female phenotype and a 46,XY karyotype), following the flowchart for the evaluation of women with primary amenorrhea in the absence of secondary sexual characteristics proposed by Salvador Pertusa *et al.* in 2009 [7] [8] (**Figure 1**). Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome was diagnosed according to its two described clinical forms: MRKH type I, the isolated form limited to uterovaginal anomalies, and MRKH type II, the form associated with other malformations [9]. The reference height used to assess the patients' anthropometric parameters was 163 cm (mean height of Senegalese women), according to the results of the 2005 Senegal Demographic and Health Survey [10] (**Figure 1**).

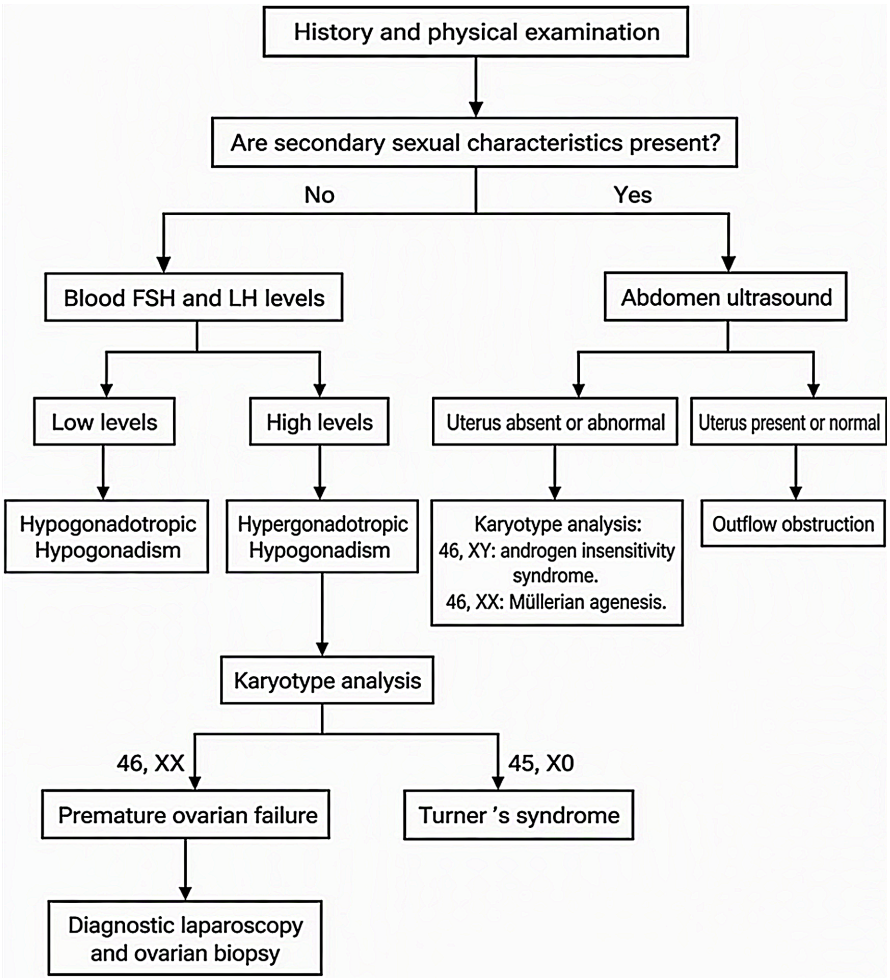

Figure 1. Flowchart for the evaluation of women with primary amenorrhea [8].

2.2. Cytogenetic Screening

To determine the cytogenetic status of the patients, R-bands karyotyping was performed for all patients from lymphocyte culture. At least twenty metaphases were examined for each patient. Additional cells (up to 100) were analyzed in cases where chromosomal abnormalities were identified on this initial analysis.

2.3. Statistical Analysis

Data were analyzed using SPSS software (version 23) and Python (version 3.12), using the pandas and SciPy libraries (Fisher's exact test, chi-square test, Pearson correlation); graphs were produced using Matplotlib. Quantitative variables were expressed as mean ± standard deviation, and qualitative variables as frequencies and percentages. The significance threshold was set at $p < 0.05$.

3. Results

In the present study, 19 patients presented with primary amenorrhea. The mean age of the patients was 23.7 ± 6.7 years, with extremes of 15 and 42 years; the predominant age group was 21 to 30 years, accounting for 58.0% of cases. Mean height was 155.8 ± 17.5 cm, with a mean body mass index of 21.1 ± 4.8 kg/m^2. The majority of patients were single (89.5% of cases), and 10.5% of patients were married. Consanguinity was found in 6 patients, or 31.6% of cases. No similar cases of amenorrhea were found among relatives of the patients (Table 1).

Table 1. Sociodemographic and anthropometric characteristics of patients with primary amenorrhea.

Variable		Frequency
Age	14 - 20 years	6 (31.6%)
	21 - 30 years	11 (58.0%)
	31 - 40 years	1 (5.2%)
	≥41 years	1 (5.2%)
Weight (kg)		53.6 ± 15.3
Height (cm)		155.8 ± 17.5
Body mass index (kg/m^2)		21.1 ± 4.8
Consanguinity	Yes	6 (31.6%)
	No	13 (68.4%)
Marital status	Married	2 (10.5%)
	Single	17 (89.5%)

In the evaluation of secondary sexual characteristics according to the Tanner classification, stage S1 was predominantly found in 35.3% of cases, followed by stages S2 and S3, each accounting for 29.4% of cases, for breast development; evaluation of pubic hair showed stage P2 to be more frequent, in 53.0% of patients, while stage P5 was found in 5.9% of patients (Figure 2).

Cytogenetic results showed that 9 patients (47.37%) had a normal karyotype (46,XX) and 10 (52.63%) had an abnormal karyotype.

The causes of primary amenorrhea identified were gonadal dysgenesis (57.8% of cases), Müllerian agenesis (37% of cases) and outflow tract anomalies (5.2% of cases) (Table 2).

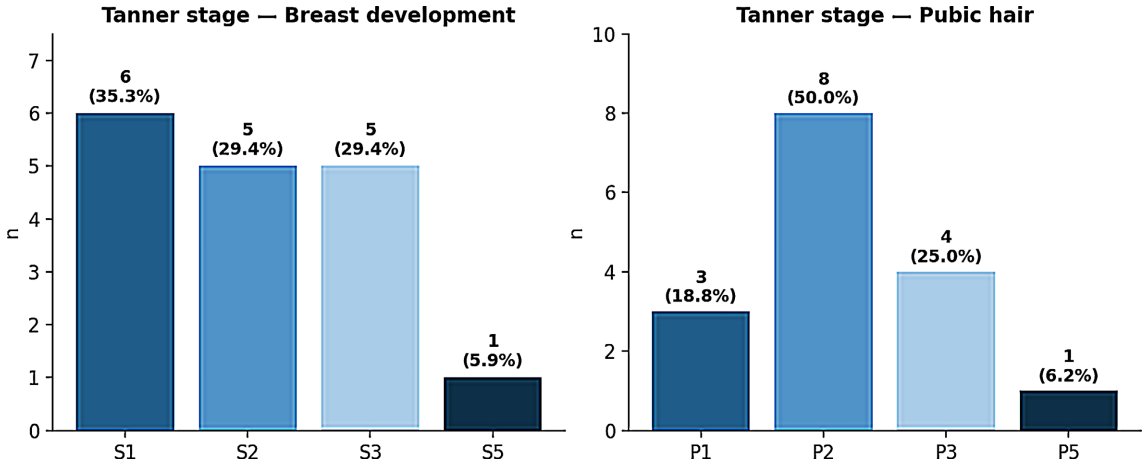

Figure 2. Evaluation of secondary sexual characteristics according to the Tanner classification ((a) Breast development; (b) Pubic hair).

Table 2. Frequency of causes and cytogenetic findings in primary amenorrhea.

Causes	n	Percentage (%)	Karyotype			
			46,XX	46,XY	45,X	Mosaic
Compartment I: Gonadal dysgenesis	11	57.8				
XX gonadal dysgenesis	1	5.2	1	0	0	0
Turner and variants	9	47.4	0	0	4	5*
Swyer syndrome	1	5.2	0	1	0	0
Compartment II: Müllerian anomaly						
Müllerian agenesis (MRKH)	7	37	7	0	0	0
Compartment III						
Outflow tract	1	5.2	1	0	0	0
Total	19	100				

*45,X/46,XX (n = 5), 46,Xdel(Xp)/45,X (n = 1).

Among the cases of gonadal dysgenesis, we identified Turner syndrome in 47.3% of cases. Swyer syndrome was diagnosed in one case on the basis of absent secondary sexual characteristics, a female morphotype on ultrasound (vulva present, partial vaginal aplasia, absent uterus and ovaries) and a low serum testosterone level of 0.010 ng/mL. One case with a normal 46,XX karyotype was classified as XX gonadal dysgenesis on the basis of sexual infantilism and a height of 170 cm. Anomalies related to Müllerian agenesis were observed in 7 cases (36.8%) of Mayer-Rokitansky-Küster-Hauser syndrome. The typical presentation, characterized by primary amenorrhea, well-developed secondary sexual characteristics, female external genitalia, an absent or rudimentary uterus and a 46,XX karyotype, was observed in three (3) patients; two (2) patients had uterine hypoplasia, and two patients were classified as MRKH in the absence of imaging, on the basis of primary amenorrhea, well-developed secondary sexual characteristics and a 46,XX karyotype. One case with hy-

pertrophy of the junctional zone between the endocervix and the ectocervix was classified as an outflow tract anomaly (Table 2, Figures 3-5).

We found that patients with a 46-chromosome karyotype (XX/XY) had normal height, with a mean of 169.0 ± 8.5 cm, whereas those with Turner syndrome or its variants had short stature, with a mean of 139.8 ± 8.4 cm. Patients in the Turner group were on average 29.3 cm shorter than those in the 46-chromosome group (95% CI: 20.5 - 38.0; $p < 0.001$) (Figure 6).

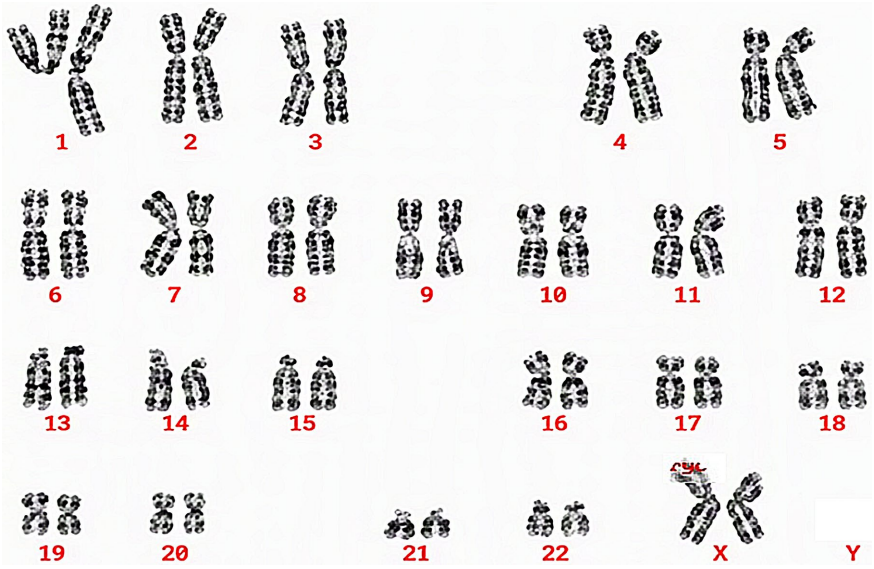

Figure 3. Karyotype of a patient with Mayer-Rokitansky-Küster-Hauser syndrome, RHG banding (400 - 550) (Cytogenetics Laboratory, Cheikh Anta Diop University, Dakar).

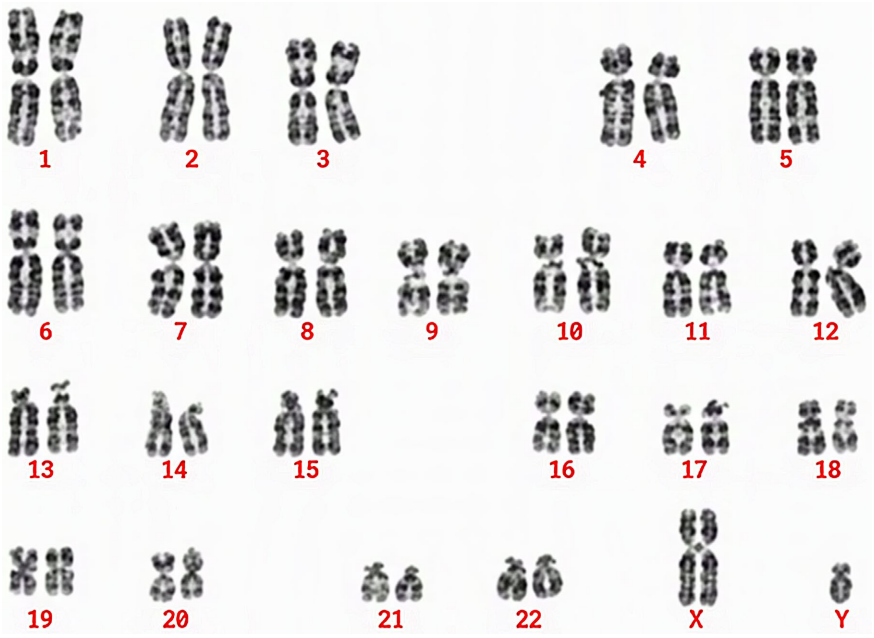

Figure 4. Karyotype of a patient with Swyer syndrome, 46,XY in a phenotypically female individual, RHG banding (400 - 550) (Cytogenetics Laboratory, Cheikh Anta Diop University, Dakar).

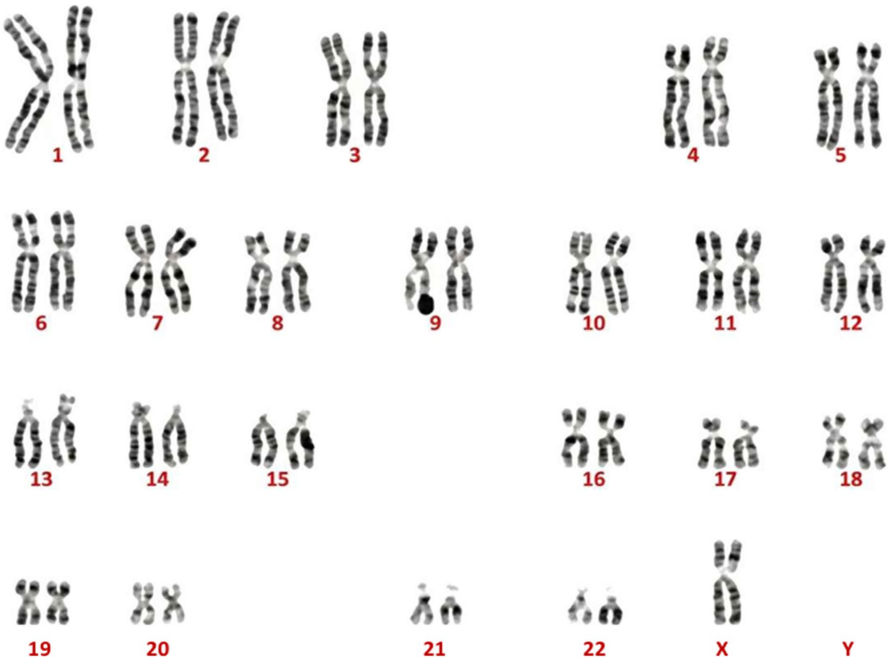

Figure 5. Karyotype of a patient with Turner syndrome, RHG (400 - 550) (Cytogenetics Laboratory, Cheikh Anta Diop University, Dakar).

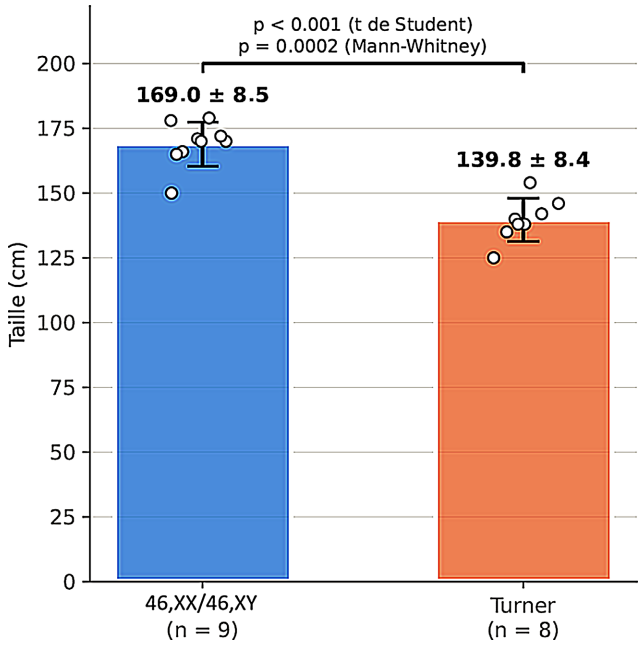

Figure 6. Comparison of mean height between groups.

4. Discussion

In our study, the mean age of the patients was higher than that reported in Pakistan in 2024, which was 17.93 ± 4.27 years (range: 13 - 37 years) [11]. However, our results are consistent with those reported in Thailand by Prasong T *et al.* in 2012 and in Morocco by Houari *et al.* in 2017, who reported mean ages of 22.4 ± 6.8 years and 22 years, respectively [12] [13].

The 21 - 30 age group was the most represented, with 58.0% of cases. In contrast, Ambareen Samad *et al.* in Pakistan in 2025 found a predominance of the 14 - 20 age group [14]. These results highlight a delay in diagnosis in our country.

Consanguinity was found in 31.6% of patients, compared with 16.67% in the study by Houari *et al.* in Morocco [13]. This difference may be explained by the small size of our study population.

Secondary sexual characteristics were poorly developed or absent in more than half of the cases. This result is consistent with that observed by Houari *et al.* in Morocco [13]. It reflects sexual infantilism due to early loss of ovarian function, which generally prevents puberty.

Most patients were single (90%); this result is consistent with those of Sumera Khan *et al.* and Ambareen Samad *et al.* in Pakistan in 2024 and 2025, who found a predominance of singles patients, at 92.7% and 87.5% of cases respectively [11] [14]. This result reflects the patients' wish to know the cause of their primary amenorrhea before any marital commitment.

Overall, 10 patients (52.6%) had an abnormal karyotype and 9 (47.4%) a normal karyotype. This result is similar to that of Nilgün *et al.* in Türkiye in 2013, who found a predominance of chromosomal abnormalities [15]. It contrasts, however, with the frequency of 22.38% reported by Elham in Iran in 2022 [16] and of 24.39% reported by Sumera Khan *et al.* in Pakistan in 2024 [11]. Moreover, approximately 40% of cases have been shown to be related to genetic abnormalities [17]. These variations are probably explained mainly by small sample sizes.

According to various published studies, MRKH syndrome now ranks as the most frequent cause of primary amenorrhea [11] [12] [18]. However, for some authors, Turner syndrome remains the most frequent chromosomal abnormality [19]. We also found Turner syndrome to be the most frequent cause. This is consistent with the Practice Committee of the American Society for Reproductive Medicine, which reports hypergonadotropic hypogonadism as the most frequent cause (40%) of primary amenorrhea [20]. These results underline the importance of cytogenetic analysis to look for chromosomal abnormalities in order to establish a definitive diagnosis.

Clinically, 46,XY pure gonadal dysgenesis presents with primary amenorrhea, sexual infantilism and normal stature, and is usually diagnosed in adolescence or early adulthood. This finding is consistent with the literature [21] [22].

A diagnosis of 46,XX pure gonadal dysgenesis was made in a 19-year-old patient on the basis of sexual infantilism, a height of 170 cm and a 46,XX karyotype, in the absence of hormonal and imaging work-up. Indeed, most authors agree that gonadal dysgenesis does not lead to breast development, owing to low circulating estradiol levels. Nevertheless, pubic and axillary hair may be normal because of normal adrenal androgen production. However, rare cases of 46,XX pure gonadal dysgenesis with incomplete breast development have been reported [8].

Our results are consistent with those of other studies of primary amenorrhea conducted in larger populations, suggesting that patients with Turner syndrome

have short stature compared with patients with other anomalies [19] [23] [24]. Indeed, short stature remains the most common manifestation of this syndrome, with adult patients being on average about 20 cm shorter than unaffected women of the same ethnic group [25].

5. Conclusion

Clinical signs can certainly point toward the probable cause of primary amenorrhea, but complementary investigations, particularly cytogenetics, make it possible to confirm the diagnosis; cytogenetic analysis is therefore a fundamental investigation in the evaluation of primary amenorrhea. Early diagnosis helps to relieve the psychological stress of the patient and her parents and to initiate appropriate treatment.

Author Contributions

All the authors contributed to the conduct of this study.

Conflicts of Interest

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

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