

Correlation between Karyotype, Puberty Stage and Volume of Reproductive Organs in Turner Syndrome: The First Transrectal Sonography Study in Indonesia

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Abstract

Background: Turner syndrome is characterized by the absence of part of or the entire X chromosome in a woman, resulting in short stature, gonadal dysgenesis, and congenital anomaly. Based on karyotype, Turner syndrome is categorized as classical (45XO) and mosaic. The aim of this study is to evaluate the correlation of the karyotype with the puberty stage, volume of the uterus, and ovary in Turner syndrome's adolescent with estrogen therapy. **Methods:** Analytic correlative cross-sectional study was done in Pediatric Endocrinology Outpatient Clinic at Cipto Mangunkusumo National Hospital since July to December 2018. Pubertal staging based on Tanner stage, uterine, and ovary volume were measured by transrectal sonography. **Results:** Of 21 study subjects, 8 were having classical karyotype and 13 were having mosaic karyotype in 12–21-year-old subjects. There was a significant correlation between karyotype and Tanner M stage (mammary stage) ($p = 0.035$). Breasts development in Turner syndrome with mosaic karyotype showed better development compared to classic karyotype. No significant correlation was found between karyotype and uterine and ovary volume in sonography transrectally. **Conclusion:** Karyotype correlates to mammary stage of Tanner but not in uterine and ovary volume in adolescents with Turner syndrome who underwent estrogen therapy.

Background

Turner syndrome, also known as monosomy X or Ullrich syndrome, is a syndrome or a group of symptoms in a woman which consists of short stature, gonadal dysgenesis, and major and minor congenital anomaly caused by an abnormality in all or parts of an X chromosome [1, 2]. This chromosomal abnormality happens randomly during the parent's oogenesis or spermatogenesis phase [1]. About 50% of all Turner syndrome populations are categorized as classical Turner syndrome (45 XO), 25% are having partial deletion of 1 X chromosome, and 20 % are categorized as mosaic Turner syndrome [2].

In an epidemiologic study, the prevalence of Turner syndrome was one out of 2,000–2,500 baby girl births [3]. Some characteristics of Turner syndrome, as stated by Henry Turner in 1938, were short stature, sexual infantile, cubitus valgus, and pterygium coli. Female with Turner syndrome, especially when having mosaic karyotype, might have various characteristics such as short stature, delayed puberty, ovary insufficiency, heart and kidney anomaly, hearing impairment, thyroid abnormality, metabolic syndrome, inflammatory bowel disease, and neurocognitive anomaly [4].

Classical Turner syndrome happens when, in parents, an error occurs during cellular division (*nondisjunction*) of eggs or sperm in meiosis phase. Classical Turner syndrome patient has only 1 X chromosome and 44 autosomes (45XO). Mosaic Turner syndrome happens when the error happens during the mitotic phase. As the result, half of the cells in the body consist of 46XX chromosomes, and the rest of the cells consist of 45XO chromosome. Both the classical Turner syndrome and mosaic Turner syndrome are not hereditary; they happen randomly. Meanwhile, if Turner syndrome happens because of partial deletion of the X chromosome, there is a possibility that the syndrome can be descended to the

next generation [1]. Nondisjunction mechanism in meiosis 1 or meiosis 2 phase might result in trisomy, tetrasomy, or monosomy in the cell (aneuploidy). Aneuploidy which is caused by nondisjunction during meiosis phase usually results in fetal abortion, fetal death, or other fatal abnormality; thus, most of the time, the baby cannot survive for a long time. Some examples of the commonly found aneuploidy are Down syndrome (trisomy 21), Turner syndrome (monosomy X), and Klinefelter syndrome (XXY) [1].

Phenotype characteristics of Turner syndrome are variable, but all of them show chromosomal abnormality because of partial or total loss of the second sex chromosome (X and/or Y chromosome). This phenotype shows that there is a haploinsufficiency of a specific gene located at the pseudoautosomal X chromosome. Haploinsufficiency is a pathological phenotype condition that happens because of the loss of one gene copy, leaving only one functional gene in a diploid organism [5]. A cohort study about the karyotype–phenotype relationship, clinical manifestations, metabolic disease, comorbidity, and mental health during the lifetime of 656 Turner syndrome patients showed that the patients with mosaic karyotype (45XO/46XX) were having lower comorbidity incidences compared to classical karyotype (45XO). This implied that karyotype might play an important role in comorbidity risk stratification in Turner syndrome [6].

In Turner syndrome screening guideline based on Endocrine Division of Indonesian Pediatric Society, karyotype examination must be done in girls with one or more findings, such as unexplainable short stature (height < 5th percentile), webbed neck, peripheral lymphedema, coarctation aorta, and delayed puberty or at least 2 findings such as abnormal nail growth, high arch palate, short 4th metacarpal, and strabismus [7, 8].

In females, 90% of the main estrogen (estradiol) is excreted by ovary and a small amount is produced from extra glandular conversion of testosterone and androstenedione. Estrogen level is very low before puberty; thus, a standard measurement before puberty in boys and girls is hard to be done, but still estradiol level remains higher in girls compared to boys [9].

Literature review regarding ovary growth in fetus with Turner syndrome showed that there were some varieties in Turner syndrome patients' ovary shape in childhood, including streak which contained fibrous tissue, and also gonad with normal shape and function [10]. Fetus with Turner syndrome showed a faster oocyte depletion compared to normal fetus. Almost all of the oocytes were depleted before birth or several months after birth. Oogonium in fetus with 46XX karyotype was seen the earliest at 18 weeks. At 20 weeks, ovary showed primordial follicle. Pre-antral follicle and antral follicle were seen on 26 weeks. On the contrary, oogonium in 45XO karyotype fetus was seen without follicle. There were some evidences that functional oocytes and follicles were found in Turner syndrome patients on birth. More follicles were found in the ovum of female adolescents and women with mosaic karyotype [11].

A standard reference for uterine and ovary volume had been established through a cross-sectional study which was done using transabdominal ultrasonography (USG). There were two groups in this study: one group consisted of 93 Turner syndrome patients starting from 12 days old to 17,85 years old and the other group consisted of 190 healthy, normal girls as control group. For all age groups, smaller uterine

compared to control group showed that uterine hypoplasia happened in Turner syndrome. The mean uterine length and uterine volume in patients with 45 XO karyotype were smaller compared to the variant karyotype. Ovary sonography has a prognostic value in predicting sexual development of girls with Turner syndrome. Karyotype and visualization of ovary were significantly correlated, and this was shown in the lowest percentage in Turner syndrome patients with 45 XO karyotype (34%) compared to other karyotype variants [10].

Methods

Subjects

Subjects were obtained from the Pediatric Endocrinology Polyclinic and Obstetric–Gynecology Endocrine Polyclinic at Cipto Mangunkusumo National Hospital. The subjects were the members of Turner Syndrome Society at Jakarta, Bogor, Depok, Tangerang, Bekasi, West Java, and Bandar Lampung from July to December 2018. Twenty-one subjects with complete data, who met the inclusion criteria (adolescents diagnosed with Turner syndrome, age range within 12–21 years old, and underwent estrogen hormone therapy for at least one month) and did not meet the exclusion criteria (had history of malignancy in adrenal glands, uterine, and ovarium, had chronic/terminal disease such as cyanotic congenital heart disease and tuberculosis in reproductive organs, or if the parents refused to participate) were included in this study. All subjects were female. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia.

Definition

Turner syndrome is defined as a syndrome or a group of symptoms in a woman which consists of short stature, gonadal dysgenesis, and major and minor congenital anomaly caused by an abnormality in all or parts of an X chromosome [1, 2]. Karyotype is the number and visual appearance of the chromosomes in the cell nuclei [1]. Puberty stage is the transition period between childhood and adulthood which is affected by various factors, marked by physical (secondary sex characteristics) and psychological changes that happen because of the sequential and regular change in endocrine activity [7]. Delayed puberty in female happens when secondary sex characteristics does not happen until 13 years old [7]. Puberty stage is classified based on Tanner scale and in this study was done by comparing secondary sex characteristics in patients with tables and pictures in Tanner scale [7]. Hormone therapy is estrogen hormone replacement therapy given to the Turner syndrome patients [7]. Uterine and ovarium transrectal USG is a radiologic imaging diagnostic examination done rectally by an experienced and trained obstetrics–gynecologist specialist, using Alpinion E-Cube 7 Diamond USG machine in this study [10, 12]. Uterine and left and right ovary volume were determined by measuring maximal longitudinal, anteroposterior, and transversal diameter (in centimeter): uterine volume formula (mL) = longitudinal diameter × transversal diameter × anteroposterior diameter × 0.5233 [10, 12].

Statistical Analysis

This research was a cross-sectional study with analytic correlative method to evaluate the correlation of karyotype to puberty stage and volume of the uterus and ovary in female adolescents with Turner syndrome on estrogen hormone therapy. Correlation between karyotype and puberty stage was evaluated using Spearman's correlation test. To determine the correlation between karyotype and uterine and left and right ovary volume, the Mann–Whitney test was done. Multivariate analysis using linear regression test to evaluate the correlation between karyotype, uterine size and volume, and left and right ovary volume based on hormone therapy duration was done. The data was analyzed using SPSS 23.0 version and considered as significant if p value <0.05.

Results

The subjects consisted of 13 mosaic karyotype and 8 classical karyotype. The characteristics of the subjects were described at Table 1.

Table 1. Turner Syndrome Characteristics

Characteristics	Classical (n=8)	Mosaic (n=13)
	(mean ± SD)	(mean ± SD)
Age (years)	15.9 (2.53)	18.2 (3.11)
Age when diagnosed (years)	11.3 (5.18)	12.3 (4.19)
Age of estrogen hormone therapy initiation (years)	14.0 (0.76)	14.3 (1.88)
Estrogen hormone therapy duration (years)		
Mother's age at conception (years)	2.1 (2.26)	3.5 (2.65)
Father's age at conception (years)	25.9 (4.39)	26.0 (3.85)
	30.5 (4.11)	28.2 (3.31)
Birth weight(gram)	2,720 (240)	2,750 (230)
Birth length (cm)	47.1 (1.46)	47.2 (1.64)

The mean age when diagnosed for classical karyotype group was 11,25 (SD = 5.18) years old while the mean age for mosaic karyotype group was 12,31 (SD = 4.19) years. The youngest age when diagnosed in this study is 3 weeks (with history of USG imaging abnormality at 20 weeks gestational age). For both karyotypes, the highest number of age when diagnosed was on the adolescence age group >12–18 years old, as written in Table 2.

Table 2. Age When Diagnosed with Turner Syndrome

	Karyotype	
	Classical (n=8)	Mosaic (n=13)
Mean age (years) (SD)	11.25 (5.18)	12.31 (4.19)
Range	0 – 15	5 - 17
Age group		
Infant (0-2 years)	1 (12.5%)	0 (0.0%)
Children (>2-12 years)	1 (12.5%)	5 (38.5%)
Adolescent (>12-18 years)	6 (75%)	8 (61.5%)

The karyotype distribution in this study consisted of 61% mosaic karyotype and 38% classical karyotype, as written in Table 3.

Table 3. Karyotype Distribution

Karyotype	n	Percentage	Total (%)
Classical			
45XO	8	38	38
Mosaic			
45XO/46XX	6	28	62
45XO/46Xi(X)(q10)	4	19	
46Xi(X)(q10)/46XX	1	5	
45XO/46XY	1	5	
45XO/46XY/47XYY	1	5	

In this study, mosaic karyotype showed better breasts development compared to classical karyotype when examined using Tanner puberty stage. The result of Spearman's correlation analysis showed a significant correlation between karyotype and Tanner mammae puberty stage ($p = 0.035$). Mosaic karyotype group showed better breasts growth and development compared to the classical karyotype as written in Table 4.

Table 4. Correlation between Karyotype and Puberty Stage.

Tanner puberty stage	Karyotype		P value ^a
	Classical (n=8)	Mosaic (n=13)	
Mammae stage			
1	1 (5%)	0	0.035
2	3 (14%)	1 (5%)	
3	3 (14%)	7 (33%)	
4	1 (5%)	5 (24%)	
5	0	0	
Pubic hair stage			
1	1 (5%)	0	0.396
2	3 (14%)	5 (24%)	
3	2 (10%)	3 (14%)	
4	2 (10%)	4 (19%)	
5	0	1 (5%)	

Note: ^a With Spearman's correlation test

In this study, no significant correlation was found between karyotype and uterine mean volume ($p = 0.426$) and right and left ovary volume ($p = 0.586$; $p = 0.663$) as written in Table 5.

Table 5. Correlation between Karyotype, Uterine Volume and Left and Right Ovary Volume.

	Karyotype		
	Classical (n=8)	Mosaic (n=13)	P value ^b
Uterine volume (mL):			
Mean (SD)	6.79 (6.43)	7.91 (6.64)	0.426
Median	5.14	5.30	
Range	0 ^c – 17.7	1.97 – 21.73	
Ovary volume dextra (mL):			
Mean (SD)	0.47 (0.87)	0.36 (0.41)	0.689
Median	0.21	0.24	
Range	0 ^c – 2.60	0 ^d – 1.28	
Ovary volume sinistra (mL):			
Mean (SD)	0.71 (1.15)	0.28 (0.32)	0.663
Median	0.22	0.15	
Range	0 ^c – 3.30	0 ^d - 1.16	

Note : ^bWith Mann-Whitney U test; ^cMullerian dysgenesis in 2 subjects; ^dBilateral gonadectomy history in 2 subjects with mosaic karyotype in Y chromosome.

To evaluate the correlation between karyotype, uterine size and volume, and right and left ovary volume in Turner syndrome based on estrogen hormone therapy duration, a linear regression test was done. The result of the linear regression showed no significant correlation ($P > 0.05$) between karyotype and uterine size, uterine volume, and right and left ovary volume, as mentioned at Figures 1, 2, 3, and 4

Figure 1. Correlation Between Karyotype and Uterine Size Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.

Figure 2. Correlation Between Karyotype and Uterine Volume Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.

Figure 3. Correlation Between Karyotype and Right Ovary Volume Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis

Figure 4. Correlation Between Karyotype and Left Ovary Volume Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.

Discussion

There were 21 subjects in this study, with mean age of 15,87 years old for classical Turner syndrome group (SD = 2,53) and 18,15 years old for mosaic Turner syndrome group (SD = 3,10). Turner syndrome diagnosis was made on various ages, and mostly the diagnosis was made during adolescence (age group >12–18 years old). Only 1 out of 21 cases (4,8%) was diagnosed at birth. Some possible USG imaging which might be seen during gestation suggestive of Turner syndrome diagnosis are increased nuchal translucency, cystic hygroma, and left heart obstruction anomaly (especially coarctation aorta) [4]. Age of diagnosis in this study was different from a study by Savendahl and Davenport which stated that Turner syndrome diagnosis was made at birth (15%), adolescence (26%), and adulthood (38%) [13]. Delay in diagnosis will have an impact on the intervention. As the result, the therapy will likely be delayed.

The mean father's/mother's age at conception for both karyotypes was below 35 years and there was no significant difference between classical and mosaic groups ($p > 0.05$). This finding matched the literature which mentioned that Turner syndrome prevalence was not affected by mother's and father's age at conception [1, 2]. There was no significant difference in the mean of birth weight and length between both karyotypes ($p > 0.05$). In this study, birth weight mean in classical karyotype was 2,720 gram (SD = 240) and in mosaic karyotype was 2.750 gram (SD = 230). In this research, birth length mean on classical karyotype and mosaic karyotype was 47,1 cm (SD = 1.46) and 47,2 cm (SD = 1.64), respectively. Delayed development characteristic in Turner syndrome happened since intrauterine phase and continued during childhood, followed by growth spurt failure that happened during puberty [4, 5, 7].

Karyotype distribution in this research consisted of 62% mosaic karyotype and 38% classical karyotype. Previous study prevalence stated that about 50% of Turner syndrome consisted of 45 XO karyotype, 25% were having partial X chromosome deletion, and 20% were having mosaic karyotype with variety, especially 45 XO/46XX, and a small number of Turner syndrome patients carried XY gene [2, 11].

In this research, the mean age of the start of estrogen hormone therapy was 14,3 (SD = 1,9) years old in mosaic group and 14,0 (SD = 0.8) in classical group. There was a difference compared to the guideline which was mentioned earlier. Since most of the diagnosis in this study was made on puberty, the estrogen hormone therapy could not be started earlier. Based on the recommendation from Cincinnati International Turner Syndrome Meeting on 2016, fertility therapy had to be offered since young age.

Oocytes preservation can be done after the patient's age reaches 12 years. Mosaic Turner syndrome patients at a young age with persistent ovary function can be counseled to preserve their fertility by doing oocyte cryopreservation [14]. In this study, every subject went through further examination with obstetrics–gynecologist endocrine consultant to examine whether there was a possibility of doing fertility preservation.

There are some differences in the protocols of starting estrogen hormone therapy in several countries. In the Royal Children's Hospital in Australia, estrogen hormone therapy is started at 13–14 years old if there are no spontaneous signs of puberty after growth hormone therapy has been given before. The purpose of this therapy is for the secondary sexual characteristics development to catch up to the patient's age, synergistically with the growth hormone effect. Natural estradiol on low dose is increased step by step for 2,5–3 years, by adding cyclic progesterone at the end of period. Estrogen hormone therapy will be delayed if possible until 13–14 years to allow growth catchup with growth hormone therapy [15]. At Sophia Children's Hospital in Netherlands, puberty induction protocol is started at 12 years old, 2 years after normal puberty age in Netherland children. Induction is started by giving natural estrogen 17 β -estradiol at a very low dose for 2 years, and the dose is slowly increased. Natural estrogen is chosen for this therapy, since natural estrogen does not have any effect on coagulation factor, lipid profile, and blood pressure compared to synthetic estrogen [16].

Significant correlation was found between karyotype and Tanner puberty stage M (*mammae*) ($p = 0.035$). Mosaic karyotype group showed better breasts growth and development compared to the classical karyotype group. This finding matched a study done by Wu and Li on 124 classical and mosaic Turner syndrome patients who came to pediatric polyclinic at the Capital Institute of Beijing. Secondary sexual characteristic growths were found to be better in mosaic karyotype [17]. Estrogen hormone plays an important role in breasts development. Low dose of estrogen hormone therapy, when given at appropriate age for children with Turner syndrome, will be helpful to make the breasts grow normally although the normal growth of breasts will be reached at the age 2 years later compared to normal girls [16]. In this study, pubic hair puberty stage (P stage) did not have a significant difference between classical and mosaic karyotypes. This result was similar with a study done by Bannink et al. at 56 children with Turner syndrome prospectively. Pubic hair growth in Turner syndrome patient was the same with normal women, although it was a bit late. In Turner syndrome, androgen hormone disturbance only happened in the ovary while androgen hormone remains normal at the adrenal gland; thus, the adrenarche/pubarche in Turner syndrome is the same with normal women [16].

No significant correlation was found between karyotype and mean uterine ($p = 0.426$) and right and left ovary ($p = 0.586$; $p = 0.663$) volumes. This result was the same with a cross-sectional study done by Elsedfy et al. at Kairo on 40 Turner syndrome patients aged 9,71–26,32 years old using transabdominal USG. The result was the size of uterine was not affected by karyotype ($p = 0.40$). Elsedfy et al. also analyzed the correlation between uterine size and the type of therapy, and no significant correlation was found [18]. This result did not match a cross-sectional study done by Haber and Ranke, using transabdominal USG in 93 Turner syndrome patients aged 12 days until 17,85 years with 190 normal,

healthy girls as control group, which stated that there was a significant correlation between karyotype and size and volume of uterus in Turner syndrome patients. The mean of uterine length and volume in patients with 45XO karyotype was smaller than the variant karyotype [10]. A research done by Liang et al. in 51 children with Turner syndrome compared to 20 healthy girls also stated that the sizes of uterus in children with 45XO karyotype in Turner syndrome were smaller compared to other types besides 45XO ($p < 0.05$) [19]. A prospective USG study for 3 years in the Royal Children's Hospital in Australia by Donnel et al. on 18 girls with Turner syndrome who had got estrogen and growth hormone therapy during infancy and adolescent years showed that normal uterine size can be reached when the exact amount of estrogen in the body can be maintained during puberty [15].

This was the first study in the world which was done using transrectal USG to examine the development of uterus and ovary in adolescents with Turner syndrome while evaluating its correlation with karyotype. Several studies which had been done previously only used transabdominal USG. In this study, the USG examination was done by an experienced obstetrics–gynecology endocrine fertility consultant. USG is a widely available diagnostic tool which is used to examine internal genital condition including the uterus, ovary, and adnexa. Routes of examination in USG include transvaginal, transabdominal, and transrectal. Transvaginal USG has several benefits compared to transabdominal, such as a clearer image production, the target organ can be located at focal distance, and the probe can be put within the reach of target organ area. However, there are several limitations too when using transvaginal USG, such as it cannot be done when there is vaginal agenesis, it cannot be done on women with intact hymen (on virgins), and it also cannot be done when there is a possibility of infection. Transrectal USG is as effective as transvaginal USG to obtain internal genitalia structure, with its probe still located within the reach of target organ area [12, 20].

In this study, there were two subjects with classical karyotype, whose uterus and ovaries were hard to identify when transrectal USG was done. Mullerian dysgenesis was suspected in these patients. This condition was similar with the finding in a study done by Haber and Ranke, which stated that only 41 (44%) out of 93 Turner syndrome patients' ovaries can be visualized. In Turner syndrome patients, the shapes of the ovary vary a lot, including streak which contains fibrous tissue and gonad with normal shape and function [10]. In this study, bilateral gonadectomy was done at two mosaic karyotype subjects with Y chromosome as a preventive measure for malignancy. Although gonadectomy had been done, we did not exclude the subjects in the analysis to see more of the ovary shape variations in Turner syndrome patients. Gonadoblastoma might happen during infancy. Thus, it was advised for a Turner syndrome patient who carries Y chromosome material at FISH test to do prophylactic gonadectomy [5, 7]. A similar situation was found in a study done by Donnel et al., which stated that 3 out of 18 patients with Turner syndrome with Y chromosome had bilateral gonadectomy [15]. A linear regression analysis done by examining the role of karyotype on the shape and volume of the uterine and the right and left ovary volume on the patients who underwent estrogen hormone therapy on certain duration showed no significant correlation ($p > 0.05$). This finding is similar with the result of the research done by Elsedfy et al. in 40 patients with Turner syndrome, which stated that karyotype did not affect the size of the uterus ($p = 0.40$) [18].

The strength of this study is that this is the first study in Indonesia which determines the correlation between karyotype and puberty stage and uterine volume and ovary using transrectal USG in adolescents with Turner syndrome.

The limitation of this study is the difficulty in collecting the subjects, since Turner syndrome is a rare disease that only happens in women. Several parents of the children with Turner syndrome did not allow their children to join this study because they feel ashamed if other people find out about their children's disease. Since July to December 2018, only 21 patients could join this study, recruited from many areas including Jakarta, Bogor, Depok, Tangerang, Bekasi, West Jawa, and Lampung.

Conclusions

1. In adolescents with Turner syndrome who underwent estrogen hormone therapy, a significant correlation was found between karyotype and Tanner mammae puberty stage. Mosaic type showed better mammae growth and development based on Tanner stage compared to classical type.
2. There was no significant correlation between karyotype and uterine volume and right and left ovary volume in Turner syndrome patients with estrogen hormone therapy duration.

List Of Abbreviations

USG : Ultra sonography

GH : Growth hormone

M stage : Mammae stage

Declarations

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Availability of data and material

The data is available in the corresponding author upon request.

Authors' contribution

NN and ABP designed the study, created the content, and did the literature research. NN, HG and KS did the data collection, data analysis and statistical analysis. NN was the major contributor in writing the whole manuscript. All authors have read and approved of the final manuscript.

Ethics approval and consent to participate

Inform assent and inform consent regarding the purpose of the study, the procedures, and the possible uncomfortableness which might be felt by the subject upon examination were explained verbally to the subject and the parents until they understand thoroughly before any procedure was done. Afterwards, the subject and the parents needed to sign the written inform consent form, stating their agreement if they agree to participate in this study. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia, July 30, 2018 and had been conformed to the ethical guidelines of the Declaration of Helsinki. Patients were anonymized and de-identified before analysis.

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Consent for publication

Not applicable.

Competing interests

The authors declare that there was no conflict of interest in this study.

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Figures

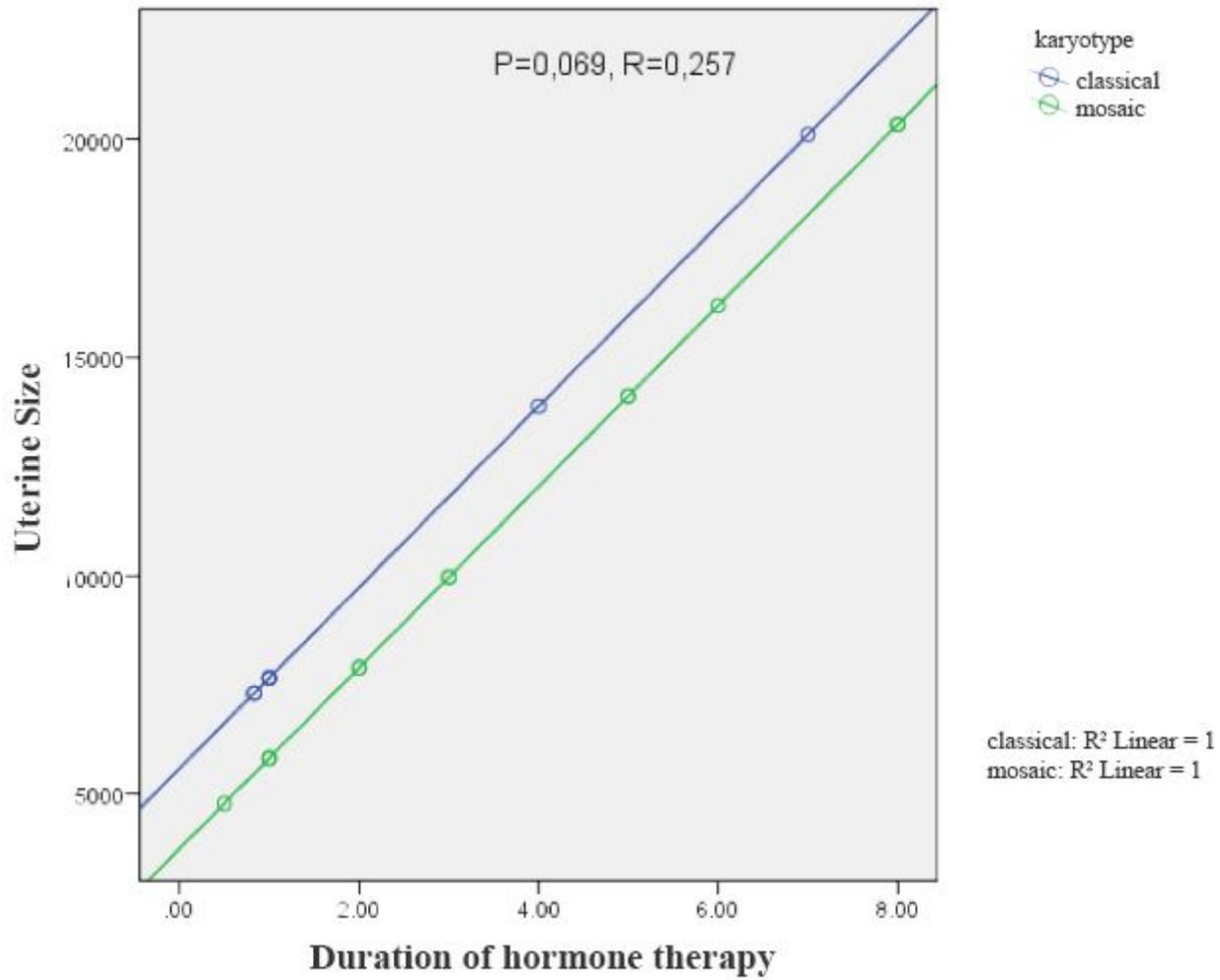


Figure 1

Correlation Between Karyotype and Uterine Size Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.

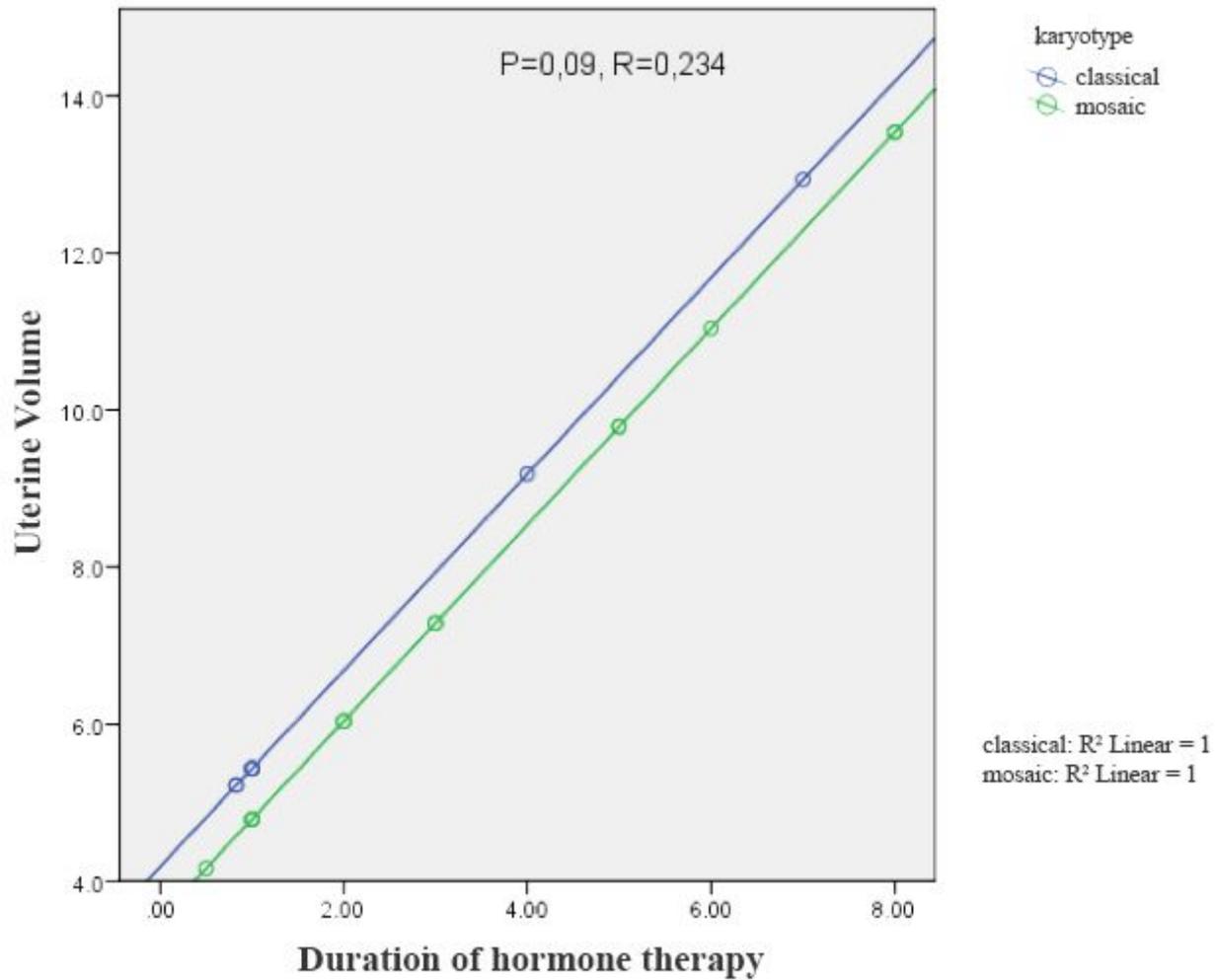


Figure 2

Correlation Between Karyotype and Uterine Volume Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.

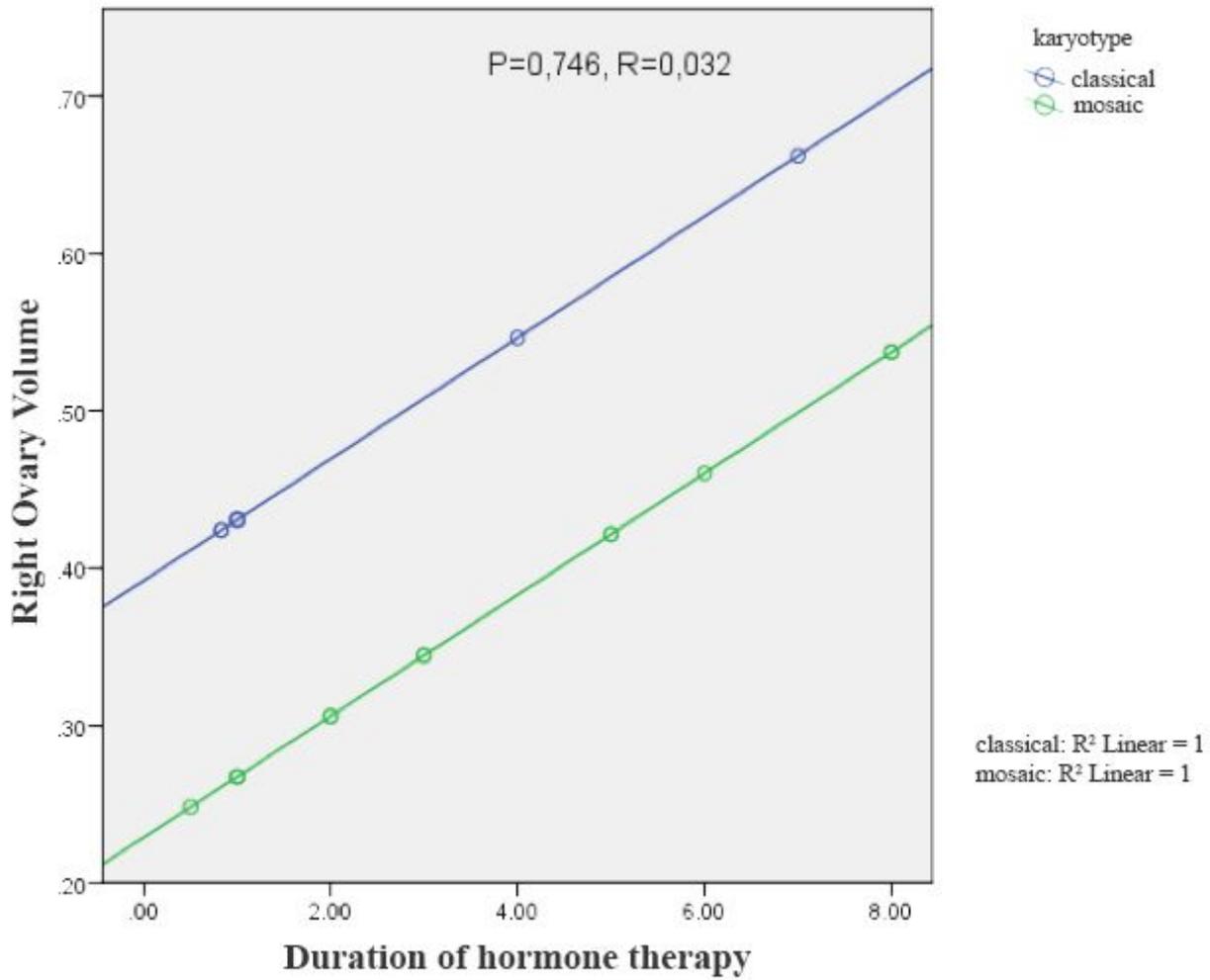


Figure 3

Correlation Between Karyotype and Right Ovary Volume Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.

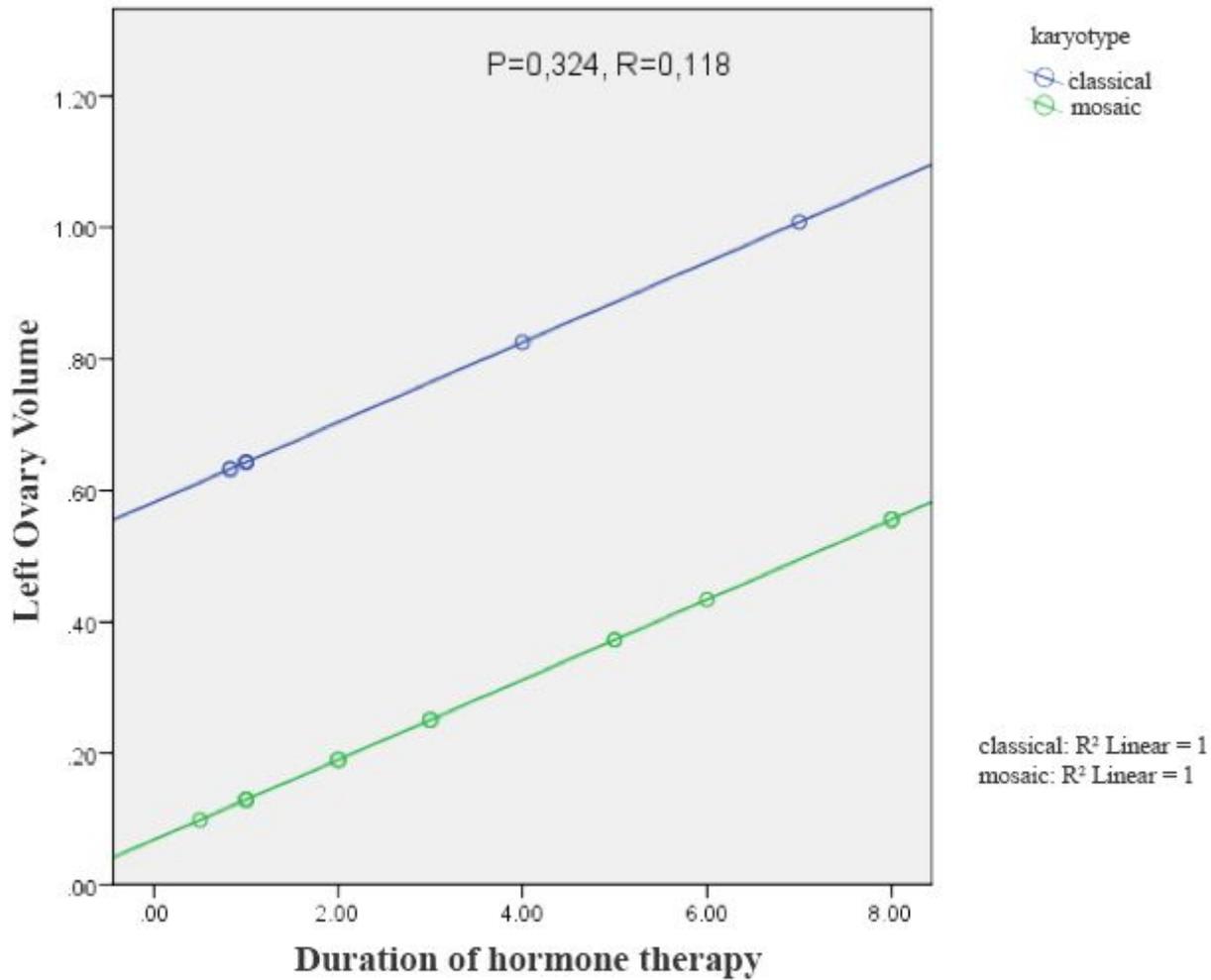


Figure 4

Correlation Between Karyotype and Left Ovary Volume Based on Estrogen Hormone Therapy Duration. Linear Regression Analysis.