

The Prevalence of Penile Abnormalities in Erzurum, Turkey

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ABSTRACT

Epidemiologic studies have suggested that the incidence of congenital penile anomalies, particularly hypospadias, is increasing in the last three decades. In this study we aimed to assess the prevalence of congenital penile anomalies (CPA). Risk factors, which were thought to be related, were examined in male children attending school and nursery in the Northeast of Turkey. A total of 2040 male students from 14 nurseries and 18 primary schools in the Erzurum city urban Center/ Turkey participated in the study. All children were examined by one single expert doctor, a pediatric surgeon, in a room which was previously isolated by the school and at a suitable temperature. The total penile abnormalities, penile torsion and hypospadias prevalances were found to be 7.3%, 6.52% and 0.78%ii, respectively. The frequency of genitoscrotum abnormalities in families (father and siblings) was found to be 4.3% for hypospadias. The degree of the penile torsion was at the most 45 with 32% and 90 with 25%. The least was 70 and 120 degrees with 0.78%. The effects of environmental agents on the development of congenital abnormalities have not been researched in our country. Publications, which indicate an increase in CPA incidences in various geographical regions over a short period of 30 years does not make it possible to render this situation by way of genetic transfer. On the other hand, contrary to some publications, our current study shows a high number of CPA in other family members form the same family, nevertheless, this situation cannot be explained with genetic transfer as it does not contain statistical meaning. However, an explanation with environmental contamination is possible.

For us to find CPA incidences in our study parallel to the highest value in the world in general puts forth that the use of environmental agents used in our country and region and its widespread should be put under control and that further studies should be carried out.

Keywords: Children, hypospadias, penile abnormalities

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INTRODUCTION

Common types of Congenital penile anomalies (CPA) in children are; Hypospadias, Penile chordee, Penile curvature, Penile torsion, Epispadias, Micropenis, Hidden penis, Ambiguous genitalia, Apenia and Unspecified genital or penile anomalies.

In addition to the variation of frequency depending on the different race and geographical regions in the world in general, the incidence rate in 2005 in the United States of America (USA) weighted at 7.8/1000 newborns. The weighted incidence increased from 7.0/1000 newborns from 1988 –1991 to 8.3/1000 from 1997–2000 (1). Although there are no conclusive data in Turkey regarding CPA incidences, there are publications indicating that hypospadias exists in 1.29–2.60/1000 boys.

The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds (2, 3). At this time of the external genitale development it is widely opened to affects of the maternal drug use and environmentally chemical disruptors. Epidemiologic studies have suggested that the incidence of CPA, particularly hypospadias, is increasing. There is a worldwide increase in incidences in the last three decades. The increasing incidence over the past 30 years of male reproductive tract abnormalities co-occurring with the increasing production and use of synthetic chemicals has raised concerns that environmental factors with antiandrogenic activity may play a role in the aetiology of these problems [hypospadias, undescended testes, decreasing sperm count] (2, 4, 5). The only treatment of hypospadias and other CPA is surgical repair of the anatomical defect, there is no consensus on the surgical repair technique however. There are also too many surgical options described in publications due to the lack of knowledge about the aetiology.

In this study, we aimed to assess the prevalence of congenital penile anomalies. Risk factors, which were thought to be related, were examined in male children attending school and nursery in the Northeast of Turkey.

MATERIALS AND METHODS

Study site

A cross-sectional epidemiological study was designed in central Erzurum Province, Eastern Turkey. According to the Regional Directorate of Education, the number of primary school students in the Erzurum urban city center was 30603.

Sampling

The total size of the sample was calculated by using the formula of Kish and Leslie ($s = Z*Z(P(1-P))/(D*D)$) by using the software of Epi Info version 3.4.3 (Kish L Survey Sampling. New York. John Wiley and Sons Inc, 1965). The total number of subjects was determined as 2238 ($d = 0.07, p = 0.3, \alpha = 0.05$, with 10% additional subjects).

The distribution of the total sample size within the school was calculated according to the number of students in each school.

Subjects and data collection

Demographic information, simple medical data's, information towards the reasons of abnormalities in question and a questionnaire towards obtaining the parent's consent was given to the children to take to their parents.

All children participating in the study were examined by one single expert doctor, a pediatric surgeon, in a room which was previously isolated by the school and at a suitable temperature. Firstly, the lengths of the penis and testicular volumes were recorded.

Following this, the groin and scrotum regions were examined in standing, lying and kneeling positions. The length of the penis was examined in an elongated position with the help of a ruler placed on the ramus pubise and in uncircumcised children, the length between the ramus pubis and glans penis was measured and recorded with the preputium pulled back. The testicular volume was however determined through using a Prader's Orchidometer made-up of plastic testicals of different dimensions.

Physical examinations in the standing and lying positions were carried out. Hypospadias was described as being more proximal than where the urethral meatus should be and ventral opening. As for the penile torsion, those above 45° were accepted as pathological.

Ethical issues

All of the subjects were informed about the nature and aim of the study. Subjects who accepted to participate provided written informed consents. An authorization was provided by the Regional Directorate of Education of Erzurum Province. The study was approved by the ethics committee of the university hospital. The school administration and teachers were informed about the study following the consent of the governorship and ethics committee. Information about the pathological cases was given to the school administration, teachers and families, thereafter, treatment for these children were provided.

Statistical analysis

Data was expressed in numbers, percentages, mean and standard deviation (SD). All questionnaires were checked and those incomplete were excluded. The data was entered to SPSS 18.0 (SPSS, Inc, Chicago, IL, USA). The penile abnormalities and age, the number of

siblings, which child in line they were, birth term, birthweight, intake of breast milk, consanguineous marriage, mothers menstruation age, pregnancy age, mothers occupational status, mothers education, fathers education and the family's monthly income was analysed using the Chi-squared test and the penile torsion and the left and right testicular volume of elongated penis length with hypospadias in independent groups were analysed using the *t*-test, *p*-value under 0.05 was considered to be significant.

RESULTS

A total of 2040 male students from 14 nurseries and 18 primary schools in the Erzurum urban Center participated in the study. The rate of obtained sample volume was found to be 91.2% and the average age was 8.29 ± 2.22 (3–12). The category distribution of children is given in Table 1.

Table 1: Grade distribution of study population.

School grade	Frequency	
	n	%
Pre-school	384	18.82
1 st Grade	379	18.58
2 nd Grade	378	18.53
3 rd Grade	338	16.57
4 th Grade	295	14.46
5 th Grade	266	13.04
TOTAL	2040	100.00

The total penile abnormalities, penile torsion and hypospadias prevalence's were found to be 7.3%, 6.52% and 0.78% respectively, given in (Table 2 and Fig. 1). When some of the risk factors, which are thought to be caused by penile abnormalities, were analysed, there was a difference in the borders, in terms of penile abnormality prevalence age groups ($p = 0.05$).

Table. 2: 2013 Annual prevalence of penile abnormalities in Erzurum (study population is 2040)

Penile abnormalities	Number of cases (n)	Percentile (n/2040)
Penile torsion	133	6.5
Hypospadias	16	0.78
TOTAL	149	7.30

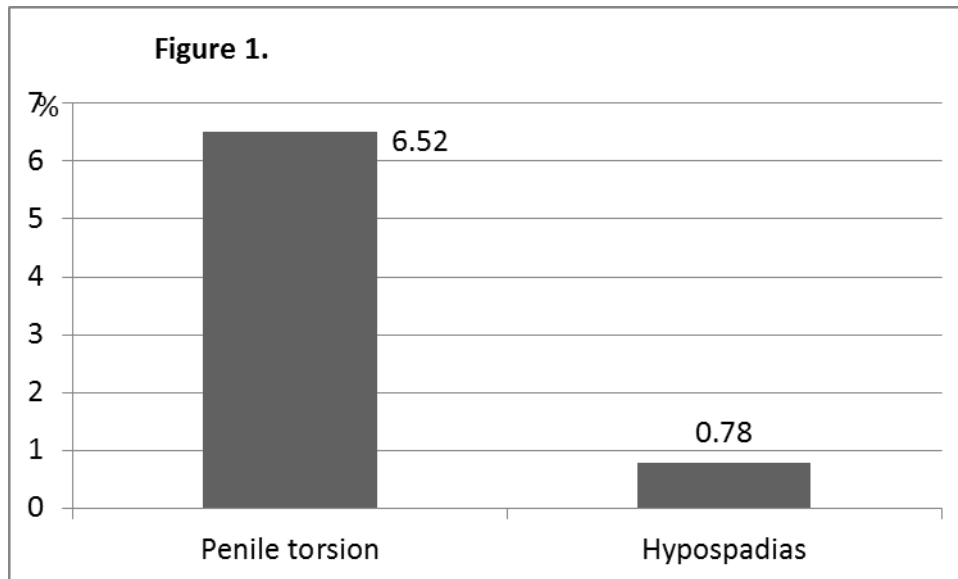


Fig: 1. The prevalence of penile abnormalities in Erzurum, 2013.

This difference was found to originate from the 4–9 age group after further analysis that were carried out ($p = 0.008$). It was also found that there was no statistics with the number of siblings, which child in line they were, birth term, birthweight, intake of breast milk, consanguineous marriage, mothers menstruation age, pregnancy age, mothers occupational status, mothers education, fathers education and the family's monthly income [$p > 0.05$], (Table 3).

Table. 3: Assessment of risk factors with penile abnormalities

		Penile anomaly				<i>p</i>
		Negative		Positive		
		Number of cases (n)	Percentile (n/2040)	Number of cases (n)	Percentile (n/2040)	
Age	3	81	97.59	2	2.41	0.05
	4	48	92.31	4	7.69	
	5	85	90.43	9	9.57	
	6	141	91.56	13	8.44	
	7	262	89.12	32	10.88	
	8	324	91.78	29	8.22	
	9	357	92.49	29	7.51	
	10	262	96.32	10	3.68	
	11	234	94.74	13	5.26	
	12	97	92.38	8	7.62	
	Number of Siblings	0–1	176	93.62	12	
2		627	92.89	48	7.11	
3		541	93.76	36	6.24	
4		272	91.89	24	8.11	
Birth order rank of the children	1	646	91.5	60	8.5	n.s
	2	589	94.24	36	5.76	
	3	323	92.82	25	7.18	
	4	162	91.01	16	8.99	
	5	57	90.48	6	9.52	
	6 ≤	81	94.19	5	5.81	
Gestational Age	Term (40 weeks)	1595	92.2	135	7.8	n.s
	Post-term	115	95.83	5	4.17	

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	Preterm (36–40 weeks)	97	95.1	5	4.9	
	Preterm (Before 36 weeks)	32	91.43	3	8.57	
Birthweight	< 2500gr	323	91.24	31	8.76	n.s
	2500–4500gr	1371	92.57	110	7.43	
	> 4500 gr	153	95.03	8	4.97	
Breast feeding	No	98	93.33	7	6.67	n.s
	< 4 months	372	91.4	35	8.6	
	> 4 months	1392	92.86	107	7.14	
First menstrual age of mother	< 9 year	30	96.77	1	3.23	n.s
	9–15 year	1242	92.62	99	7.38	
	> 15 year	297	93.4	21	6.6	
Consanguineous marriage	Yes	286	91.67	26	8.33	n.s
	No	1586	92.86	122	7.14	
Pregnancy age of mother	15–19	136	91.89	12	8.11	n.s
	20–24	580	92.21	49	7.79	
	25–29	562	94.14	35	5.86	
	30–34	325	93.66	22	6.34	
	35–39	152	91.02	15	8.98	
	> 40	34	91.89	3	8.11	
Mother's work status	Yes	233	93.20	17	6.8	n.s
	No	1653	92.61	132	7.39	
Mother's work status	Yes	233	93.20	17	6.8	n.s
	No	1653	92.61	132	7.39	
Mother's education	Illiterate	202	91.40	19	8.6	n.s
	Primary School	1022	92.66	81	7.34	
	Secondary School	169	92.35	14	7.65	
	High School	254	93.38	18	6.62	
	Graduate	232	93.93	15	6.07	
Father's education	Illiterate	28	93.33	2	6.67	n.s
	Primary School	458	91.42	43	8.58	
	Secondary School	350	93.33	25	6.67	
	High School	561	92.73	44	7.27	
	Graduate	483	93.79	32	6.21	
Monthly family income	< 527 TL	450	91.65	41	8.35	n.s
	527–1054 TL	695	92.05	60	7.95	
	> 1054 TL	720	94.24	44	5.76	

The frequency of genitoscrotum abnormalities in families (father and siblings) was found to be 4.3% for hypospadias. Penile torsion was not found. The 50% of the Hypospadias mealar's was granüler and 41.7% was coronal located. The 56% of the penile torsion was on the left side. The degree of the penile torsion was at the most 45 with 32% and 90 with 25%. The least was 70 and 120 degrees with 0.78% (Table 4).

Table 4. Penile abnormality properties

		Number of cases (n)	Percentile (n/total)
Localization of the urethral meatus	Glanuler	6	50.00
	Coronal	5	41.67
	Subcoronal	1	8.33
	TOTAL	12	100
Direction of penile torsion	Counter clockwise	58	43.94
	Clockwise	74	56.06
	TOTAL	132	100
Rotation degree	45 ⁰	41	32.03
	60 ⁰	25	19.53
	70 ⁰	1	0.78
	75 ⁰	21	16.41
	80 ⁰	5	3.91
	90 ⁰	32	25.00
	110 ⁰	2	1.56
	120 ⁰	1	0.78
TOTAL		128	100

The left and right testicular average volume was found to be less than those without penile torsion. For right testical $2.5 \pm 0.8 \text{ mL}^3$ and $2.8 \pm 1.2 \text{ mL}^3$ ($p = 0.02$); $2.5 \pm 0.8 \text{ mL}^3$ and $2.8 \pm 1.3 \text{ mL}^3$ ($p = 0.01$) can be given for the left testical, respectively. Statistically, no difference was found between both sides in terms of average testicular volumes in those with or without hypospadias ($p > 0.05$). The average elongated penis length for those with and without penile torsion and hypospadias were found to be statically familiar ($p > 0.05$, Table 5).

Table. 5: Penile length and testicular volume statistics comparison table

		Penile length (cm)			Right testicular volume (mL)			Left testicular volume (mL)		
		Mean	SD	<i>p</i>	Mean	SD	<i>p</i>	Mean	SD	<i>p</i>
Penile torsion	Yes (n = 1907)	6.61	1.07	0.2	2.78	1.24	0.02	2.79	1.25	0.01
	No (n = 133)	6.72	0.86		2.53	0.83		2.51	0.83	
Hypospadias	Yes (n = 2024)	6.62	1.06	0.2	2.77	1.23	0.3	2.77	1.23	0.3
	No (n = 16)	6.31	0.8		2.39	0.55		2.39	0.55	

The six samples with penile torsion kept their problems even if they were circumcised. The 50% (8/16) of families noticed the hypospadias abnormalities. It was determined that five of these were noticed at the age of under one year, one at the age of two and two at the age of four.

DISCUSSION

Congenital penile anomalies is known to be seen throughout the world at various frequencies at different geographical regions and races. There is no comprehensive study in Turkey, which puts forward the true prevalence of CPA. Our study is the first wide scope epidemiologic field study to be carried out in this area. The most wide scope study in the past was by Yücesan *et al* in 1993, which was a congenital abnormality combing of school children. However, the results of this study did not include our region.

Until 1970's the postulated reported prevalence of hypospadias was 0.3–0.8% of male births (6). Since the 1970's, multiple reports from several countries have shown an increase in the prevalence of hypospadias (4, 6, 7). Lund *et al* in Denmark from 1977 to 2005, identified the prevalence of hypospadias increased from 0.24% in 1977 to 0.52% in

2005, corresponding with an annual increase in prevalence of 2.40% (7). Nelson *et al* reported the weighted incidence increased from 7.0/1000 newborns in 1988 to 1991 to 8.3/1000 in 1997 in the USA (1). On the contrary to all publications regarding the general increase of hypospadias and CPA in the world, Fisch *et al* reported that retrospectively the total prevalence of hypospadias in New York State from 1992 to 2005, found no change (8). Prevalence percentage of hypospadias in prospective population-based studies or systematic surveys of hospital records shows geographic differences (9). A review of the literature revealed the incidence of hypospadias has ranged from 0.8 to 8.2 per 1000 live male births (10). Yucesan *et al* reported the prevalence of congenital abnormalities in 19750 Turkish school children and they found hypospadias was present in 0.66/1000 school-aged children (11). In another study, Yesilipek *et al* (12) from Turkey have reported prevalence's of this abnormality to be 2.06/1000–2.60/1000 neonates in Turkey. In the present study, the prevalence of hypospadias was found in about 7.8 per 1000 students. If we compare our results with Yucesan *et al* and Yesilipek *et al* reports, there is an increase in the last three decades in Turkey. If we compare our results with those from all over the world, our results are one of the highest reported to date. This variation may represents geographic and racial differences (13).

In our study, patients diagnosed with CPA were especially from the 4–9 age groups and this was found to be statistically significant. The reoccurrence of decline of CPA prevalence in children under the age of four leaves it impossible to explain this with genetic transmission. On the other hand, it gives rise to thought from a study carried out 4–9 years ago throughout the Erzurum urban city on children in groups found with high prevalence, to be effective in children of mothers who fell pregnant only at that period with the effect of a contaminating agent, which was temporarily effective.

It is indicated that first degree relatives of individuals with Hypospadias are 10% likely to also be born with hypospadias (14–16). While in a study that Manson *et al* carried out could not find a significance difference between single and multiple births, they found that the frequency of a CPA risk in the first child was significantly higher in comparison to the families other children (14). Bauer *et al* indicated that in at least one person from the family of 4.2% of hypospadias patients have been stricken by the same illness (17). Our findings have put forward that only first degree relatives of 4.3% patients have CPA, which is a form of result that is supportive of those of Bauer *et al* (17). However, it has been determined that none of the first degree relatives of those with penile torsion had penile torsion and were not treated for this purpose. Moreover, the number of siblings in the household and in which line these children were among the siblings was queried.

A correlation could not be found between the presence of CPA and statistical number of siblings and in which line the children were to there siblings.

Consanguineous marriage

The rate of consanguineous marriages seen amongst the parents of children with congenital abnormalities was 8.9% while this figure was 8.2% amongst the parents of the rest of the children (18).

In consanguineous families and small case series have identified allelic variants in genes controlling androgen action and metabolism that cause hypospadias, but the relevance of these findings to the general population is unknown. Concern has also focussed on whether exposure to endocrine disrupting chemicals (EDC) with antiandrogenic activity is the cause of this increase (14).

Aschim *et al* found a borderline significant (48%) increased risk of hypospadias when the parents were second cousins or closer, and declared that hypospadias was not uncommon

in children of consanguineous parents (19). Aschim *et al* determined that there was a high hypospadias risk found which was at the border of a significant 48% probability in the parents, second degree cousins and much closer relative of hypospadias patients (19).

Friedman *et al* reported that, in instances where they found multiple cases of hypospadias in close relatives or in the family, they usually found parent consanguinity (20).

As for us, we determined in our study that there was a consanguineous marriage in 8.3% of CPA patients. Consanguineous marriage is widespread in Erzurum urban city (18), where the study was carried out. Nevertheless, the low existence of CPA puts forth environmental pollution/contamination agents of the hypospadias aethiology to be more effective than genetic transfer.

Term of birth and birthweight

Carmichael *et al* stated that there was a serious increase in the risk of hypospadias in births before the gestational week (21). In the study of Gatti JM *et al* it was reported that the cause of SGA and patients accepted as neonatal Intensive Care unit (NICU) was seen to have hypospadias 10 times more than the general population. However, we did not find any statistical relevance between CPA gestational week and weight birth as Neto *et al* (22) and Czeizel *et al* (23) had stated. This case presumably could be due to 92% of the participants of our study being mature and born after the 36th gestation week and 83% being born over 2500 gr.

Breast milk intake

It was determined that 68% of those in our study with CPA had taken at least four months of breast milk. However, a significant association between breast milk, nutrition and CPA was not found.

Mothers first menstrual age

In our current study a research towards the mothers first menstrual age and the presence of CPA was carried out. There appeared no significance.

Pregnancy age

Some publications stress the existing relation between advanced mothers age and advancing prevalence of CPA (24) Pierik FH *et al.* A 50% increase in severe cases has been demonstrated in children of mothers >35 years old compared to mothers < 20 years old (14, 24). Mean hypospadias rates in children of mothers 35 years old or older were significantly greater than those in children of mothers younger than 35 years (8). Even though there are many publications relating to the a significance between pregnancy age and hypospadias, it was determined that 84% of the mothers in our study fell pregnant in the 20–29 age group, however, no significant relevance could be found between CPA and a mothers pregnancy age.

Mother's occupational status

There are publications stating relevance between a mothers vocation and their child's CPA (25). The mothers occupational status was questioned during a survey conducted in our current study and as a result the mothers of 6.86% of children with CPA were working, however, we found this result to be not significant. On the other hand, the job type was not asked in the survey, which can be considered as a limitation of our study. A question whether the mothers field of work involved exposure to chemical pollution should have also been asked.

Educational status

Parental educational status was questioned as a CPA risk factor in our survey. A previous study (Vrijheid *et al* 2003) reported that the mother's educational status was not a risk for CPA (26). A supporting this publication was not found in our study and the result was not found significant.

Family's state of income

When the families state of income was researched some publications found that the socio economic level had a significant relevance to CPA (4, 27). Pierik *et al* also stated that low socio-economic conditions were a risk for hypospadias (28). However, we determined in our current study that children with CPA were distributed homogenously into all income groups and on the contrary to current publications, no significant relevance between income level and CPA were found.

Method of family planning

Henderson *et al* reported that the high estrogen level in women exposed to diethylstilbestrole during the fertilizing stage negatively affects the development of genital organs (29). Damber *et al* reported that the continuing use of oral contraceptives after fertilization increases the estrogen level in the fetus (30). In contradiction to these publications, Noorgan *et al* reported that in the study they carried out found no relevance between the use of oral contraceptive by mothers and the increase of risk of hypospadias (9). In parallel to Norgaard *et al* (9) we could not find relevance between the development of CPA and the use of oral contraception in our study.

Implementation of vitro fertilization

Women undergoing *in vitro* fertilization (IVF) procedures typically receive treatment with progesterone in the first trimester to support the pregnancy after embryo transfer (14). It was postulated that this treatment is the cause of increased risk for hypospadias following IVF procedures (16). Experimental studies have shown that progestin's administered to laboratory animals during pregnancy can cause hypospadias (14, 31).

A meta-analysis of human studies also did not find an association between progestin exposures and external genital anomalies in male infants (32). In addition, Ericson *et al* found that an increased risk for hypospadias was specific for intra-cytoplasmic sperm injection (ICSI), and not for all the other IVF procedures in which progestin support was administered (33). We could not find a relevance between IVF and the development of CPA, too.

Use of drugs during pregnancy

It has also been suggested that maternal exposure to progestin (*ie*, natural progesterone and synthetic progesterone and testosterone derivatives that produce biologic effects similar to those of progesterone) during early pregnancy may increase hypospadias risk by interfering with the production or action of fetal androgens, which are critical to normal closure of the urethra (4, 34).

This study observed an increased risk of second and third degree hypospadias among infants delivered to women who took progestin during early pregnancy to help them become pregnant or to prevent pregnancy complications or loss (34).

In our study, another frequent reason of CPA was found to be penile torsion. Campbell suggested identifying the presence of penile torsion by referring to the position of the median raphe (35). In our experience, penile torsion can be easily identified from the orientation of the urethral meatus of an erect penis. The urethral meatus rotates accordingly in penile torsion, but it remains vertically oriented in pure ventral or lateral penile curvature (36).

In our study, the mean penile length was measured to be 6.61 ± 1.07 . It is known that penile length has geographic differentiates in the world. Cheng *et al* reported that the mean penile length and diameter are slightly but significantly smaller in newborns of Chinese origin compared to newborns of Caucasian and East-Indian origins (37). Cinaz *et al* reported mean penile length 6.63 ± 0.68 for 7.1 – 8 years old boys in Turkey (38). If we compare our results with Cinaz *et al* report, there is no difference between two studies.

In 2001, Skakkebak *et al* put forth the hypothesis that some male reproductive disorders were interlinked and originated from a disturbed testicular development *in utero* (39). This hypothesis was called testicular dysgenesis syndrome (TDS). The TDS hypothesis was based on clinical, epidemiological and basic scientific evidence for a fetal origin of testis cancer, the well-established link between genital malformations in newborn boys and adult reproductive disorders, and on observations from experimental animal studies and wildlife such as urogenital abnormalities associated with exposure to environmental EDC such as phthalates, specifically decreased semen quality, and increased rates of testis cancer and hypospadias (8). Together with this existing evidence suggested that the prenatal period may be the most vulnerable phase in which impairment of testis differentiation may result in permanent adverse effects. There is a worldwide increase in incidence of CPA and hypospadias. Endocrine disrupting chemicals with antiandrogenic activity may be the cause of this increase.

Effectively, in November, 2000, the US Food and Drug Administration no longer required that progestational drugs (which include natural progesterone and all synthetic progestin, other than progestin-containing products for contraception) carry a warning regarding genital defects (40).

The effects of environmental agents on the development of congenital abnormalities have not been researched in our country. Publications, which indicate an increase in CPA incidences in various geographical regions over a short period of 30 years does not make it possible to render this situation by way of genetic transfer. On the other hand, contrary to some publications, our current study shows a high number of CPA in other family members form the same family, nevertheless, this situation cannot be explained with genetic transfer as it does not contain statistical meaning. However, an explanation with environmental contamination is possible. For us to find CPA incidences in our study parallel to the highest value in the world in general puts forth that the use of environmental agents used in our country and region and its widespread should be put under control and that further studies should be carried out.

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