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## Original Article

<http://wjpn.ir>**Prevalence of Fetomaternal Indications of Therapeutic Abortions in Yazd Province**

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**ABSTRACT**

**Background:** Therapeutic abortion is defined as intentional termination of pregnancy in order to save the mother's life and health or when the fetus has an abnormality incompatible with normal life. The aim of this study was to evaluate causes of issuance of therapeutic abortion in women referred to the Yazd province Legal Medicine Organization to terminate the pregnancy.

**Methods:** In this cross sectional study, all the applications for therapeutic abortions from March 2014 to March 2016 approved by the legal medicine organization of Yazd province were included and recorded. The data was analyzed by SPSS software.

**Results:** From 333 permissions for abortion during three years, 299 cases (89.8%) were issued for the reason of fetal indications and 34 cases (10.2%) for maternal indications. The most prevalent fetal abnormalities indicated for abortion were central nervous system disorders (especially Anencephaly and Spina Bifida); Hydrops Fetalis and Down syndrome, respectively and the most frequent maternal disorders were cardiovascular diseases.

**Conclusion:** The current study shows that therapeutic abortions due to fetal abnormalities are increasing. It seems that educating health professionals and people and increasing their awareness about preventing fetal abnormalities and also contraception in women with maternal diseases indicated for abortion could be an effective way to reduce the rate of abortion.

## Introduction

**A**bortion refers to the termination of pregnancy by any means before the fetus can survive outside the uterus and may be spontaneous or induced. Induced abortions are either elective (illegal) or therapeutic.<sup>1</sup> According to the World Health Organization, 19 million unsafe abortions occur annually and an estimated 68,000 women die as a consequence of unsafe abortions each year all over the world. About 99% of all maternal deaths arise in developing countries<sup>2</sup> Indications for termination of pregnancy reflect the laws of the country and the religion. Abortion is legally permitted in many countries under definite conditions, In Iran termination of pregnancy is limited to therapeutic abortion.<sup>3</sup>

Therapeutic abortion is a kind of induced abortion when continuing pregnancy may lead to threatening of mother's life and health or birth of fetus with severe congenital anomalies<sup>4</sup> Congenital anomaly (birth defect) is defined as a structural or functional defect that occur during intrauterine life and may be detected prenatally, or be visible at birth or later in life. Congenital anomalies are a global health problem and responsible for many cases of perinatal mortality, stillbirths and spontaneous abortions and death in early post natal period. Annually an estimated 7.9 million children are born with a serious birth defect and 3.3 million children under five years die from birth defects, who they survive may develop a long term disability which can cause a significant effect on individuals, families, healthcare system and societies.<sup>5</sup> Regarding to severity of abnormality, congenital anomalies are classified to major or minor. They can confine to a single system or involve multiple systems.<sup>6</sup>

The prevalence of congenital anomalies varies greatly from country to country and even in the same country from one region to another. Such variations could be explained by ethnic, environmental factors and ecological and socio-economic differences.<sup>6</sup>

Prevention of congenital anomalies in the developing countries requires the implementation of several steps. A first step is the providing of good epidemiological data on the prevalence and types of birth defects and genetic disorders.<sup>7</sup>

The Guideline for Therapeutic Abortion containing indications that it was legislated by the Islamic parliament in 2005. According to the current law any request for issuing permission for therapeutic abortion is merely acceptable through the Legal Medicine Organization; if three specialist make definite diagnoses about the fetus being malformed or retarded, thus causing the mother to suffer severely, or about the mother's own life-threatening conditions only before ensoulment of fetus (before four months). The Legal Medicine Organization has defined 100 fetal and maternal disorders to apply for a legal abortion license. Some fetal indications are Hydrops Fetalis with any etiology; conditions resulting in neonatal death such as Anencephaly and disorders leading to handicap or disability; maternal indications include: life-threatening maternal conditions such as active phase of HIV infection, malignancy (i.e. cervical and breast cancer, leukemia and colorectal cancer), Molar Pregnancy, renal diseases, severe heart diseases, autoimmune diseases such as Systemic Lupus Erythematosus (SLE), etc.<sup>3</sup>

The WHO categorizes unsafe abortion as a major public health problem as well as one of the easiest preventable causes of maternal mortality. Most abortions are safe in countries where the procedure is lawfully permitted, in the other word when therapeutic abortion is legally available, it is generally safe.<sup>8,9</sup> Awareness of physician and pregnant women of abortion indications and referring to Legal Medicine Organization at the right time can significantly reduce illegal and unsafe abortion. Assessing causes of applications for therapeutic abortion, undoubtedly contributed to find new indications which may lead to birth of healthy infants and reduce illegal abortion. The present paper was aimed to

determine types and prevalence of indications for therapeutic abortion in pregnancies that they were authorized to terminate by Legal Medicine Organization of Yazd province during a period of three years.

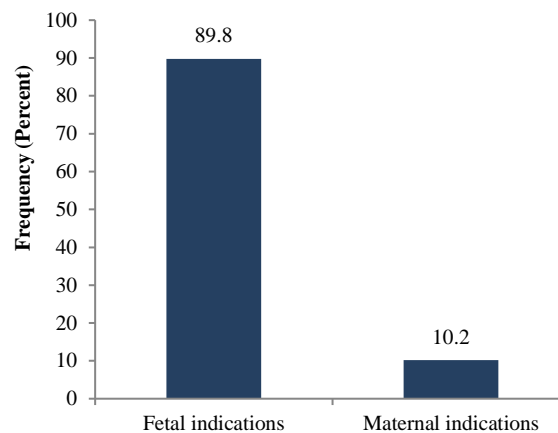
## Materials and Methods

This cross sectional study was performed using all medical documents of women who visited the Yazd Province Legal Medicine Organization to apply for a legal abortion license and were approved and authorized, between March 2014 and March 2016. The data recorded for each woman included: age, residence, level of education, occupation, gestational age, type of fetal or maternal indications for the abortion and their diagnostic methods. Incomplete data was omitted from the study. The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences. As ethical point, the patients identity information were kept confidential. The data was analyzed by SPSS using analytical statistics to determine distribution frequency and means of all variables.

## Results

A total of 333 licenses for abortion were issued by the Yazd province Legal Medicine Organization between March 2014 and March 2016. In 89.8% of cases ( $n = 299$ ) the reasons for issuance of abortion license were fetal abnormalities and in the rest (10.2% or 34 cases) were the maternal disorders (Figure 1). Most of the abortions licenses were issued in 2016 (41.1%). The mean age of the mothers was  $30.2 \pm 6.4$  (age range: 17-46). The highest applications for abortion were in the mothers at age range of 30-35 years (28.3%) and the least were in mother's  $\geq 20$  years (3.3%). Among which 333 women, 2.7% ( $n = 9$ ) were illiterate, 18% ( $n = 60$ ) had primary and middle school education, 31.5% ( $n = 105$ ) had diploma, 42.6% ( $n = 142$ ) had higher education and level of education of 5.1% ( $n = 17$ ) was not mentioned.

Approximately 79% ( $n = 263$ ) of the women were housewives and the rest were involved in other jobs.



**Figure 1.** Distribution of indications for therapeutic abortions in women applying for a legal abortion license at the Yazd Province Legal Medicine Organization (March 2014 -March 2016).

The abortion licenses were predominantly issued for fetuses at gestational age of 15-19 weeks (66.1 %) and then for fetuses at gestational age of 10-14 weeks (27.9%). Gestational age for 6.0% of the fetuses was less than 10 weeks (Table 1). There were two or more fetal abnormalities indicated for abortion in some fetuses. Totally, 353 fetal abnormalities were recorded. The main fetal abnormalities indicated for abortion were central nervous system disorders (30.0%), Hydrops Fetalis (15%); and Down syndrome (11.3%) (Figure 2). Skeletal Dysplasia was the major abnormality of musculoskeletal system. Autosomal Recessive Polycystic Kidney (ARPKD) was the major abnormality of genitourinary system. Omphalocele and Hypoplastic Heart Syndrome were the most common anomalies in gastrointestinal system and cardiovascular system, respectively (Table 2). The most prevalent maternal causes of abortion were cardiovascular diseases and severe hypothyroidism (Table 3). None of the mothers had infective diseases such as toxoplasmosis, rubella or herpes.

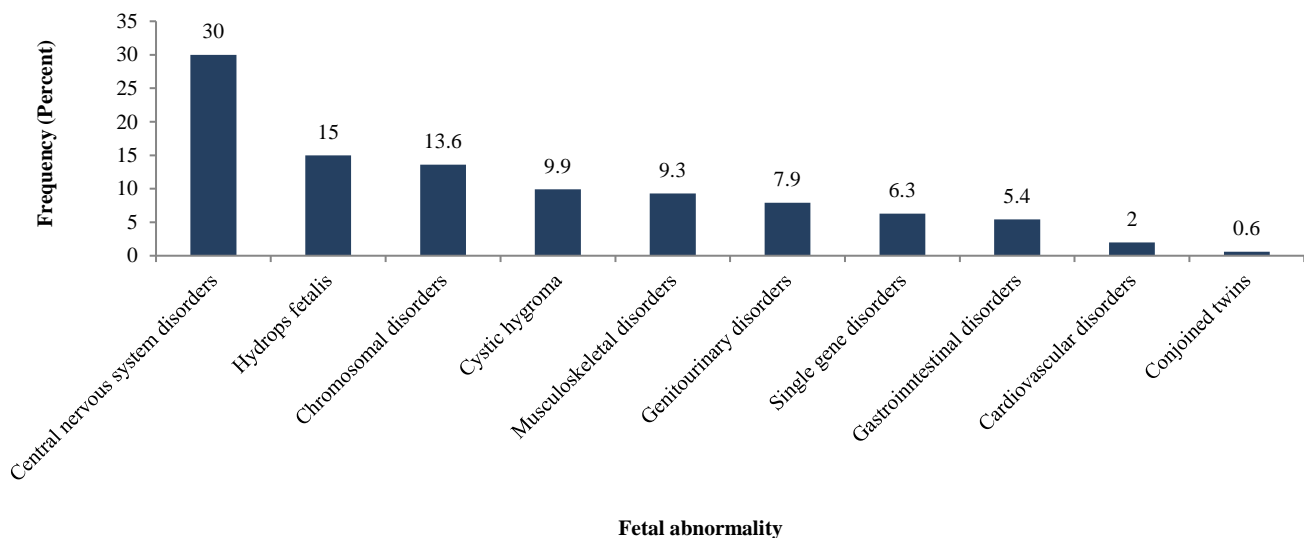
**Table 1.** Characteristics of women applying for a legal abortion licence at the Yazd Province Legal Medicine Organization

Variable	Frequency	Percent
Maternal Age		
≥ 20	13	3.9
20-25	51	15.3
25-30	88	26.4
30-35	93	28
35-40	59	17.7
40 ≤	29	8.7
Total	333	100
Level of Education		
Illiterate	9	2.7
Primary and middle school	60	18
Diploma	105	31.5
Higher education	142	42.6
Unknown	17	5.1
Total	333	100
Occupation		
Housewife	263	79
Others (employed, self-employed)	70	21
Total	333	100
Gestational age based on ultrasound (weeks)		
≥ 10	20	6
10-14	93	27.9
15-19	220	66.1
Total	333	100

## Discussion

This retrospective study examined causes of issuance of legal abortion license from Yazd Legal Medicine Organization during 3 years. The study showed 89.8% (n = 299) of abortion licenses were issued due to fetal

abnormalities and 10.2% (n = 34) due to maternal diseases. The most frequent fetal indications for abortion were central nervous system disorders, Hydrops Fetalis and Down syndrome while most frequent maternal indications were cardiovascular diseases and severe hypothyroidism.

**Figure 2.** Distribution of therapeutic abortions according to fetal indications

**Table2.** Distribution of fetal abnormalities according to systems involved.

<b>Abnormality</b>	<b>Frequency</b>	<b>Percent</b>
<b>Neurological System</b>		
Anencephaly	25	7.1
Encephalocele	10	2.8
Spina Bifida (Spina Bifida Occulta, Meningocele, Myelomeningocele)	25	7.1
Hydrocephalus	11	3.1
Ventriculomegaly	10	2.8
Dandy Walker Syndrome	6	1.7
Holoprosencephaly	10	2.8
Others (Hydrencephaly, Microcephaly, Acrania, Joubert Syndrome)	9	2.5
Total	106	30
<b>Genetic Disorders</b>		
<b>Chromosomal Abnormalities</b>		
Down Syndrome (Trisomy 21)	40	11.3
Edward Syndrome (Trisomy 18)	4	1.1
Patau Syndrome (Trisomy 13)	1	0.3
Triploidy	2	0.6
Trisomy 8	1	0.3
Total	48	13.6
<b>Single Gene Disorders</b>		
Major Thalassemia	13	3.7
Haemophilia	5	1.4
Spinal Muscular Atrophy (SMA)	2	0.6
Phenylketonuria (PKU)	1	0.3
Ichthyosis	1	0.3
Total	22	6.3
<b>Musculoskeletal System</b>		
Severe Skeletal Dysplasia	12	3.4
Diaphragmatic Hernia	4	1.1
Achondroplasia	7	2
Others ( Arthrogryposis, Multiple Skeletal Anomalies)	10	2.8
Total	33	9.3
<b>Cardiovascular System</b>		
Hypoplastic Heart Syndrome (HLHS & HRHS)	4	1.1
Severe Valvular Stenosis (aortic stenosis & pulmonary Stenosis)	2	0.6
Single Ventricle Heart	1	0.3
Total	7	2
<b>Gastrointestinal System</b>		
Omphalocele	14	4
Gastroschisis	2	0.6
Others	3	0.8
Total	19	5.4
<b>Genitourinary System</b>		
Autosomal Recessive Polycystic Kidney (ARPKD)	12	3.4
Multicystic Dysplastic Kidney (MCDK)	2	0.6
Severe Hydronephrosis	3	0.8
Structural Renal Abnormalities + Severe Oligohydramnios	11	3.1
Total	28	7.9
Conjoined Twins	2	0.6
Cystic Hygroma	35	9.9
Hydrops Fetalis	53	15
Total	353	100

**Table 3.** Distribution of therapeutic abortions according to maternal indications

Maternal Diseases	Frequency	Percent
Cardiovascular diseases	7	20.6
Hypothyroidism	6	17.6
Diabetes	3	8.8
Kidney diseases	2	5.9
Blood pressure	1	2.9
Cirrhosis	1	2.9
Thyroid cancer	1	2.9
Lupus	1	2.9
Hemiplegia followed by stroke	1	2.9
Hemolytic anemia	1	2.9
Malignant Peripheral Nerve Sheath Tumors (MPNST)	1	2.9
Treatment-Resistant Depression (TRD)	1	2.9
Placental Anomalies		
Hydatidiform mole	2	5.9
Placenta accreta	2	5.9
Placenta increta	4	11.8
Total	34	100

Our findings were consistent with some other studies previously reported. In the study of Soleimanpour et al. in Esfahan, as well as the study of Naeji et al. in Tehran, respectively 75.8% and 88% of abortions have fetal indication for abortion.<sup>10,11</sup> In both studies central nervous system disorders, Hydrops Fetalis and trisomies have been the most common cause of abortion. The main maternal cause of abortion in Naeji study was cardiovascular diseases. In another study by Forouzesh et al. in Hormozgan 82.56% of therapeutic abortions were due to fetal abnormalities and 13.52% of due to maternal causes.<sup>12</sup> In their study the main fetal indications for abortion were central nervous system disorders (especially Anencephaly and Microcephaly) and Major Thalassemia and the main maternal indication for abortion were renal disorders. In the study of Dadipoor et al. and Ghadipasha et al.;<sup>13,14</sup> cardiovascular disorders were the main maternal indication for abortion. In both studies the greatest proportion of the women applying for an abortion license for fetal indications had a fetus with Major thalassemia where it was rare in our investigation. It shows that thalassemia is now under the control of health care system in the country.

The causes of difference between the

prevalence of congenital anomalies in various regions of the country may reflect different methods of detection and recording, or true differences in frequency due to consanguineous marriage rate, dissimilar environmental exposures, genetic constitutions or the interaction of both.

According to our findings central nervous system disorders (Anencephaly and Spina Bifida) were the most frequent fetal abnormalities licensed an abortion. Folic acid deficiency is a well-known factor predisposing to neural tube defects and possibly other congenital anomalies.<sup>15</sup> Despite this fact, most women are not aware of folic acid benefits to prevent neural tube defects. It is recommended that all the women who want to become pregnant consume 400 mg of folic acid from a month before conception to the end of first trimester daily.<sup>16</sup>

Another high frequent fetal abnormality in the present study and some other similar studies were chromosomal abnormalities (especially trisomy 21). A large number of studies have reported that fetal chromosomal abnormalities including trisomy 21, trisomy 18, and trisomy 13 have a direct association with advanced maternal age.<sup>17</sup> Therefore couples should be encouraged to complete reproduction before 35 years of age of



mother. By reducing birth rate, family planning may contribute to a decline in birth prevalence of chromosomal abnormalities. It is estimated combined with encouragement to complete reproduction before the age of 35, family planning can contribute to a 50% reduction of Down syndrome.<sup>18,19</sup>

With regard to this point that in many cases permission for abortion is not issued because gestational age is over 19 weeks, for this reason it may make a trend to illegal abortion. So that it is necessary for experts to aware of indications of therapeutic abortions and to improve the diagnostic skills for early diagnosis of fetal abnormalities.

### Conclusion

The present study shows high prevalence of therapeutic abortion due to fetal abnormalities. For reducing the rate of fetal abnormalities it suggests: to improve the epidemiological knowledge about genetic disorders and birth defects, to select preventive programs according to prevalence, severity and the predicted outcomes of interventions and improve prenatal services, including family planning and maternal nutrition. For women with cardiovascular disorders contraception is indispensable.

### Conflict of Interests

Authors have no conflict of interests.

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## Original Article

<http://wjpn.ir>

## Association between Transforming Growth Factor Alpha TaqI Polymorphism and Susceptibility to the Nonsyndromic Cleft Lip and/or Palate in an Iranian Population: A Case Control Study

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### ABSTRACT

**Background:** The TGF- $\alpha$  TaqI C >T polymorphism is a well-characterized variant for nonsyndromic cleft lip and/or palate (NS CL/P), but it has shown inconsistent results of association with nonsyndromic CL/P across a number of studies. Thus, we have performed this case-control study to clarify the association between the TGF- $\alpha$  TaqI C >T polymorphism and NS CL/P risk.

**Methods:** One-hundred ten cases with NSCL/P and 110 controls were recruited to the current study. We have genotyped the TGF- $\alpha$  TaqI C >T polymorphism using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The odds ratio (OR) and 95% confidence interval (CI) were applied for strength of association TGF- $\alpha$  TaqI C >T polymorphism with NSCL/P.

**Results:** The TGF- $\alpha$  TaqI C >T polymorphism CC, CT and TT genotypes frequencies in the NSCL/P cases were 30.9%, 57.3% and 11.8%, respectively while the corresponding frequencies in the controls were 37.3%, 52.7% and 10.0%, respectively. The frequency of C and T alleles in the case were 59.5% and 40.5%, respectively while the corresponding allelic frequencies in the controls were 63.6% and 36.4%. There was no significant difference in the genotype and allele frequency for TGF- $\alpha$  TaqI C >T polymorphism between cases and controls. The minor allele frequency (MAF) of TGF- $\alpha$  TaqI C >T polymorphism among healthy controls was 0.36.

**Conclusion:** Our study indicates that the TGF- $\alpha$  TaqI C >T polymorphism was not significantly associated with increased risk of NS CL/P in the Iranian population. However, our results still need to be confirmed by further large and well-designed case-control studies.

## Introduction

**N**onsyndromic cleft lip and palate (NSCL/P) is the most common birth defects, with an incidence of 1 to 2 in 1000 live births.<sup>1,2</sup> There are notable differences in prevalence of NSCL/P among different ethnic groups, and it is more common among men, compared with women.<sup>3</sup> Although a combination of factors associated with multiple genetic and environmental factor are important for development of NSCL/P, the exact pathogenesis is still unknown.<sup>4,5</sup>

In recent years, regarding advances in genetics and molecular biology, various efforts have been made to understand the risk and related factors of NSCL/P, to predict its occurrence and prevention.<sup>6,7</sup> There were many candidate gene studies associated with NSCL/P.<sup>8</sup> Although many genes or regions had positive results in one or more of the early studies, few of those findings were consistently positive across all studies. One of the most important genes is transforming growth factor  $\alpha$  (TGFA).<sup>9</sup>

The combined effect of TGFA mutation and environmental influence in NSCL/P has been analyzed by several studies in different populations<sup>8</sup>. This association supports a role for this gene as one of the genetic determinants of craniofacial development.<sup>10</sup> Three common polymorphisms of the TGFA gene, including RsaI, BamHI, and TaqI in intron 5 and in exon 6, have been investigated in association with NSCL/P. Recently, the possible association of BamHI and RsaI polymorphisms in TGFA in developing NSCL/P was identified in an Iranian population. Because individual susceptibility plays an important role in the development of NSCL/P, understanding the genetic background and etiology of these diseases is essential for both risk assessment and finding effective methods for prevention and treatment.<sup>11, 12</sup>

To date, several studies from different ethnicities have been evaluated the association

of TGF- $\alpha$  TaqI C > T polymorphism with NSCL/P risk, but the results remain conflicting. Moreover, there is a study on association of this polymorphism with NSCL/P in the Iranian population.<sup>13</sup> Thus, we performed this case-control study to determine whether TGFA TaqI polymorphism was associated with NSCL/P in Iranian patients.

## Materials and Methods

**Study Population:** The study protocols were approved by the Institutional Ethics Committee of the Kashan University of Medical Science. Informed consent was obtained from parents of children prior to any data collection. A total of 110 children with nonsyndromic CL/P, and 110 age and sex matched children as controls were consecutively enrolled in current study between April 2016 and March 2017. All cases were Iranian who diagnosed with NSCL/P at birth. Excluding criteria were as follow: family history of orofacial clefts or craniofacial anomalies, dental anomalies, congenital anomalies, learning disabilities, attention deficits, hearing impairment and speech deficits.

**DNA extraction and genotyping:** From each participant, five ml of peripheral blood samples were collected in tubes containing  $\mu$ l of 0.5 M EDTA and stored at -20 C. genomic DNA was extracted from peripheral blood using the salting out method. Genotyping of the TGF- $\alpha$  TaqI C > T polymorphism (rs731236) was performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) method. The primers sequences were as: forward primer, 5'-TCACTTCCCCTTTTTCATCTG-3'; and reverse primer, 5'-CGAGGAGGCTCCTGAGGTG-3'. The PCR cycle of +915 was performed by a stage of pre-denaturation at 95°C for 5 minutes, then 35 cycles of 95°C for 30 seconds, 58.4°C for 30 seconds, and 72°C for 30 seconds, followed by a final extension at 72°C for 10 minutes. The pattern of restriction

fragments for homozygote wild-type (CC), heterozygote (CT) and mutant homozygote (TT) were 179 bp, 179+122+53 bp, and 122 + 53 bp, respectively. The PCR products were digested by two TaqI restriction enzymes (Fermentas, Vilnius, Lithuania) at 37°C. The RFLP fragments were detected on 2% agarose gel and stained with ethidium bromide (EtBr). Moreover, we have sequenced 10% of samples to confirm the results of genotyping.

**Statistical Analysis:** A raw genotyping data for PCR-RFLP assays was input into Excel software of Microsoft Office 2013. All statistical analysis of data was calculated by the Statistical Package for the Social Sciences (SPSS) software package version 19.0 (SPSS, Inc., Chicago, IL, USA), which a  $P < 0.05$  was considered as the level for significance. The chi-square test was performed to compare genotype and allele frequency of TGF- $\alpha$  TaqI C > T polymorphism in the cases and controls. Moreover, the odds ratio (OR) and 95% confidence interval (CI) were calculated from CMA software for strength association TGF- $\alpha$  TaqI C > T polymorphism with NSCL/P. Hardy-Weinberg Equilibrium (HWE) was tested for TGF- $\alpha$  TaqI C > T polymorphism for controls using chi-square test.

## Results

The characteristics of cases and controls are shown in Table 1. The mean age of cases and controls at was  $7.41 \pm 4.31$  and  $8.11 \pm 6.31$  years, respectively. The analysis showed that there was no significant difference between cases and controls by age and sex ( $P > 0.05$ ), which indicating that matching was

appropriate. Ninety-seven patients (24.5%) had unilateral NSCL/P and the other 83 (75.5%) had bilateral NSCL/P. Of those 110 cases, 17 (15.4%) and 29 (26.4%) were only cleft lip and only cleft palate, respectively (Table 1).

The genotypes and alleles frequency of TGF- $\alpha$  TaqI C > T polymorphism in cases and controls are shown in Table 2. The distributions of genotype in the control group for TGF- $\alpha$  TaqI C > T polymorphism was in accordance with Hardy-Weinberg equilibrium ( $P = 0.144$ ), and minor allele frequency of this polymorphism in controls was 0.36. As seen in Table 2, The TGF- $\alpha$  TaqI C > T polymorphism wild homozygote (CC), heterozygote (CT) and mutant homozygote (TT) genotypes frequencies in the NSCL/P cases were 34 (30.9%), 63(57.3%) and 13(11.8%), respectively while the corresponding frequencies in the controls were 41 (37.3%), 58 (52.7%) and 11(10.0%), respectively. The frequency of wild and mutant alleles in the case were 131(59.5%) and 89(40.5%), respectively while the corresponding allelic frequencies in the controls were 140(63.6%) and 80 (36.4%). The association of TGF- $\alpha$  TaqI C > T polymorphism with NSCL/P risk is shown in Table 2. We have not found a significant difference in the genotype and allele frequency for TGF- $\alpha$  TaqI C > T polymorphism between cases and controls. Moreover, there was no significant association between TGF- $\alpha$  TaqI C > T polymorphism and susceptibility to the NSCL/P in the Iranian children (Table 2).

**Table 1.** Characteristics of the cases and controls.

	Cases (n = 110)	Control (n = 110)	P
Age ( $\pm$ SD)	7.41 $\pm$ 4.31	8.11 $\pm$ 6.31	0.631
Gender			
Male	64 (58.2)	60 (54.5)	0.587
Female	46 (41.8)	50 (45.5)	
lateral			
Unilateral	28 (25.4)	-	-
Bilateral	83 (75.5)	-	-
$\pm$ CL/CP			
Only CL	17 (15.4)	-	-
Only CP	29 (26.4)	-	-

**Table 2.** A comparison of NSCL/P patients and healthy control samples of allele and genotype distribution of TGF- $\alpha$  TaqI C > T polymorphism.

Polymorphism	Cases (n = 110)	Control (n = 110)	OR (95% CI)	P
Genotype		0.144		
CC	34 (30.9)	41 (37.3)	Ref.	
CT	63 (57.3)	58 (52.7)	1.202 (0.706-2.045)	0.684
TT	13 (11.8)	11 (10.0)	1.206 (0.515-2.823)	0.666
Allele				
C	131 (59.5)	140 (63.6)	0.841 (0.573-1.236)	0.378
T	89 (40.5)	80 (36.4)	1.189 (0.809-1.747)	0.378
Genetic Models				
Dominant (GG+AG vs. AA)			1.407 (0.792-2.501)	0.244
Recessive (GG vs. AG+AA)			2.360 (1.055-5.280)	0.037

OR: Odds Ratio; CI: Confidence Interval.

## Discussion

NSCL/P is the most common craniofacial malformation.<sup>1</sup> The pathophysiology of NSCL/P is not well understood, but progress has been suggested a multifactorial model of genetic inheritance for NSCL/P based on the interaction of genetic and environmental factors.<sup>3</sup> Studies have showed that infection, drug intake and folic acid supplement during pregnancy might be associated with the occurrence of NSCL/P.<sup>14</sup> By the advances in genetics and molecular biology, several studies have focused on the role of TGF- $\alpha$  TaqI C > T polymorphism in etiology of NSCL/P, as a result of its role in cell proliferation and differentiation during primary palate morphogenesis.<sup>12</sup> However, the exact role of TGF- $\alpha$  TaqI C > T polymorphism played in development of nonsyndromic NSCL/P still remain obscure.<sup>11,12,15</sup>

In the past two decades, different studies have been evaluated the association of TGF- $\alpha$  TaqI C > T polymorphism with risk of NSCL/P. However, only a study by Bagheri et al., have evaluated the association of TGF- $\alpha$  TaqI C > T polymorphism with NSCL/P among Iranian children (113 children with NSCL/P and 209 controls). Their result showed that the TGF- $\alpha$  TaqI C > T polymorphism was not associated with the risk of NS CL/P in the Iranian children.<sup>13</sup> In consistence with their results, the current study showed that the TGF- $\alpha$  TaqI C > T

polymorphism was not significantly associated with increased risk of NS CL/P in the Iranian population. Studies showed that TGF- $\alpha$  TaqI C > T polymorphism is among the few genetic factors that have shown significant interactions with various environmental factors, including maternal smoking and vitamin use. Therefore, the agreement between the current study and the previous study in the Iranian children could be explained by taking into consideration similar environmental influence. Similarly, Souza et al., have evaluated the association of TGF- $\alpha$  TaqI C > T polymorphism with NSCL/P using a transmission disequilibrium test (TDT) in a Brazilian population. Similarly, they have found that TGF- $\alpha$  TaqI C > T polymorphism did not associated with increased risk of NSCL/P.<sup>16</sup> Moreover, their results did not show correlation between exposure to tobacco or alcohol during pregnancy and increased risk of NSCL/P. However, Zhu et al., have reported that the parental smoking may interact with TGF- $\alpha$  TaqI C > T polymorphism of Chinese populations in occurrence of NSCL/P.<sup>17</sup> However, Zhu et al., did not found an association between TGF- $\alpha$  TaqI C > T polymorphism and the increased risk of NSCL/P in Chinese population.<sup>18</sup>

Inconsistent with our results the pooled data showed different role for TGF- $\alpha$  TaqI C > T polymorphism in development NSCL/P. In 2013, Lu et al., in a meta-analysis of 27 case-control studies evaluated the

association between TGF- $\alpha$  TaqI C > T polymorphism and CL/P risk. Their results showed a significant association between TGF- $\alpha$  TaqI C > T polymorphism and CL/P under all five genetic models. Moreover, they have found an increased risk among Caucasians and Asians, but not among mixed populations.<sup>12</sup> In the most previously published meta-analysis based on 26 studies (3,234 cases and 4,348 healthy controls), Yan et al., have reported that the TGF- $\alpha$  TaqI C > T polymorphism was significantly associated with an increased risk of nonsyndromic CL/P. Moreover, their stratifications by ethnicity showed that TGF- $\alpha$  TaqI C > T polymorphism was associated with susceptibility to nonsyndromic CL/P among White and Asian Populations. However, they have reported that the wild allele of TGF- $\alpha$  TaqI C > T polymorphism had a protective effect against NSCL/P in White and Asians populations. They have suggested that the GF- $\alpha$  TaqI C > T polymorphism is likely to be low-penetrance polymorphism with a very weak effect and also another explanation could be the high between-studies heterogeneity of included studies in the pooled data.<sup>11</sup> Therefore, to clarify this finding larger sample sizes and well-designed studies using well-matched controls.

In summary, the current study indicates that the TGF- $\alpha$  TaqI C > T polymorphism was not significantly associated with increased risk of NS CL/P in the Iranian population. However, our results still need to be confirmed by further large and well-designed case-control studies.

### Conclusion

The current study indicates that the TGF- $\alpha$  TaqI C > T polymorphism was not significantly associated with increased risk of NS CL/P in the Iranian population. However, our results still need to be confirmed by further large and well-designed case-control studies.

### Conflict of Interests

Authors have no conflict of interests.

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## Original Article

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## The Relationship of Intrauterine Growth Restriction with Placental Pathologic Changes in Newborns

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### ABSTRACT

**Background:** Intrauterine growth restriction is a multifaceted problem and is associated with a significant increase in the level of morbidity and perinatal mortality. According to some studies, failure of the placenta is responsible for the most cases of intrauterine growth restriction. The aim of this study was to evaluate the placental pathologic changes in the intrauterine growth restriction (IUGR) samples and compare them with normal cases.

**Methods:** A study population consisted of 60 intrauterine growth restriction neonates and 60 normalized neonates born at Tehran Imam Khomeini Hospital between June 2016 and July 2017. The placenta was weighed, immediately after delivery, and the umbilical cord was separated, then stored in 10% formalin and sent for pathological examination as soon as possible. Data collection was performed according to the following items: the pathologist's report, the results of the infants' examination, and the data in the neonatal cases.

**Results:** The intrauterine growth restriction group showed a high frequency of placenta infarction ( $P < 0.001$ ), inflammation of the villous ( $P < 0.001$ ), villous fibrosis ( $P = 0.044$ ), villous vascularization disorder ( $P = 0.001$ ), prevalence of chorioamnionitis ( $P = 0.027$ ), prevalence of Syncytiotrophoblastic knots ( $P < 0.001$ ) and placental necrosis ( $P = 0.048$ ) than normal group. However, the mean weight of the placenta ( $P < 0.001$ ), the length and width of the macroscopic placenta changes was less ( $P < 0.001$ ).

**Conclusion:** The results of the current study showed that a major part of the macroscopic and histological changes are detectable in the intrauterine growth restriction samples, which are considerably more common than normal, although they are not pathognomonic, but in the future, more accurate results can be obtained from more extensive studies.

## Introduction

The intrauterine growth restriction (IUGR) means fetal growth is less than the normal growth potential of a specific infant which is due to genetic or environmental factors. IUGR can be a natural response to nutrient deprivation or oxygen deprivation.<sup>1</sup> Around the world, 30 million infants suffer from the IUGR every year. IUGR mainly occurs in Asia.<sup>2</sup> Pathophysiologically, intrauterine growth disturbances can be related to maternal, placental, or fetal related factors. Nearly one-third of IUGRs are due to maternal factors and two-thirds of them related to placenta and infants.<sup>3</sup> Prenatal diagnosis of IUGR is based on prenatal ultrasound, biophysical profiles and assessment of the fetal acid-base status and Doppler Velocimetry. In the failure of the placenta the umbilical artery resistance increases and diastolic flow in the umbilical artery was decreases or reverses. The findings indicate that in the absent and reversed-end diastolic flow approximately 60 to 70 % of the villous placenta is damaged, and in the severe IUGR, the middle cerebral flow increased.<sup>4</sup>

Intrauterine growth restriction is a problem that is associated with a significant increase in the level of morbidity and perinatal mortality. IUGR infants are at risk for metabolic disorders, polycythemia, and intracranial hemorrhage (IVH), NEC, BPD, and ROP. Early neonatal complications included hypothermia, hypoglycemia, hypocalcemia, polysystemic, jaundice, etc.<sup>5,6</sup> With regard to long-term complications, you can also cite adult problems such as diabetes, hypertension, obesity, cardiovascular disease and dyslipidemia. It also has more problems in terms of learning and education.<sup>6</sup> The placental insufficiency is responsible for most cases of IUGR, and the human placenta is the most reliable control for the infants before and after birth. Similarly, several microscopic abnormalities are commonly identified in the IUGR-related placenta, which, of course, are

not pathognomonic for the IUGR-placenta. These changes were included villous infarctions, placental abruption, a variety of abnormal villous morphology, increasing the thickening of basal membranes of trophoblast, villous fibrosis, and the decreasing in the volume of the villi of the nonspecific inflammatory lesions.<sup>7-9</sup>

In the study of Salafia et al., it has been reported that increasing in the placental changes such as infarction and villous fibrosis in IUGR groups were 55% versus 33% in the control group.<sup>10</sup> In spite of the some conducted studies, the relation between placental pathognomonic changes for IUGR or related etiologies has not been confirmed.

Considering the importance of the issue and the lack of studies and information in this regard, especially in developing countries, it was decided to perform a study at the Imam Khomeini Hospital of Tehran to evaluate the relationship between IUGR and placental pathological changes in the neonate born at Imam Khomeini Hospital in Tehran in the years of 2016-2017 and assess the status of these newborns.

## Materials and Methods

This cross-sectional or case-control study was performed on 60 IUGR infants and 60 normal infants born at the Imam Khomeini Hospital in Tehran for 13 months during the period of June 2016 to July 2017. In the case group, the inclusion criteria was included selecting IUGR neonates, and exclusion criteria included congenital anomalies, the presence of the fatal genetic syndrome and the history of ARTs syndrome. In the control group, IUGR neonates were not selected and the neonates of the control and experimental groups were selected consecutively. Exclusion criteria included congenital anomalies, the presence of the genetic fatal genetic disease and the history of ARTs syndrome.

Immediately after delivery, the placenta was weighed and after cutting the umbilical cord, the placenta was stored in formalin 10%. Then, the placenta samples were sent to

the pathology lab in the shortest time. The samples were examined by a pathologist with optical microscopes and the pathologic outcome was reported. Infants who were entered the study was examined by a neonatal physician. Then, according to a researcher-made questionnaire the information was collected based on items, including the history of mother, and the cases of mother and neonate's.

The diagnosis of the IUGR was based on the results of an examination of the newborn by a neonatologist and also the report of gynecologists based on prenatal ultrasonography. Chronic maternal diseases were as following: cardiovascular disease, kidney disease, liver disease, diabetes, hypertension, hypothyroidism, autoimmune disease, and maternal infections, including UTI and vaginal infection. The pathology of the placenta was divided into abnormal and normal categories. The data collection tool was a researcher-made questionnaire. SPSS 23 software was used to analyze the data. To characterize the qualitative variables, the frequency and percentage were used and to describe the quantitative variables, the mean and standard deviations were administered. To compare qualitative variables Chi-square was used and for quantitative variables, t-test or Mann-Whitney was run. Logistic regression test and Mantel Haenszel test were used. The P-value was less than 0.05.

## Results

A total of 120 samples were included in the study, of which 60 neonates with IUGR and 60 neonates were normal. Comparison of baseline data in two groups of healthy infants and IUGR showed that the prevalence of cesarean section in the IUGR group was significantly higher (98.3% vs. 48.3%,  $P < 0.001$ ). The mean of gestational age and neonatal weight in the IUGR neonates compared with the normal neonates was statistically significant ( $P < 0.001$ ). The prevalence of preeclampsia, chronic maternal diseases, the prevalence of pregnancy-related infections and vaginal infections in mothers with the IUGR was

significantly higher than that of normal-born mothers (Respondtively  $P < 0.032$ ,  $P < 0.006$ ,  $P < 0.001$ , and  $P < 0.001$ ) (Table 1).

In examining the pathological examination of the placenta, in many indices, there was a significant difference between the two groups with and without the IUGR. The results were illustrated in Table 2.

On the placental pathology, it was investigated into two categories: natural and abnormal (based on the Throne study).<sup>15</sup> In the IUGR, abnormal pathological abundance was higher and the possibility of the pathologic placenta was 1.76 times (68% versus 42%). To ensure that the gestational age was not considered as interference in the abnormal pathology, the binary logistic regression was used to measure the significant effect of gestational age and placental insufficiency in the IUGR.

The independent variable was considered as an abnormal pathology. The only factor associated with the placental abnormal pathology was the IUGR, and not the preterm, in other words abnormal placenta may increase the prevalence of IUGR for 5.5 times.

However, in comparison with the case and control groups, both the placental pathology and the gestational age were significant, but the regression test showed that the incidence of IUGR was not due to the lower GA, but due to placental insufficiency and the abnormal placental pathology.

Both in the IUGR and preeclampsia, the abnormal placental pathology was higher. The Mantel Haenszel test was run to show that if preeclampsia was interference. Then, it was found out whether or not there was a preeclampsia; the abnormal placental pathology was higher in IUGR. In preeclampsia, all placentas were abnormal, but otherwise, due to the IUGR, the abnormal placentas were significantly higher.

The logistic regression test also showed that in the presence of preeclampsia, IUGR has led to placental abnormalities (about two times), but preeclampsia has not shown such an effect.

**Table 1.** The underlying and general characteristics of the IUGR and normal infants born in Imam Khomeini Hospital Complex in 2016-2017

Characteristics	Normal Group (%)	IUGR Group (%)	P
Type of delivery			< 0.001
Cesarean section	29 (48.3)	59 (98.3)	
Vaginal Delivery	31 (51.7)	1 (1.7)	
Level of Education			0.144
High School	27 (45.0)	13 (22.0)	
Diploma and Associate Degree	25 (41.7)	27 (45.8)	
Bachelor	8 (13.3)	16 (27.1)	
Master's and Ph.D.	0 (0)	3(5.1)	
Number of Gravities			0.283
One	24 (40.0)	33 (55.0)	
Two	21 (35.0)	18 (30.0)	
Three	11 (18.3)	5 (8.3)	
≤ 3	4 (6.7)	4 (6.7)	
Maternal Chronic Diseases	11 (18)	33 (55)	< 0.001
Pregnancy-Related Infections	8 (13.3)	22 (36.7)	0.006
Vaginal infection	1 (1.7)	8 (13.3)	0.032
Urinary tract infection during pregnancy	7 (11.7)	13 (21.7)	0.142
Underlying disease			
Cardiovascular disease	0 (0)	1 (1.7)	0.999
Kidney disease	0 (0)	2 (3.3)	0.869
Liver disease	0 (0)	1 (1.7)	0.999
Diabetes	1 (1.7)	1 (1.7)	1.000
Hypertension	0 (0)	2 (3.3)	0.869
Hypothyroidism	10 (16.7)	7 (11.7)	0.556
History of smoking	1 (1.7)	1 (1.7)	1.000
Preeclampsia history	0 (0)	13 (21.7)	< 0.001
Sex (male)	31 (51.7)	30 (50.0)	0.855
Mother's age (years)	28.78 ± 6.09	29.83 ± 4.54	0.286
Maternal BMI (kg / m 2)	28.32 ± 4.71	28.18 ± 5.11	0.880
Gestational age (weeks)	38.17 ± 2.21	32.34± 3.11	< 0.001
Baby weight (g)	3120.33 ± 540.58	1428.00 ± 610.26	< 0.001
Pregnancy weight gain	11 ± 4.3	10.2 ± 5.7	< 0.101

## Discussion

The findings of this study showed that the majority of pathologic parameters of the placentas in the IUGR samples were significantly different from those of normal ones, the main of which was the reduction of the placental weight ( $P < 0.001$ ), the reduction of the length and width of the macroscopic placenta ( $P < 0.001$ ), placental infarction ( $P < 0.001$ ), villous inflammation ( $P < 0.001$ ), villous fibrosis ( $P = 0.044$ ), villous vascularization reduction ( $P = 0.001$ ), Syncytiotrophoblastic knots ( $P < 0.001$ ), placental necrosis ( $P = 0.048$ ) placenta edema ( $P = 0.003$ ) and villous loss ( $P = 0.012$ ). The results of other studies have indicated that the

most common placental changes include patchy placental infarction, increasing the thickness of the trophoblastic basal membrane, villous fibrosis, terminal villous hypervascularization, decreasing in villous volume, and non-specific inflammatory lesions.<sup>7-9</sup> In the present study, it was shown that these pathogenic changes are not IUGR, and in fact, each of these pathogenic changes can be observed only in a few patients. For example, in our study, the placental infarction, the reduction of the number of villous and the villous fibrosis was considered as the most common pathological changes observed in only half of the patients, while these changes, even in normal samples, were observed in 5 to 23% of the subjects.

**Table 2.** Placental characteristics in IUGR and normal groups in the Imam Khomeini Hospital in 2016-17

Characteristics	Normal Group (%)	IUGR Group (%)	P
Placental weight (g)	587.02 ± 119.15	397.55 ± 192.31	< 0.001
Macroscopic length of placenta	17.42 ± 3.14	14.07 ± 3.31	< 0.001
Macroscopic width	15.09 ± 4.36	11.17 ± 2.32	< 0.001
Macroscopic diameter	3.44 ± 2.51	4.11 ± 3.16	0.203
Placental infarction	5 (8.3)	28 (46.7)	< 0.001
Inflammation of villi	13 (21.7)	35 (58.3)	< 0.001
Villous fibrosis	23 (38.3)	35 (58.3)	0.044
Reduction of Cancio capillary membrane	1 (1.7)	4 (6.7)	0.364
Villous vascularization disorder	1 (1.7)	13 (21.7)	< 0.001
Coriomaniacitis	2 (3.3)	9 (15.0)	0.027
Calcification	8 (13.3)	4 (6.7)	0.224
Syncytiotrophoblastic knots	3 (5.0)	20 (33.3)	< 0.001
Placental necrosis	2 (3.3)	8 (13.3)	0.048
Presence of cytotrophoblast cells	0 (0)	1 (1.7)	0.999
Localized necrosis points	3 (5.0)	10 (17)	0.04
Presence of umbilical vein and artery	59 (98)	60 (100)	0.315
Placenta edema	7 (12)	21 (21)	0.003
Villous loss	0 (0)	6 (10)	0.012

This suggests that although these changes are apparent in most of the patients with the IUGR, they may have a diagnostic value and differentiation among the patients with the IUGR and the normal ones.

However, is the importance is that similar frequencies of pathological changes reported in other studies. In the study of Stallmach et al., Macroscopic lesions such as placental necrosis were observed in 92% of cases.<sup>11</sup> In another study, Salafia and colleagues suggested that villous infarction and fibrosis in the IUGR group were 55% versus 33% of the control group,<sup>10</sup> which was consistent with the results of the study. Sato et al. also observed that infarction and embryonic vascular thrombosis were more prevalent in the IUGR than normal ones.<sup>12</sup> The results of Zhonghua and colleagues showed that the low birth weight of the IUGR neonates compared to the normal ones was due to the decrease in the level of placental villous and capillary level of the embryo.<sup>13</sup> In the study done by Aherne, in the placental premature, the decrease in size and volume of the placenta was quite evident. In addition, decreasing the placenta parenchyma, the decrease in average villi surface, especially the capillary surface, was quite evident in IUGR cases, which was consistent with the current study.<sup>14</sup>

According to the Thorne study, there were two categories of placentas if there were some abnormal parameters in placentas then they were considered as an abnormal one. In the present study, it was used the same category and then the comparison was done between the two groups. Comparing the groups together, in the IUGR, the frequency of abnormal pathology is significantly more (41-68% versus 42% -25) (P = 0.003 and IUGR 1.76, respectively) (P < 0.001).

### Conclusion

In a general conclusion, it can be said that, firstly, a large part of the macroscopic and histologic pathological changes are detectable in the IUGR sample, which is significantly more common than normal, although not pathognomonic, and the same is true in the similar studies. In the vast majority of studies, there was no control group and, given the high cost, these limitations were created and descriptive studies were conducted. In our study, the advantage was having a control group that has produced a higher level of evidence. Our study limitation was lower GA. In the future, with the wider studies, we would eliminate this limitation, and certainly better results in studies can be achieved by eliminating this disruptive effect.

## Conflict of Interests

Authors have no conflict of interests.

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## Original Article

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## Investigating the Relationship between Resiliency and Psychological Well-Being of Nurses in ICU & NICU of University Hospitals of Shiraz in 2012

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### ABSTRACT

**Background:** Human resources, especially nurses, have a significant role in health care services due to the nature of their service and their direct relationships with patients. In this regard, nurses are encountered with higher stressful factors resulting from their responsibilities in providing ease and comfort for patients. Resiliency is one of the main purposes of health promotion and is considered to be a protective agent. Moreover, psychological well-being refers to striving for perfection in order to realize the potential and real individual talents and abilities. This study aims to determine the relationship between resiliency and psychological well-being of nurses in ICU & NICU of Shiraz in 2017.

**Methods:** This is a descriptive-correlational research. The statistical society consists of 150 nurses working in ICU & NICU of university hospitals in Shiraz. The tools of data collection were psychological well-being and resiliency questionnaires. The collected data were analyzed via SPSS software and descriptive-inferential statistics.

**Results:** According to the Table, 86% of the subjects are females, and 14% are males; 53.4% of them are single, and 44.6% of them are married; 84% of them have bachelor degree, and 16% of them have master degree. Average age and work experience of the subjects are 31.38 and 4.79 years, respectively. Average resiliency and psychological well-being scores of the nurses are estimated to be  $66.03 \pm 16.72$  and  $119.55 \pm 24.35$ , respectively. Their significant relationship was approved by Pearson test  $P = 0.002$ .

**Conclusion:** The results indicated that resiliency and psychological well-being of the nurses have significant relationship; with an increase in resiliency, their psychological and mental health increases. Therefore, some programs and interventions are recommended for nurses in order to improve their resiliency, and consequently, promote their psychological well-being.

## Introduction

Human resources are the essential components of health care system. Their key roles are highlighted in preservation and development of social health. The direct and close relationship of human resources with individual well-being is one of the most significant sustainable development areas in human societies.<sup>1</sup> One of the resources is the group of nurses which form 70% of health care team. Therefore, their well-being is of great importance.

Health has always been an important issue in human history. However, its physical dimension has been mostly focused on, not other psychological dimensions.<sup>2</sup> Psychological well-being refers to sufficient dominance and skill in relation with the surrounding environment, especially love, work, and entertainment.<sup>2</sup> Positive psychology has attracted the attention of many researchers during the last few decades.<sup>3</sup> This viewpoint emphasizes capabilities and belongings of an individual; it also believes that health, positive psychological well-being and understanding its nature can improve life quality and actualize the latent talents.<sup>4</sup> Psychological well-being refers to striving for perfection in order to realize the potential and real individual talents and abilities.<sup>5</sup>

One of the main structures which affect psychological well-being is resiliency.<sup>6</sup> Nowadays, resiliency has a specific role in psychological well-being areas and has been introduced in researches and theories for more than two decades. In fact, resiliency is capacity and ability of a person in endurance against difficult conditions along with preservation of psychological well-being and its improvement.<sup>7</sup> Moreover, resiliency is a process, ability, or consequence for positive compatibility with threatening and complex situations.<sup>8</sup> It also refers to active and constructive participation in the surrounding environment which creates an ability for a biological-psychological balance against

dangerous situations, and provides a successful compatibility for the person. Resiliency is one of the main purposes of health promotion and is considered to be a protective agent.<sup>6</sup> Resilient people not only survive, but also become successful. The ability to survive and become dominant over difficulties is exactly the main definition of resiliency. People with high levels of resilience have higher self-confidence and enjoy better psychological compatibility in comparison with people with low levels of resiliency.<sup>9</sup> Therefore, by enhancing resiliency, people can resist and overcome stressors, anxieties and factors that cause many of their psychological problems.<sup>10</sup>

Nursing is a kind of job which is always encountered with numerous stressful factors in the workplace. The nature of this job is interwoven with a combination of roles related to technical activities, professional skills, human relationships, and empathy. Each of these items are followed by multiple responsibilities for the nurse. In this regard, Cahudry believes that nursing is one of the stressful professions. National Institute of Health (NIH) among 130 occupations, nurses ranked 20th in referral to physicians for problems related to physical and mental health problems.<sup>11</sup> Therefore, it seems that nurses are always exposed to physical and psychological disorders and negative stresses due to the sensitivity of their occupational responsibilities and their continuous interaction with patients.<sup>12</sup>

The researcher is now trying to investigate the relationship between resiliency and psychological well-being in nurses of the ICU & NICU as an important step towards improving their health. This study aims to determine the relationship between resiliency and psychological well-being of nurses in ICU & NICU of Shiraz.

## Materials and Methods

This is a descriptive-correlational research. The statistical society consists of all the



nurses working in ICUs (NICU, Dialysis, and CCU) of university hospitals in Shiraz. The research environment is university hospitals in Shiraz including Namazi Hospital. Entrance criteria of the research are nurses working in ICUs & NICU, 2 years work experience, conscious consent about participating in the research, and bachelor degree or higher in nursing; the exit criteria is a history of family problems, and the removal criteria is refusal from filling the questionnaires. The samples were selected via simple random method and sample size was estimated to be 150 nurses based on G\*Power3 software ( $\alpha = 0.05$ , power = 80%, effect size = 0.56).<sup>11</sup> Before executing the research, the proposal was approved in graduate program and ethics committees of Yazd University of Medical Sciences with ethical code of IR.SSU.REC.1296.145. A list of working nurses was prepared by referring to nursing office of the province and the qualified nurses were identified. Afterwards, the researchers referred to the qualified nurses and explained the proposal form them in order to take a written and conscious consent. After further explanation of research objectives, psychological well-being and resiliency questionnaires were distributed among the nurses in order to be filled in one week. The questions and the way of completing the questionnaires were clarified. Reef Psychological Well-Being Questionnaire was used for data collection. Reef had designed this questionnaire in 1980 including 54 questions and 6 sub-scales. In further analysis, shorter forms of questions 84, 54, and 18 were also provided. In the present study, a version of the questionnaire with 54 questions and 6 sub-scales was used. Sub-scales of this questionnaire are: 1- self-acceptance, 2- positive relationships, 3- independency, 4- dominance over the environment, 5- purposefulness in life, and 6- personal growth. Each question includes a 6-point scale ranging from 1 to 6 (strongly agree, somewhat disagree, disagree, agree, somewhat agree, and strongly agree). In this

questionnaire, some questions are scored directly, and some of them are scored in reverse. In order to calculate the score of each sub-scale, a total of all the scores of the questions related to that sub-scale are calculated. By adding the scores of 54 questions, the score of psychological well-being can be calculated. Higher score indicates better psychological well-being. Content and structural validity were approved in different studies.<sup>12</sup> Each of the 6 sections include 9 questions with 6 minimum and 56 maximum scores. In the present study, Conner-Davidson resiliency questionnaire is used. This questionnaire consists of 25 statements. The answers are scored based on Likert scale from 0: never to 4: almost always. In order to calculate total score of the questionnaire, scores of all the questions are added. The final score will range from 0 to 100. The higher the score, the higher the resiliency of the respondent is, and vice versa. Cut-off score of this questionnaire is 50. In other words, a higher than 50 score indicated people with acceptable resiliency. The level of resiliency increases with increase of cut-off score, and vice versa. Validity and reliability of this questionnaire are approved in Iran.<sup>13</sup> SPSS software version 20, descriptive statistics (mean, variance, standard deviation, and frequency), independent T-test, variance analysis, and Pearson correlation test are used for data analysis. It should be noted that normal distribution of the data were analyzed via Kolmogorov-Smirnov test ( $P = 0.05$ ).

## Results

According to the Table, 86% of the subjects are females, and 14% are males; 53.4% of them are single, and 44.6% of them are married; 84% of them have bachelor degree, and 16% of them have master degree. Average age and work experience of the subjects are 31.38 and 4.79 years, respectively. Average resiliency score of the nurses is estimated to be  $66.03 \pm 16.72$  with minimum obtained score of 20 and maximum 99.

**Table 1.** Mean and standard deviation of total score of psychological well-being and its dimensions

Psychological well-being	Mean	Standard Deviation	Minimum Score	Maximum Score	Minimum Score of the Questionnaire	Maximum Score of the Questionnaire
Self-acceptance	17.32	5.75	6	24	6	54
Positive relationships	16.94	3.57	7	22	6	54
Independency	24.57	4.8	16	34	6	54
Dominance over the surrounding Environment	17.82	3.25	11	29	6	54
Purposefulness in life	19.17	6.21	6	26	6	54
Individual promotion	23.73	5.31	13	35	6	54
Total psychological well-being	119.55	24.35	73	158	36	324

The results of statistical independent T-test and Pearson test indicated that average resiliency score has no significance difference or relationship with demographic information (gender, marital status, education, age, and work experience) ( $P > 0.05$ ).

Mean and standard deviation of total psychological well-being are estimated to be  $119.5 \pm 24.35$  which are presented in Table 1.

The results of statistical independent T-test and Person indicated that total score of psychological well-being has a significant difference with demographic information only in education level ( $P = 0.003$ ,  $T = 3$ ). Therefore, psychological well-being score of bachelor nurses is estimated to be  $115.29 \pm 25.87$ , and score of master nurses is estimated to be  $127.82 \pm 18.72$ . No significant difference was observed regarding gender, marital status, age, and work experience ( $P > 0.05$ ).

The results of Pearson statistical analysis indicated that resiliency and psychological well-being have direct relationship and correlation. With an increase in mean score of resiliency, psychological well-being increases

as well (Table 2).

### Discussion

The results of analysis indicated that in terms of demographic information, most of the subjects were females and single with bachelor degree. According to the results, mean and standard deviation of resiliency score are estimated to be  $66.03 \pm 16.72$ . Since minimum score is 0, maximum score is 100, and cut-off score is 50, it can be said that resiliency of the subjects is slightly higher than average level. However, it is so far from optimal resiliency. Other studies indicated average resiliency of the nurses. Guo et al. conducted a study on burnout and its relationship with resiliency in nurses; they reported average resiliency for the nurses which indicates the need for further studies in this field.<sup>14</sup> Moreover, Amini et al. analyzed the relationship between resiliency and occupational burnout of the nurses. They concluded that mean and standard deviation of resiliency was  $61.52 \pm 16.26$ . Minimum resiliency score of the nurses was 23, and maximum score was 97.<sup>15</sup>

**Table 2.** The relationship between mean and standard deviation of resiliency score, and mean and standard deviation of psychological well-being score

Pearson correlation	Resiliency	Self-Acceptance	Positive Relationships	Independency	Dominance Over the surrounding environment	Purposefulness in Life	Individual Promotion	Total Psychological Well-Being
Sig (2-tailed)		0.228	0.242	0.166	0.115	0.169	0.187	0.255
N		0.005	0.003	0.042	0.161	0.038	0.022	0.002
		150	150	150	150	150	150	150

Algerin V et al., in their analysis of nurses' occupational stress, compatibility, and resiliency, indicated resiliency score of the nurses to be  $72.68 \pm 12.79$  which is considered to be average.<sup>16</sup> Pourafzal et al. reported resiliency score of nursing students to be  $66.96 \pm 12.79$ . It indicates that nearly 90% of the students obtained high resiliency score which is so promising with regard to their major.<sup>17</sup> Ren et al. claimed that mean and standard deviation of nurses' resiliency in their study is  $59.99 \pm 13.59$  which is evaluated to be significantly lower than resiliency level of ordinary people.<sup>18</sup>

Resiliency score resulting from this study had no significant difference with other groups regarding demographic information. Most of the papers in the review of literature have focused on gender which indicated no significant difference. Khodabakhshi et al. conducted a study on occupational burnout of the nurses based on psychological resiliency which indicated that males have higher resiliency in comparison with females, but this difference is not significant.<sup>19</sup> Vetter et al. also claimed that there is no significant difference in resiliency of male and female students.<sup>20</sup>

According to the results, psychological well-being score is estimated to be  $119.55 \pm 24.35$  which is indicative of low psychological well-being regarding minimum 36 and maximum 324 scores. It is so far from optimal and acceptable psychological well-being. Furthermore, regarding different dimensions of psychological well-being, it is observed that self-acceptance, positive relationships, dominance over the surrounding environment, and purposefulness in life obtained low scores, but independency and individual promotion obtained average scores. Similar studies have evaluated psychological well-being of the nurses to be average. Zadhasan et al. estimated the scores of different dimensions of psychological well-being in nurses. The score of purposefulness in life is  $31.44 \pm 9.64$ , self-acceptance is  $31.67 \pm 10.20$ , positive relationships is

$31.50 \pm 9.68$ , independency is  $30.44 \pm 8.34$ , dominance over the surrounding environment is  $30.15 \pm 9.22$ , individual promotion is  $34.27 \pm 9.99$ , and total score of well-being is  $189.49 \pm 50.11$ . It should be noted that they used Reef questionnaire including 84 questions.<sup>21</sup> Babalola et al. reported a positive psychological well-being for 84.5% of the nurses.<sup>22</sup>

According to the results of this study, total score of psychological well-being has a significant difference with demographic information only in education level, so that bachelor master nurses had obtained higher scores in comparison with bachelor nurses. Van der Heijden believes that work place conditions has the highest relationship with psychological well-being of nurses.<sup>23</sup> Yousefi and Khayatian claimed that there is no significant difference between psychological well-being of nurses working in cancer, obstetrics and gynecology, and internal wards of the hospital.<sup>24</sup> Moreover, Kavosi et al. reported no significant difference between psychological well-being of nurses working in different wards of the hospital.<sup>25</sup> Arafa believes that one of the predictors of psychological well-being in nurses is work experience.<sup>26</sup>

The results of Pearson test indicated that resiliency and psychological well-being are correlated, so with an increase in the score of resiliency, mean score of psychological well-being increases. These results are consistent with the reported results of Souter et al.<sup>27</sup> and Salvatore et al.<sup>28</sup>

Psychological well-being of people with high resiliency is better than people with low resiliency. Furthermore, the reported results of Mortazavi's study indicate significant and average relationship between resiliency and psychological well-being. Jackson et al. (2007) also stated that nurses can have the ability to resist psychological pressures using resiliency as a tool.<sup>29</sup>

## Conclusion

According to the results, there is a significant

relationship between psychological well-being and resiliency, so that with an increase in resiliency, psychological well-being increases as well. Therefore, some strategies should be taken into consideration in order to improve nurses' resiliency, and as a consequence, improve their psychological well-being. In this way, their mental health can be promoted.

### Conflict of Interests

Authors have no conflict of interests.

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## Original Article

<http://wjpn.ir>

## The Effect of Nursing Residency Program on the Clinical Competency of Novice Nurses Working in the ICU & NICU from the Viewpoint of Head Nurses

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### ABSTRACT

**Background:** The ultimate goal of nursing is to ensure the recovery and health of patients through providing high quality care. However, novice nurses who are working in clinical settings need help and are not aware of the system's expectations. In this study, we investigated the effect of a nursing residency program on the clinical competence of novice nurses working in the intensive care units of Yazd governmental hospitals from the viewpoint of head nurses.

**Methods:** In this interventional study, the clinical competence of 31 novice nurses was studied. The participants were randomly assigned into two groups of experimental and control. The nursing residency program consisted of 20 hours of training, support, and counseling in eight months for the experimental group. Data gathering tool in this study was a clinical competence questionnaire for novice nurses. The head nurses filled out the questionnaires before, immediately after, and three months after the training course. Data were then analyzed by SPSS (version 22) and running independent t-test, and repeated analysis of variance.

**Results:** According to the viewpoint of the head nurses, The clinical competence scores of novice nurses working in the ICUs & NICU, were  $(150.15 \pm 23.1)$ ,  $(174.35 \pm 2.75)$ , and  $(168.3 \pm 32.45)$  for the experimental group and  $(134.75 \pm 24.75)$ ,  $(116.05 \pm 29.7)$ , and  $(146.3 \pm 22)$  for the control group before, immediately after, and three months after the intervention, respectively. The difference between mean scores of two groups was not significant before the intervention and three months later, although of the mean scores of two groups differed significantly before the intervention and immediately after the intervention. With respect to clinical competence scores, the different between two groups was significant in three stages.

**Conclusion:** The results on the efficacy of nursing residency program in improving the clinical competence of novice nurses working in the ICUs & NICU were positive from the viewpoint of heads nurses. Accordingly, we propose execution of programs related to all issues over which nurses need to upgrade their clinical competencies and for the novice nurses of other parts of the hospital.

## Introduction

The ultimate goal of nursing is to ensure the recovery and health of the patients by providing high quality care. However, novice nurses who are working in clinical settings need help and are not aware of the system's expectations. The managers are not aware of novice and inexperienced nurses' level of competence and this is considered as one of the major problems in the clinical environment.<sup>1</sup> Nevertheless, the number of novice nurses who take care of patients in hospitals, due to lack of nursing staff, is significant.<sup>2</sup> In order to respond appropriately to requests from the hospitalized patients, novice nurses must have enough knowledge and skills.<sup>3</sup> In a study on nursing professionalism criteria, Azimian et al. (2013) concluded that, new graduates lacked the necessary skills in logical thinking, time management, communication skills, and group work according to the viewpoint of nursing educators.<sup>4</sup> One of the important concepts emphasized in the nursing education system is clinical competence.<sup>5</sup> Clinical competence is a combination of ethics and values, which is reflected in a nurse's knowledge and skill. Honesty, care, communicational skills, and compatibility are recognized as the indications of individual competence.<sup>6</sup> Education-based competence is an evident and distinct term, but there is no agreement on the definition and measurement criteria of clinical competence.<sup>7,8</sup> In fact, competence is an abstract concept and situation in which incompetence is absent.<sup>9</sup> In 1984, Benner defined competence as the ability to perform the nursing duties along with the knowledge to achieve desirable results.<sup>10</sup> Motahhari et al. defined clinical competence as the contemplative and continuous use of the technical skills, knowledge, clinical reasoning, emotions, and values in clinical settings.<sup>11</sup> In other definitions and for all health care providers, competence is evaluated through safety care performed by the nurses and their beliefs.<sup>12</sup>

The comprehensive concept of competence is the combination of general competencies, discipline knowledge, and professional performance.<sup>13</sup> According to Bagheri et al., existence of competence in nursing led to safe performance and high quality care services, which in turn resulted in patient satisfaction, professional development, and reduced health costs.<sup>14</sup> It should also be noted that patients admitted to ICUs & NICU have dysfunction in their vital organs and therefore simultaneous determination of the priorities, speed, and precision are crucial in performing the nursing care services. Consequently, the nurses working in these wards should have high clinical competence and be able to determine the priorities with the least amount of time.<sup>15</sup> To hit this target, they must have the power of critical thinking, creativity, competence, and analysis based on the problem-based learning and research capability.<sup>16</sup> The induction program implies training of the newly graduated nurses by providing the occupational and clinical information to be employed in the hospital setting.<sup>17</sup> The induction program is then considered as a mediating factor between the clinical competence and environment adaptation for novice nurses.<sup>18</sup>

Nowadays, no efficient, scientific, and up-to-date induction program exists for the novice nurses and in some cases qualification is not considered serious due to lack of working forces. Even in some cases, despite dissatisfaction of the head nurses about provision of work forces in the ICUs & NICU, novice nurses were employed in these wards. Even throughout Australia, no agreement exists on the standard of passing the transition process and induction programs for the nurses.<sup>19</sup>

A review by Edward et al. (2015) showed that the support strategies, regardless of the type of support, had useful effects in improving the process of transition from student life to professional life for both nurses and their managers.<sup>20</sup> Bridging this gap in the transitional phase is achieved by optimized

familiarization of the novice nurses to obtain clinical competence.<sup>14,21</sup> Therefore, common collaborations and plans between faculty departments and the clinical group of hospitals can reduce the existing gaps in academic education and clinical expectations.<sup>22</sup> Many studies were conducted on clinical competence, but most of them were based on nursing process. Clinical competence dimensions were also studied according to investigation, determination, planning, implementation, and evaluation of the nursing process stages.<sup>23,24</sup> In Iran, Motahari et al. (2008) investigated the clinical competence in five hospitals of Booshehr city and reported that the clinical competence of nurses were unfavorable in some areas such as education, guidance, and quality assurance.<sup>11</sup> Nursing instructors should further evaluate the effects of novice nurses' education on the patients' outcomes in order to assess the value of this program in the transitional phase.<sup>25</sup> Of course, it should be noted that training and supervision are important skills and nurses with responsibilities in departments are not necessarily always good educators to adopt this role.<sup>26</sup> Evidence suggests that novice nurses should be supported in the induction programs and throughout the transition phase.<sup>27</sup> However, more research is required to select the best evaluation methods for various dimensions of clinical competence.<sup>10</sup>

Considering the lack of nurses and the necessity to ensure the clinical competence of nurses working in ICUs & NICU, one of the suggestions is the implementation of nursing residency program that includes occupational, behavioral, supportive, and counseling training and practical classes. Some studies were conducted on the clinical competence of nurses or educational courses and their impact on clinical competence in Iran, although their approach was different from the current research. Moreover, we proposed a multilateral program in which education and support were integrated and nurses were not left unattended in this transition period; from student life to professional life. One of the

evaluation factors in this realm is the effectiveness of the program from the viewpoint of supervisors and direct head nurses. So, we evaluated the effect of a nursing residency program on the clinical competence of nurses working in ICUs & NICU of hospitals affiliated to Shahid Sadoughi University of Medical Sciences in Yazd, Iran.

### **Materials and Methods**

In this semi-experimental study, all of the undergraduate nurses working in ICU, PICU, CCU, transplantation, neurosurgery, dialysis, burn ICU, NICU, and emergency care units of Yazd Educational Hospitals for less than two years were included. The exclusion criteria included having non-continuous B.S degree in other fields such as anesthetist technician and paramedic diploma, as well as long-term leave such as maternity leave or part-time work in the ICU & NICU.

**Data collection tool:** In order to investigate the clinical competency, a two-part questionnaire was used, the first part of which was related to personal information (age and gender) and the second part was about the competency inventory for registered nurse (CIRN) developed by Lio et al. The Persian version of nurse's competency questionnaire was translated by Elham Ghasemi et al.<sup>28</sup> This questionnaire comprises of seven dimensions, including clinical care (10 items), leadership (9 items), interpersonal relationships (8 items), ethical and legal performance (8 items), professional development (6 items), coaching and training (6 items), the tendency toward conducting research, and critical thinking (8 items). The questionnaire's rating and interpreting method is based on a five-point Likert scale, so that zero means lack of competence (never), 1 almost lack of competence (rare), 2 moderate competence (sometimes), 3 more than moderate competence (often), and 4 indicates a high degree of competence (always).

In this study, the range of clinical competence score was 0-220. In this regard,



the total score within the range of 165-220 was considered as a high competence, a score in 110-165 showed moderate competence, and a total score of less than 110 indicated low competence. The Cronbach's alpha of the total Persian questionnaire is 0.967, 0.676 for the professional progress dimension, and 0.873 for the clinical care dimension.<sup>28</sup> The reliability of the questionnaire was also calculated and confirmed (0.93) in this study. Before starting the intervention, the researcher distributed the clinical competency questionnaire among the head nurses to evaluate the novice nurses and fill the forms. Then, the completed questionnaires were analyzed and the nurses with moderate (total score of 110-165) or poor (total score less than 110) competence scores were selected to participate in this study.

Three educational hospitals in Yazd, affiliated to Shahid Sadoughi University of Medical Sciences, were considered. Novice nurses of one hospital were regarded as the experimental group and those at the other hospitals were considered as the control group. At the first session, the lecturers explained the content of the program as well as the date and time of the classes for the the experimental group.

The researcher guided, supported, evaluated, and backed the novice learners and had a modeling and trusting role who answered the participants' questions throughout the study. From the beginning of the classes up to three-month after the intervention, which lasted eight months, the researcher was considered as a consultant and link between the faculty members and nurses.

Teachers used the learning methods based on simulation (role playing and learning skills), lectures, and problem-based teaching. At the end of the intervention, head nurses assessed the clinical competence of the novice nurses working in their ward using the clinical competence questionnaire. Three months later, in order to evaluate the effects of training, the clinical competence questionnaire was again completed by the head nurses. After

collecting the data, results of clinical competency questionnaires were analyzed using SPSS (version 22) and running descriptive and inferential statistical tests.

Ethical considerations in this study included obtaining the permission from the Ethics Committee (IRCT code: 121678), obtaining permission from the hospital authorities, and obtaining written informed consents from the participants of the study, prior to the clinical study. We further considered confidentiality of information and the participants' willingness to start and continue their collaboration.

## Results

In this study, after determining the clinical level, 60 novice nurses working in ICUs & NICU of hospitals as well as 32 nurses (19 controls and 17 test groups) with moderate and poor clinical competence were selected. Among this population, four participants of the experimental group were excluded since they were on maternity leave and had more than two sessions of absence, which in this case, the training and supportive program had to be administered for 13 participants of the experimental group. In our study, 25 (78.1%) novice nurses were female and seven (21.9%) were male. The highest relative frequency of female nurses was in the control group (73.7%), while this rate was 84.6 percent in the control group and the two groups were not significantly different in terms of gender ( $P = 0.671$ ). The mean score of clinical competence in the first stage was  $134.75 \pm 24.75$  for the control group and  $150.15 \pm 23.1$  for the experimental group, which was not statistically significant ( $P = 0.081$ ). The comparison of the mean scores of different dimensions of clinical competence in two groups before the intervention is shown in tables 1-4.

The mean of clinical competence scores was  $116.05 \pm 29.7$  in the control group and  $174.35 \pm 2.75$  in the experimental group immediately after the intervention, which was statistically significant ( $P = 0.001$ ).

**Table 1.** Comparison of the mean scores of different aspects of clinical competence in two groups before the intervention

Clinical competence		Maximum score	Control group Mean $\pm$ SD	Experimental group Mean $\pm$ SD	P
From the viewpoint of head nurses	Clinical care	40	24.4 $\pm$ 5	28.4 $\pm$ 3.5	0.02
	Leadership	36	22.05 $\pm$ 4.29	24.3 $\pm$ 4.32	0.178
	Interpersonal relationships	32	19.28 $\pm$ 3.68	22.4 $\pm$ 3.68	0.026
	ethical and legal performance	32	20.4 $\pm$ 3.12	24.4 $\pm$ 3.52	0.002
	Professional progress	24	14.46 $\pm$ 2.82	15.6 $\pm$ 3.54	0.321
	Coaching and training	24	14.64 $\pm$ 2.94	14.64 $\pm$ 3.18	0.994
	Having tendency toward doing research and critical thinking	32	19.52 $\pm$ 3.44	20.64 $\pm$ 3.92	0.385
Total		220	134.75 $\pm$ 24.75	150.15 $\pm$ 23.1	0.081

The comparison of the clinical competence mean scores in different dimensions after intervention for the two groups is represented table 2. Results showed significant differences in all dimensions in two groups.

In the third stage, the mean of clinical competence scores was  $146.3 \pm 22$  for the control group and  $168.3 \pm 32.45$  for the experimental group; however, the difference between two groups was not statistically significant ( $P = 0.032$ ). Comparison of the mean scores of different dimensions of clinical competence in two groups three months after the intervention is indicated in table 3. Results showed significant differences in some dimensions.

According to table 3, the trend of changes in the control group was not significant but in the experimental group it was significant ( $p$ -value  $< 0.001$ ).

## Discussion

In the current study, we examined the effect

of nursing residency program on the clinical competence of novice nurses. Based on the findings, before the intervention, the nurses' clinical competence scores from the viewpoint of head nurses were moderate in both the control ( $134.75 \pm 24.75$ ) and the experimental ( $150.15 \pm 23.1$ ) groups. No significant statistical difference was observed between the clinical competence scores of the two groups. Prior to the intervention, the clinical competence of the novice nurses from the viewpoint of head nurses was moderate for the clinical care dimension but it was weak for the other dimensions, including leadership, interpersonal relationships, ethical and legal performance, professional development, coaching, and education, tendency to research and critical thinking. It seems that novice nurses were more trained in the clinical care dimension than in the other clinical competence dimensions; so, they need more education in other areas, which was also confirmed by the head nurses in this study.

**Table 2.** Comparison of the mean scores of different aspects of clinical competence in two groups after the intervention

clinical competence		Maximum score	Control group Mean $\pm$ SD	Experimental group Mean $\pm$ SD	P
From the viewpoint of head nurses	Clinical care	40	20 $\pm$ 5.8	32.8 $\pm$ 1.6	$< 0.001$
	Leadership	36	17.82 $\pm$ 5.4	27.99 $\pm$ 0.99	$< 0.001$
	Interpersonal relationships	32	16.08 $\pm$ 4.48	25.36 $\pm$ 1.6	$< 0.001$
	ethical and legal performance	32	19.2 $\pm$ 3.84	26.56 $\pm$ 1.12	$< 0.001$
	Professional progress	24	13.26 $\pm$ 3.54	18.96 $\pm$ 0.42	$< 0.001$
	Coaching and training	24	12.78 $\pm$ 2.82	18.18 $\pm$ 0.72	$< 0.001$
	Having tendency toward doing research and critical thinking	32	17.04 $\pm$ 4.72	24.56 $\pm$ 0.72	$< 0.001$
Total		220	116.05 $\pm$ 29.7	174.35 $\pm$ 2.75	$< 0.001$

**Table 3.** Comparison of the mean scores of different aspects of clinical competence in two groups three months after the intervention

Clinical competence		Maximum score	Control group	Experimental group	P
			Mean ± SD	Mean ± SD	
From the viewpoint of head nurses	Clinical care	40	26.2 ± 4.8	30.9 ± 6	0.022
	Leadership	36	23.4 ± 4.14	27.9 ± 5.31	0.014
	Interpersonal relationships	32	21.12 ± 3.04	25.12 ± 3.92	0.003
	ethical and legal performance	32	22.8 ± 2.24	26.72 ± 4	0.005
	Professional progress	24	15.4 ± 2.52	17.46 ± 4.44	0.110
	Coaching and training	24	16.2 ± 2.28	17.04 ± 4.44	0.531
	Having tendency toward doing research and critical thinking	32	21.8 ± 3.92	23.2 ± 5.84	0.278
	Total	220	146.3 ± 22	168.3 ± 32.45	0.032

In the present study, the head nurses assessed the clinical competency level of novice nurses immediately after the intervention and found that it was poor for the control group, but high for the experimental group. The difference between the scores of the two groups considering clinical competence was significant. According to head nurses and regarding the dimensions of clinical care, interpersonal relationships, ethical and legal performance, professional development, coaching and education, tendency to research, and critical thinking, the control group was at the moderate level but the experimental group was at the high level and the difference between the two groups was significant. In general, after the intervention, head nurses found that the clinical competence level was moderate in the control group and high in the experimental group, which showed a significant difference. Therefore, based on our results, the nursing residency program led to improvement of

clinical competence in the novice nurses and this change was evident in all dimensions. Trepanier (2012) regarded the support program as an experienced trainer for the novice nurses that included direct teaching and clinical work, experiencing different wards, and conducting emotional expression sessions. Trepanier believed that coaching and counseling helped the transition phase from the student to occupational life.<sup>29</sup>

Verret and Lin (2016) reported that the presence of a trainer in novice nurses' education programs and facilitate stronger relationships among employees.<sup>30</sup> Wilgis and McConnell (2008) investigated the conceptual map as an educational strategy for improving nurses' critical thinking skills during an introduction program. They studied 14 novice nurses and concluded that participants' scores improved from 14.071 to 16.428 during the program.<sup>31</sup>

Previous studies showed that the induction programs varied in terms of content and length of course in different treatment centers.

**Table 4.** The trend of changes in the total score mean of clinical competency announced by head nurses in two groups

Group	Before the intervention	Immediately after the intervention	Three months after the intervention	P
	Mean ± SD	Mean ± SD	Mean ± SD	
Control	134.75 ± 24.75	116.05 ± 29.7	146.3 ± 22	0.002
Experimental	150.15 ± 23.1	174.35 ± 2.75	168.3 ± 32.45	0.03
Total	141.35 ± 24.75	139.7 ± 36.85	155.1 ± 28.6	0.041
P	0.081	< 0.001	0.032	

Repeated measures test & Independent T test

Edwards et al. (2015) found that supporting strategies had beneficial effects on the transition of nurses from the non-professional to professional life. Of course, in most studies, regardless of the type of support, these programs had a positive overall effect, but future studies with good designs are necessary for reliable and valuable results.<sup>20</sup> Rush et al. (2013) concluded that the presence of an appropriate program for novice nurses could improve skills.<sup>32</sup> In a study by Beyea et al. (2010), the results showed that the simulation and support programs for novice nurses provided an environment for assessing the competence and recognition of educational needs.<sup>33</sup> Henderson et al. (2015) and Baldwin et al. (2016) concluded that the major problems of novice nurses in the first year were related to communication with patients and staffs as well as their lack of staff support. In this regard, induction programs and support of experienced staffs may be effective for nurses' roles.<sup>34</sup> In most studies, this program was a combination of classes and workshops, with both general and specialized lessons, along with learning opportunities, discussions, and scenarios. The following topics are presented and discussed in this program: nursing process, critical thinking, professionalization, communication skills, ethical and legal issues, and conflict management.

In general, the trend of changes in clinical competence scores of the control group from the viewpoint of head nurses showed that the scores were moderate and statistically significant. In other words, immediately after the intervention, the scores in the control group decreased significantly. Moreover, the difference in the experimental group was also significant. It is thus noteworthy that in the experimental group, the clinical competency scores immediately after the intervention were higher than the scores obtained three months later. It should also be mentioned that the control and experimental groups were in different hospitals and not exposed to each other. In a nutshell, we can conclude that the

novice nurses have higher eagerness to implement their leanings at the beginning of their graduation, but sometimes later their eagerness reduce due to the working shifts, involving in the working environment, and the impact of colleagues.

It seems that head nurses gave lower scores to the clinical competence of the novice nurses of the control group immediately after the intervention than before the intervention. This finding can be due to high expectations of head nurses from the novice nurses after the intervention. However, three months after the intervention, when the novice nurses improved their skills and clinical competencies during work, head nurses rated them better. Meanwhile, the head nurses observed significant changes in the clinical competence of the experimental group and considered higher scores for them, but over time, the effect of these changes was dimmed. So, the head nurses revised the scores and gave lower scores to the clinical competence of their novice nurses.

### Conclusion

In this study, the novice nurses working in ICUs & NICU of both control and experimental groups experienced positive changes in their clinical competence, which was expected due to the initial in-service training in the control group and the impact of colleagues. However, this research showed that the trend of changes for the mean of clinical competence scores, from the viewpoint of head nurses, was different and statistically significant between the experimental and control groups. In general, we suggest further studies to examine the actual efficacy of this program.

**Limitations:** Among the study constraints, we can mention the small number of samples that determines the need for more extensive studies in several centers. In addition, evaluation of the intervention in a longer time was not possible due to time constraints.

### Conflict of Interests

Authors have no conflict of interests.

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Original Article

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## Evaluation of the Oral Propranolol Effect on Retinopathy of Prematurity: Randomized Clinical Trial

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### ABSTRACT

**Background:** Despite rapid advances in neonatal care in both industrialized and developing countries, retinopathy of prematurity (ROP) still remains the main reason of infants' blindness and visual impairment. There is some evidence that Beta-adrenergic system may be involved in infants' ROP. Considering that few studies have been done on effects of oral propranolol on prevention retinopathy pre maturity in premature infants, we designed this clinical trial to investigate the effects of oral propranolol on infants.

**Methods:** This study is a clinical trial in which 27 premature infants with gestational age greater than 27 weeks and afflicted with retinopathy pre maturity grade 1 and 2 hospitalized at Shahid Sadoughi hospital of Yazd city. They were randomized to receive 0.5 mg/kg/12hours oral propranolol or control. Premature infants were controlled and hospitalized at NICU and their BP, heart rate and Hyperemesis gravidarum (H.G) were monitored.

**Results:** Twenty-four newborns were included, 12 in the control group and 12 in the propranolol group and 3 of infants were excluded from the study (2 of propranolol group and 1 of control group) 81.34 percent of treatment group were recovered and healed compared to 66.7 percent of control group which not significantly difference.

**Conclusion:** Some studies about Beta Blockers' recessive effect on ROP have been done which in most recovery was the result but some serious side effects were also reported. In this study there was no positive effect on recovery of ROP but the percent of recovery was slightly higher in propranolol group compared to control group. Fortunately there were no reports of side effects this time due to usage of lower dose propranolol. Recent studies state that propranolol cannot be used as a good alternative to other treatments but it can prevent the disease from getting worse. We can also reduce its side effects by changing the dosage.

## Introduction

Despite rapid advances in infant care, in both industrialized and developing countries, ROP remains the main cause of blindness and vision impairment in infants.<sup>1</sup> The incidence of the disease is associated with birth weight and gestational age (GA), and, it is more prevalent in premature and very low weight newborns.<sup>2</sup> The risk factors associated with ROP are not fully understood, but prematurity and ROP at birth represent major factors. Oxygenation, respiratory distress, apnea, bradycardia, heart disease, infection, hypercarbia, acidosis, anemia, and need for transfusion are considered as relevant factors. Generally, GA, lower birth weight and sick newborns are associated with a higher risk for ROP.<sup>3</sup>

The pathogenesis of ROP seems to include two distinct phases, where the second phase characterized by hypoxia, which induces vascular endothelial growth factor (VEGF) and neovascularization.<sup>4</sup> Understanding the ROP pathophysiology has increased the use of selective therapies that target the pathway for angiogenesis. There is evidence that the beta-adrenergic system may be involved in neonatal ROP. For example, polymorphisms of the  $\beta$ -adrenergic (B-AR) receptor in many black infants may be responsive to their lower ROP progression compared to non-black infant. In addition, blocking the B-AR with propranolol (the non-selective blocker of B1-AR and B2-AR)<sup>5</sup> suggests the recession of infantile hemangioma,<sup>1</sup> the most common neonatal tumor that is often associated with ROP,<sup>3</sup> suggesting that B-AR blockers maybe as effective at ROP. The evidence is confirmed by experimental findings from animal studies with oxygen-induced retinopathy<sup>6</sup> that show increased retinal norepinephrine and B-ARs that regulate the production of VEGF and retinal neovascularization in response to hypoxia. According to these studies and the significant reduction in neovascularization with topical propranolol,<sup>7-10</sup> therapeutic use of B-AR

blockers was proposed to counter retinal neovascularization in ROP.

Based on these observations and considering that so far, only a few studies have been conducted on the effect of oral propranolol on preventing the development of retinopathy of prematurity in preterm infants, which have not achieved a definite result regarding its efficacy and dosage, this clinical trial was designed to evaluate the effect of oral propranolol administration on premature infants and ROP.

## Materials and Methods

When ethics approval was gained from the Ethics Committee of Shahid Sadoughi University of Medical Sciences and we gain IRCT code (IRCT20100520003982N1) and informed consent was obtained from the parents of infants prior to the trial. This double-blind clinical trial was conducted on premature infants with GA more than 28 weeks and birth weight of less than 1500 g, with retinopathy of prematurity stage I and II admitted to NICU at Shahid Sadoughi Hospital in Yazd, Iran. Regarding to exclusion criteria, Infants with GA less than 26 weeks, IVH grade II and III, neonates with congenital anomalies, kinds of heart diseases except PDA, congenital infections (TORCH) and acute sepsis were excluded from the study. Thirty neonates were included in each group. However, due to the short term of the study, and considering that the first ROP examination is conducted at day 28<sup>th</sup> of birth, when some neonates with ROP are discharged from NICU, to monitor the complications of the treatment, they needed to be hospitalized for at least one week and complete cardiovascular monitoring. However, their family did not allow re-admitting their infants for the study. In order to match the case and control group, the study was conducted only on infants who had a long length of stay (at least 35 days) at the hospital. Twenty-eight days after birth, all preterm infants with birth weight of less than 1500 g were examined by the retinal fellowship using indirect



ophthalmoscopy (with KEELER ophthalmoscope SL4, made in the UK), and the retinopathy stage was determined. Infants with retinopathy stage I and II were divided into A and B groups according to the randomized table. Randomization of infants was conducted by a statistic consultant by using a random number table.

They were randomly assigned in the case or control group. For the case group, medication therapy began in the first two days with a dose of 0.25 mg/kg/dose and then 0.5 mg/kg/dose oral propranolol (pranol 10 from OLIDARU) every 12 hours, and continued until the patient required laser therapy or intraocular injection, or, slowly or completely recovered without invasive treatment whereas The control group received no medications. Prior to starting the treatment for the case group, full heart diagnostic examination was conducted by a pediatric subspecialist to ensure that they can take propranolol safely. Following the initiation of prophylaxis treatment with propranolol, neonates underwent complete cardiovascular monitoring and BP control at NICU for at least one week (using Datascope Passport 2 monitors, made in the United States) and hypoglycemia monitoring to stop medication in case of complications (apnea, bradycardia, hypertension, or hypoglycemia). It should be noted that due to the low birth weight of these infants, hospitalization for one week was part of the routine process of treatment for them, and some of them required more than one week to reach the desired weight for discharge. Therefore, one week monitoring imposed no additional costs on newborns in the case group. After a week, in the case of discharging newborns from NICU, they were treated as an outpatient and parents were instructed on the warning signs to refer to the Emergency Department of Shahid Sadoughi Hospital if any problem occurred; an NICU bed was booked for emergency cases, and a direct contact number was provided for parents to contact residents or physicians in case of having any questions. Other

supportive and therapeutic interventions were similar in both groups and were based on the protocols of the ward. In addition, no costs were imposed to the parents for medications used in the study, and medications were provided by an assistant. The retinopathy process in neonates in both groups was monitored weekly to the end of the recovery from ROP by a retinal fellowship using indirect ophthalmoscopy, which is part of the NICU routine program, and it is conducted every 1-2 weeks in all premature infants to ensure the complete recovery of ROP. If necessary, a therapeutic intervention including laser or injection was performed in both control and case groups. To ensure blindness of the study, the retinal fellowships who examined the infants and determined the patient's recovery, as well as the statistic counselor who performed the data analysis, did not know which neonates were in the case or control group.

For all infants, all data related to independent variables including gestational age, birth weight, initial weight in the study (using the ZYKLUS med scale, made in Germany), gender, type of delivery, APGAR score at birth and at 5 minutes after birth, length of oxygen intake and how to receive oxygen, number of surfactants dosage, frequency of transfusion, previous sepsis, PDA, apnea before treatment, NEC, pneumothorax, retinopathy grade, and data related to dependent variables including Apnea, bradycardia, hypertension, retinopathy stage after starting treatment, laser therapy or injection, weight at discharge, length of stay, and complications and mortality were entered into the pre-designed questionnaire and recorded.

**Statistical Analysis:** Data were analyzed using SPSS software and Chi-square, T-test, Mann-Whitney and the Wilcoxon signed-rank test, where  $P > 0.05$  was considered significant.

## Results

Twenty seven babies participated in this study. They were divided into two groups. The experimental group received propranolol

0.25 mg/kg/dose for the first two days and then 0.5mg/kg/dose every 12 hours. The control group received no medication. The average drug intake period was 3 months. 2 babies of the experimental group (one in the third day of treatment due to BS = 35 but without any sign, resulted from daily BS monitoring, and the other one because of not continuing the treatment after discharge) and a baby of the control group (because of referring bias due to not referring to the center for the follow ups after discharge) were excluded from the study (Table 1).

There was not a significant difference between Stage ROP frequency distribution in the two control and experimental groups (P = 0.089). There was no significant difference between the average number of days for receiving free oxygen, C-PAP, and ventilator in the two control and experimental groups. Moreover, there was not a significant difference between the average weight at the beginning of the study in the two control and experimental groups (P = 0.758). Besides, there was no significant difference between gestational age in the two control and experimental groups (P = 0.446). There was a significant difference between the average

drug intake period in the experimental group on the response to treatment and not responding to the treatment (P = 0.050). There was no significant difference between ROP frequency distribution in the two control and experimental groups (P = 0.640). However, the two patients in the experimental group who needed treatment were treated by laser. The 4 patients in the control group who needed treatment were all injected intravitreally (Table 1).

**Discussion**

This clinical trial study was related to the effect of Propranolol drug in the patients with ROP. The hypothesis was that Propranolol, as a beta blocker, can stop the increase of VEGF rate in the lesion site and decrease neovascularization in the site. The study showed that the improvement of ROP disease in the treatment receiving (experimental) group was 81.3% compared to 66.7% in the control group. According to collected data, more improvement through taking Propranolol can prevent from treating the patients by laser and bevacizumab and this can decrease the side effects of the two treatment methods that are aggressive, as well.

**Table 1.** Comparing of Variables between control and case groups

Variables	Cases (n = 12)	Controls (n = 12)	P-value
Pregnancy age (weeks)	29.9 ± 3.1	29.1 ± 1.3	0.45
Birth Weight (gram)	11117.5 ± 227	1220.8 ± 234	0.28
Weight (gram)	1365.8 ± 318	1402.9 ± 261	0.75
Weight after study (gram)	1416 ± 464	1558.7 ± 254	0.36
First Apgar	6.33 ± 2.4	5.58 ± 2.1	0.49
5 <sup>th</sup> Apgar	8.5 ± 2.5	7.8 ± 2.1	0.43
Admission duration (days)	49.6 ± 12.6	50.5 ± 22.8	0.90
Need of Resuscitation	4(33.3)	6(50)	0.68
Corton use for mother	10(83.3)	11(91.7)	1.00
Surfactants	10(83.3)	9(75)	1.00
Transfusion	6(50)	4(33.3)	0.68
Length of oxygen intake days	9.3 ± 18.08	18.66 ± 15.1	0.93
Intake C PAP (days)	8.4 ± 10.7	7.1 ± 8.00	0.43
Ventilator usage (days)	7.4 ± 6.2	5.7 ± 4.5	0.67
Previous sepsis	6(50)	2(16.7)	0.19
Apnea before treatment	2(16.7)	2(16.7)	1.00
PDA	3(25)	0(0.00)	0.09
StageI ROP	6(50)	10(83.3)	0.08
StageII ROP	6(50)	2(16.7)	0.08

Mean ± SD

The major part of the previous studies has been related to using beta blocker for improvement of the new vascularization in the animal samples. Six studies have recently been done in the field of using Propranolol in the experimental and the control groups. In Ozturk MA and the colleague's study, which was related to the efficiency of the oral Propranolol in the infants, it was shown that taking Propranolol in 0-1 steps cannot improve the disease and change the treatment procedure; however, it can be useful in step 2 for treatment of the patients. In Filipp and the colleagues' study in the field of safety of the use and effect of the drug, it was shown that taking the drug can be useful in the decrease of the disease level and prevent from the increase of the disease to step 4 and also prevent from treating by laser and using bevacizumab in the patients, but its side effects were noticeable. Also, in Aldo Bancalari and the colleagues' study on the oral Propranolol with less dosage, it was shown that the oral Propranolol drug can prevent from the improvement of the disease and increase the need for the aggressive treatments and no important side effects were seen. In a study, Makhoul and the colleagues found that taking the Propranolol drug can decrease the patients' need for the aggressive treatment, but because of the small number of the samples, the results were not significant. This group took a less dosage of the drug, too and no specific lesion was seen. It seems that the treatment by Propranolol in the first steps of the disease is not so effective. In a study with systematic review by Buhner and Bassler, related to the analysis of Filipp and Makhoul's studies, it was shown that 6 patients out of the 35 ones taking Propranolol needed the aggressive treatment. Meanwhile, in the control group, 14 patients out of 36 ones needed other treatments. Generally, in different studies, higher dosages were accompanied by serious side effects. This study tested the least dosage of Propranolol and the percentage of improvement in the experimental group

taking the drug was more compared to the control group, but no significant relation was found between taking and not taking the drug in the patients. One of the causes for the existing different views in the studies is the small number of the patients in each experimental group and the high rate of decrease of the patients' number in the studies. The change of the retinopathy and the ocular areas of the disease in each study can be a reason for this, too.<sup>11-15</sup>

Because of the patient's need for drug discontinuation and more aggressive therapies, drug consumption duration is different. In this study, the difference of the drug consumption duration between the group that has shown reactions to the cure and the group without reactions has shown significant, while in Ozturk MA study, the drug consumption duration has been a variable and there has not been a significant relation between the two groups, unlike our study. In Korkmaz L and the colleagues' study, the drug consumption duration in each group has had a more significant relation and the patients in the reaction group have had longer drug consumption duration. The difference among the studies can be a result of the difference among the number of the subjects that have had a need for more aggressive actions.<sup>14,15</sup>

In this study, the only side effect has been one case of hypoglycemia in the third day of the cure (Bs = 35) in which the patient showed no sign of the hypoglycemia but he was let out of the study. In other similar studies including Makhoul and Aldo Bancalari studies, no side effects were seen. In Ozturk and the colleagues' study, among the 147 patients 4 ones showed a need for the ventilator and in Levent Korkmaz that included 171 patients, 5 ones were let out of the study because of apnea and hypoglycemia. In the studies without side effects, the dose for the patients has been up to 2 mg per day and in the studies without the effects, the patients received the dosage of 1.5 mg per day. In our study that was with 1 mg dosage

per day, the patents showed effects. You should pay attention that taking Propranolol can have its specific and important side effects, including hypotension, bradycardia in the patients, closure of the airways and hypoglycemia.<sup>15-17</sup>

### Conclusion

The study shows that Propranolol cannot replace other drugs for the cure as a good one but it can stop patients' getting worse and the growth of the disease to higher levels in the short time. It requires more complementary studies to detect the capabilities and to assess its effect rate in more people.

### Conflict of Interests

Authors have no conflict of interests.

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## Case Report

<http://wjpn.ir>**VACTERL Association in a Newborn – A Rare Case Report**Mohammad Hosein Lookzadeh<sup>1,2</sup>, Fatemeh Tahghighi<sup>1,2\*</sup>, Abdolhamid Amooee<sup>3</sup><sup>1</sup> Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran<sup>2</sup> Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran<sup>3</sup> Department of Surgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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**ABSTRACT**

Syndrome or association VACTERL is a group of several birth defects of congenital anomalies in an individual. There must be at least 3 anomalies simultaneously for this syndrome to be referred, including spinal anomalies, anorectal anomalies, cardiac disorders, esophageal atresia with tracheoesophageal fistula, renal anomaly and limb anomalies. The organs involvement in VACTERL may present different severity and quality, from asymptomatic to life-threatening cases. Various studies have reported the other congenital associations such as cerebrovascular and pulmonary anomalies in addition to the above-mentioned called as the non-VACTERL association. The patient in this study had all 6 VACTERL syndrome criteria. The feature of this patient was the involvement of his limb and kidney anomaly, which were different on both sides. However, in previously reported cases, these two anomalies were both in one direction and on the same side. Finally, the VACTERL syndrome and Non-VACTERL Association in this patient represented in the form of esophageal atresia with trachea esophageal fistula and atrial septal defect, and the presence of a kidney with severe hydronephrosis and sacral agenesis and imperforated anus, recto vesical fistula and limb anomalies in the form of one-phalanx fingers on the left.

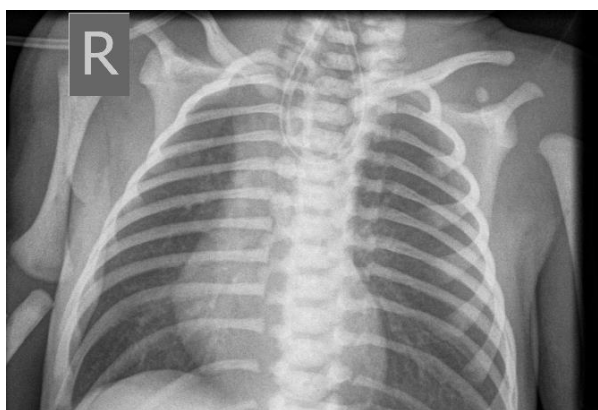
**Introduction**

VACTERL is a set of several congenital anomalies that involve different organs of the body. The prevalence of this syndrome is about one in 10000 to 40000 live births<sup>1,2</sup> and is more

often seen in the infants of diabetic mothers<sup>3</sup> and mothers who have used statin group drugs during pregnancy.<sup>4,5</sup> Most cases are sporadic; however, familial cases have been rarely reported in this syndrome.<sup>6</sup> Treatment usually involves supportive measures, medical treatments, and surgical repair.<sup>7</sup>

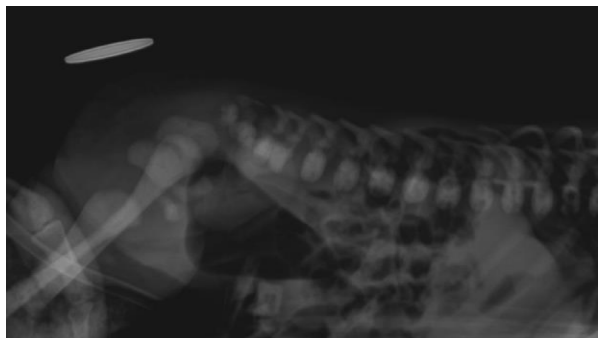
## Case Report

The patient was a 5-hour-old female infant who was sent to a NICU Center due to severe sialorrhea and respiratory distress. The baby was born with a gestational age of 33 weeks by normal delivery from parents with a distant family relationship. The mother had no history of chronic diseases like diabetes or history of surgery and exposure to radiation or specific drug use and has been under the full supervision of an obstetrician. No abnormal condition has been reported in the embryonic ultrasound. The baby was placed under oxygen hood due to tachypnea, and then, the naso-gastric tube was inserted, which faced a barrier (Figure 1).



**Figure 1.** The picture show esophageal atresia which the NG tube recoil

It was found in other examinations that the anal is closed and meconium is excreted from the tip of Mea (through the fistula between the rectum and the urinary system) (Figure 2).



**Figure 2.** X-ray abdomen showed dilation of the descending and recto sigmoid colon without the gas shadow in the distal rectum and also sacral agenesis

The left hand fingers were one-phalanx (Figure 3), while other organs were normal. In search of other associated anomalies, we detected sacral agenesis in the lumbosacral radiography (Figure 2).



**Figure 3.** The picture show one phalanx fingers of left hand

In renal ultrasonography, the right kidney showed agenesis with severe left renal hydronephrosis (Figure 4). ASD was reported in echocardiography. None of the testicles were touched in the scrotum in the genital examination, which was reported in a two-way UDT ultrasound. The infant navel (umbilicus) contained an artery and two veins.



**Figure 4.** The picture show moderate to severe unilateral hydronephrosis

The newborn was undergone a surgery to repair esophageal atresia and close the fistula between the esophagus and the tracheal tube and also to place a colostomy and close the rectovesical fistula during the first week and received 4 weeks of special care, and was finally discharged with oral breastfeeding. The baby was hospitalized again after a week due to fever and lethargy and treated with antibiotics due to urinary tract infection. However, he was

subjected to vesicostomy surgery due to lack of response to antibiotic therapy, increased urea and creatinine levels, severe hydronephrosis of the left kidney and neurogenic bladder. Eventually, the patient developed seizure due to urosepsis, leading to his death.

### Discussion

VACTERL was first reported in 1972 by Quan and Smith.<sup>8</sup> Seventy percent of anomalies include esophagus and tracheal involvement, while the involvement of the vertebra and heart accounts for 68% and 65%, respectively.<sup>9</sup> The heart involvement is more likely to occur in the forms of VSD, ASD, or Tetralogy of Fallot and less as the displacement of large vessels. Anal atresia is seen in 55% of cases. The kidneys involvement has been seen in 51% of the cases.<sup>9</sup> In reported cases, 70% include other organs' involvement as defects in the development of the genitalia, anomalies of the respiratory system and vascular anomalies as umbilical cord unit artery in NON VACTERL association cases. Limb anomalies have been seen in more than 70% of cases as the small thumb, polydactyly, syndactyly (webbed fingers) and the forearm bones dysplasia.<sup>9</sup> In most reported cases, limb involvement is associated with kidney involvement in the same position.<sup>6</sup> The feature of the case study had all the six known anomalies in the VACTERL syndrome. However, in the previous cases, the limb and kidney anomalies were reported on one side. In case of this patient, the limb involvement was on the left side and the kidney anomalies were on the right side, which was different from all the previously reported cases.

### Conclusion

Multiple congenital anomalies is rare but nowadays pediatricians and obstetricians must consult with relative parents to prevent congenital disease like this.

### Conflict of Interests

Authors have no conflict of interests.

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