



# The Effect of Maternal Age on the Incidence of Major Malformations and Operations in Children with Down Syndrome

## Down Sendromlu Çocuklarda Anne Yaşının Majör Malformasyon ve Operasyon İnsidansı Üzerine Etkisi

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### ABSTRACT

**Objective:** Children with Down syndrome have a high incidence of major malformations and corrective surgery. Some patients do not need any surgery, while some cases are operated for several indications. There are few studies investigating the effect of maternal age on the phenotype of these children, despite the fact that increasing maternal age is a known risk factor for giving birth to Down syndrome. We aimed to investigate the incidence of surgery for major malformations and disorders in children with Down syndrome and its relationship with maternal age at birth.

**Methods:** We revised the records of 218 children with Down syndrome for maternal age at birth and for surgical interventions.

**Results:** There were 84 children who had at least one operation with 38.5% incidence. A total of 49 children had cardiac surgery, 16 had gastrointestinal, 17 had head and neck area, 12 had ophthalmological, 12 had genitourinary, 5 had hernia, and 2 had orthopedic surgeries. The mean maternal age was 32.7 (minimum: 15; maximum: 44), and there was no significant difference between operated and non-operated groups for mean maternal ages (32.41 and 32.93, respectively;  $p=0.89$ ). For any type of surgery, there was no significant difference between the groups with maternal ages 35 and over and those under 35.

**Conclusions:** Maternal age at birth has no effect on the incidence of malformations and the probability of operation in Down syndrome.

**Keywords:** Congenital malformations, Down syndrome, maternal age, surgical interventions, trisomy 21

### ÖZ

**Amaç:** Down sendromlu çocuklarda majör malformasyon ve düzeltici cerrahi insidansı yüksektir. Bazı olgular birden fazla endikasyon için ameliyat olurken, bazı hastalar ameliyat gerektiren bir sorun yaşamaz. Anne yaşının artması Down sendromlu çocuk doğurmak için bilinen bir risk faktörüdür, ancak anne yaşının bu çocukların fenotipi üzerindeki etkisini araştıran fazla çalışma yoktur. Çalışmamızda Down sendromlu çocuklarda majör malformasyon ameliyatlarının insidansını ve doğumdaki anne yaşı ile ilişkisini araştırmayı amaçladık.

**Yöntemler:** Down Sendromlu 218 çocuğun dosyalarını, doğumdaki anne yaşı ve cerrahi müdahaleler açısından retrospektif taradık.

**Bulgular:** En az bir ameliyat geçiren çocuk sayısı 84, insidansı %38,5 idi. Çocukların 49'u kalp ameliyatı, 16'sı gastrointestinal, 17'si baş boyun bölgesi, 12'si göz, 12'si genitoüriner, 5'i fıtık ve 2'si ortopedik ameliyat geçirdi. Ortalama anne yaşı 32,7 (minimum: 15, maksimum: 44) idi ve opere olan ve olmayan gruplar arasında ortalama anne yaşı açısından anlamlı fark yoktu (sırasıyla 32,41 ve 32,93,  $p=0,89$ ). Anne yaşı 35 ve üzeri olan ve 35 yaş altı olan gruplar arasında herhangi bir ameliyat türü açısından anlamlı fark bulunmadı.

**Sonuçlar:** Down sendromlu çocuklarda en sık yapılan operasyonlar kalp, gastrointestinal ve baş boyun bölgesi operasyonlarıdır. Doğumda anne yaşının Down sendromunda malformasyon insidansı ve operasyon olasılığı üzerine etkisi izlenmemektedir.

**Anahtar kelimeler:** Konjenital malformasyonlar, Down sendromu, anne yaşı, cerrahi müdahaleler, trizomi 21

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## INTRODUCTION

Down syndrome is the most common genetic cause of moderate intellectual disability and multiple congenital abnormalities. In live births, its incidence is 1/780 to 1/850<sup>1,2</sup>. It results from excess genetic material of chromosome 21, which usually occurs secondary to meiotic nondisjunction error during gametogenesis in mothers (90% of case). Advanced maternal age, aged 35 and above, are the major risk factors for meiotic nondisjunction<sup>3</sup>.

Children with Down syndrome experience various structural and functional organ system problems that require surgical intervention. Approximately 50% of the patients have congenital heart disease, especially cushion defects, atrioventricular septal defect, and perimembranous ventricular septal defect. They may have major organ anomalies, such as cataracts, diaphragmatic hernia, esophageal atresia, annular pancreas and duodenal atresia, anal atresia, and Hirschsprung disease. Additionally, they have a high incidence of otolaryngological surgeries due to recurrent upper airway infections causing obstruction, sleep apnea, and otitis media. They may also need orthopedic, ophthalmological, or urogenital surgeries<sup>2,4,5</sup>. As a result, a child with Down syndrome has a high risk of having at least one operation during childhood. However, while some of the children have multiple malformations and disorders that require multiple interventions, others have never experienced serious disorders. In Down syndrome, the severity of the phenotype and presence of various malformations may be affected by the environment, as well as some modifier genetic factors<sup>6</sup>.

In limited studies reported, it was determined that very young mothers (mothers younger than 20 yr old) and older mothers (older than 30 yr of age) had higher incidences of congenital malformations other than chromosomal anomalies compared with other age groups<sup>7,8</sup>. While advanced maternal age is already a risk factor for trisomic pregnancies, it may also be a risk factor for severe disease.

In this study, we aimed to investigate the incidence and types of surgical interventions in our pediatric Down syndrome patients and to investigate the relationship between major congenital malformations and the incidence of surgery with the maternal age at birth.

## MATERIALS and METHODS

### Ethics Committee Approval

This study was approved by the Local Ethics Committee of University of Health Sciences Turkey,

Kanuni Sultan Suleyman Training and Research Hospital (decision no: 2018/12/64).

### Patients

We conducted a retrospective study, revising the records of patients with Down syndrome who were observed at the Medical Genetics Clinic between 2010 and 2018. Patient data, such as gender, karyotype, maternal age at birth, history of surgery, if any, type of surgery, follow-up period, and age at first and last visit were investigated and the relationship between maternal age at birth and incidence and type of surgical interventions, as well as the correlations between the duration of follow-up and first and last visit ages were evaluated.

### Statistical Analysis

Nominal and ordinal variables were described with frequencies, whereas numerical variables were described with means and standard deviations. Kolmogorov-Smirnov test was used for normality tests of numerical variables. Since all distributions were non-normal, non-parametric tests were used. Mann-Whitney U test and Fisher's Exact likelihood ratio test were used as hypothesis tests. Spearman's rho test was used for correlation analysis. All analyses were performed at SPSS software version 17.0 for windows at 95% confidence interval with 0.05 significance level.

## RESULTS

A total of 218 Down syndrome patients were evaluated (89 women and 129 men). Of them, 38.5% (n=84) had at least one operation, and 134 had none. The difference between gender groups in terms of being operated was statistically insignificant ( $p=0.182$ ) (Table 1).

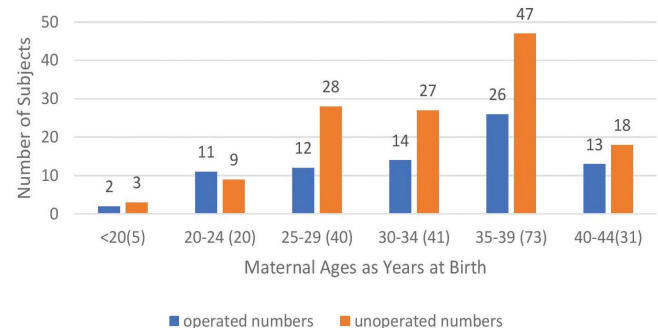
Classical trisomy accounted for 94% of the cases (n=205), Robertsonian translocation and mosaicism carriers were 2.5% (n=5) each, and 1% (n=2) of the patients had partial duplication of 21q.

Types of surgical interventions were listed in Table 2; 58% (n=49) of the cases had cardiac operations, 14% had genitourinary operations (11 cryptorchidism + 1 vesicoureteral reflux), 20% (8% in total cohort) had head and neck area (10 tonsillectomy/adenoidectomy + 4 tympanostomy + 2 tongue tie + 1 tracheostomy) operations, 14% had ophthalmological surgeries [8 nasolacrimal duct stenosis (NLDS) + 3 cataracts + 1 strabismus], and incidence of gastrointestinal (GI) tract operations was 19% (6 duodenal atresia + 4 Hirschsprung disease + 3 anal atresia + 1 intestinal malrotation + 1 Meckel's diverticulum + 1 gastroesophageal reflux), 6%

of the patients had hernia operations (1 diaphragmatic, 1 umbilical, 3 inguinal hernias), 2 had urachus cyst, and 2 had hip luxation correction operations (Table 2). While 61 of the cases had one type of operation, 23 (10.5% of the total cohort) of the cases had multiple interventions for different indications (20 were operated twice, 2 were operated three times, and 1 had four types of operations), and multiple interventions for the same indication were not recorded (e.g., two or three cardiac surgeries of one patient). In addition, for some operation categories, one patient may have more than one type of operation, for example, two of the patients undergo adenoidectomy/tonsillectomy and tympanostomy operations. One of the patients had both NLDS and cataract operation.

We obtained information about the ages of the mothers at birth for 210 of the cases; 78 of which were operated, and the distribution of the operated and non-operated cases according to maternal age at birth is shown in Figure 1.

Numbers of Operated and Unoperated Subjects for Each Maternal Age at Birth



**Figure 1.** The distribution of operations according to maternal ages at birth. The numbers in the brackets are the total number of the subjects in each age group.

**Table 1. Operated and non-operated distributions based on gender.**

|                       | Female     | Male        | Total       | p-value |
|-----------------------|------------|-------------|-------------|---------|
| Operated<br>n (%)     | 38 (42.7)  | 46 (35.7)   | 84 (38.5)   | 0.182*  |
| Non-operated<br>n (%) | 51 (57.3)  | 83 (64.3)   | 134 (61.5)  |         |
| Total<br>n (%)        | 89 (100.0) | 129 (100.0) | 218 (100.0) |         |

\*Fisher's Exact test.

**Table 2. Types, numbers, and ratios, and frequencies of operations.**

| Type of operation             | Number | Frequency in the operated group | Frequency in total | Type of operation         | Number | Frequency in the operated group | Frequency in total |
|-------------------------------|--------|---------------------------------|--------------------|---------------------------|--------|---------------------------------|--------------------|
| Cardiac                       | 49     | 58%                             | 22.4%              | Urachus cyst              | 2      | 0.24%                           | 0.09%              |
| Cryptorchidism                | 11     | 13%                             | 0.5%               | Hip dysplasia-dislocation | 2      | 0.24%                           | 0.09%              |
| Tonsillectomy ± adenoidectomy | 10     | 12%                             | 0.45%              | Tongue-tie                | 2      | 0.24%                           | 0.09%              |
| Nasolacrimal duct stenosis    | 8      | 9%                              | 0.36%              | Tracheostomy              | 1      | 0.12%                           | 0.045%             |
| Duodenal atresia              | 6      | 7%                              | 0.27%              | Intestinal malrotation    | 1      | 0.12%                           | 0.045%             |
| Umbilical ± inguinal hernia   | 4      | 0.47%                           | 0.18%              | Diaphragmatic hernia      | 1      | 0.12%                           | 0.045%             |
| Hirschsprung disease          | 4      | 0.47%                           | 0.18%              | Gastroesophageal reflux   | 1      | 0.12%                           | 0.045%             |
| Tympanostomy                  | 4      | 0.47%                           | 0.18%              | Strabismus                | 1      | 0.12%                           | 0.045%             |
| Cataracts                     | 3      | 0.36%                           | 0.14%              | Meckel diverticula        | 1      | 0.12%                           | 0.045%             |
| Anal atresia                  | 3      | 0.36%                           | 0.14%              | Vesicoureteral reflux     | 1      | 0.12%                           | 0.045%             |

When we listed surgeries of the cardiac and other congenital malformations according to maternal ages, 71 of the 210 cases had undergone surgery for congenital malformations (Table 3).

Age at first and last visit was significantly higher in the operated group ( $p=0.030$  and  $p=0.002$  respectively), while there was no significant difference in the mean maternal age between the two groups ( $p=0.890$ ) (Table 4). The follow-up period had a more regular distribution in both the operated and non-operated groups compared with the age at first admission. The mean follow-up period

was higher in the operated group, and the difference was statistically significant ( $p=0.002$ ) (Table 4).

Karyotype, congenital malformation operation, GI operation, and cardiac operation distribution differences between maternal age below 35 and maternal age at 35 or higher age groups were statistically insignificant ( $p>0.05$ ) (Table 5).

## DISCUSSION

During the 8 yr that we observed 218 children with Down syndrome, 84 (38.4%) of the children underwent

**Table 3. Types of congenital malformations and distribution of them according to maternal age at birth.**

| Type of surgery                              | Maternal age |            |            |            |            |           |
|----------------------------------------------|--------------|------------|------------|------------|------------|-----------|
|                                              | <20 (5)      | 20-24 (20) | 25-29 (40) | 30-34 (41) | 35-39 (73) | ≥40 (31)  |
| Cardiac                                      | 1            | 6          | 5          | 9          | 18         | 7         |
| Cryptorchidism                               | 0            | 2          | 2          | 0          | 3          | 2         |
| Nasolacrimal duct stenosis                   | 1            | 2          | 2          | 1          | 2          | 0         |
| Duodenal atresia                             | 0            | 1          | 1          | 1          | 1          | 1         |
| Umbilical / ± inguinal hernia                | 0            | 0          | 0          | 0          | 2          | 1         |
| Hirschsprung's disease                       | 0            | 1          | 0          | 2          | 1          | 0         |
| Cataracts                                    | 0            | 0          | 1          | 0          | 1          | 1         |
| Anal atresia                                 | 0            | 0          | 0          | 2          | 1          | 0         |
| Urachus cyst + Meckel's diverticula          | 0            | 0          | 1          | 0          | 0          | 0         |
| Hip dysplasia-dislocation                    | 0            | 0          | 0          | 0          | 2          | 0         |
| Tongue-tie                                   | 0            | 1          | 0          | 0          | 1          | 0         |
| Intestinal malrotation                       | 0            | 1          | 0          | 0          | 0          | 0         |
| Diaphragmatic hernia                         | 0            | 0          | 0          | 0          | 0          | 1         |
| Total number considering multiple operations | 2            | 11         | 10         | 13         | 23         | 12        |
| Operation ratio (n)                          | 40%<br>2     | 50%<br>11  | 25%<br>10  | 29%<br>13  | 32%<br>23  | 39%<br>12 |

**Table 4. Age at first and last visits, duration of follow-up, and maternal age differences between operated and non-operated patients.**

|                                | Non-operated<br>mean ± SD<br>median (25%-75%) | Operated<br>mean ± SD<br>median (25%-75%) | Total<br>mean ± SD<br>median (25%-75%) | p-value* |
|--------------------------------|-----------------------------------------------|-------------------------------------------|----------------------------------------|----------|
| Age at first visit (months)    | 4.28±13.65<br>1 (0-2)                         | 6.58±20.93<br>2 (1-4)                     | 5.17±16.82<br>1 (1-3)                  | 0.030**  |
| Duration of follow-up (months) | 29.24±30.99<br>19 (2-50)                      | 43.58±35.58<br>40 (7.25-73.5)             | 34.79±33.50<br>26 (3-60.5)             | 0.002**  |
| Age at last visit (months)     | 33.63±32.16<br>27 (4-54)                      | 50.14±40.04<br>43 (16.25-78.75)           | 40.02±36.24<br>31 (6-66)               | 0.002**  |
| *Maternal age (yr)             | 32.93±6.11<br>34 (28-37)                      | 32.41±7.02<br>34.5 (27.75-38.25)          | 32.74±6.45<br>34 (28-38)               | 0.890    |

SD: Standard deviation.

\*Mann-Whitney U test, \*\* $p<0.05$

surgery at least once, and 10.5% had multiple surgeries; 58% (n=49) of the patients had cardiac operations, 14% (n=12) had genitourinary, 20% (n=17) had head and neck area, 14% (n=12) had ophthalmological, 19% (n=16) had GI tract operations, and 6% (n=5) of the patients had hernia operations. When we evaluated the maternal age and distribution of congenital malformation operations, maternal age of 48 of the patients were older than 30 yr of age and 35 of were older than 35 yr of age, while only 23 of the patients with congenital malformations had a maternal age younger than 30 yr of age (Table 3). However, when we calculated the correlation of maternal age with the incidence of operation for congenital malformations, there was no significant difference between the operated and non-operated groups for mean maternal ages at birth (32.41 and 32.93, respectively;  $p=0.89$ ) (Table 4). When the relationship between the maternal age at birth and the incidence of surgical interventions was compared, no significant difference was found between the groups with maternal ages of 35 and over and those under 35 yr of age, neither in terms of cardiac surgery, surgical interventions in general, or GI surgery (Table 5).

The incidence of congenital cardiac defects is nearly 50% in Down syndrome<sup>9,10</sup>. We do not have exact information about the average operation incidences for Down syndrome, but according to surgery indications and cardiac malformations of Down syndrome, usually

both indications and the defects parallel with each other. According to the numbers of series, we estimate that approximately 35% of the Down syndrome patients experience a cardiac surgery<sup>5,9,11</sup>. In our series, 49 (22.4%) of 218 patients had a cardiac operation. This corresponded to a significantly lower number. We suppose that it is partly due the premature death of some patients in the neonatal period and partly due to the young age of our cohort (Table 4).

The most common GI malformation requiring corrective surgery is duodenal atresia followed by anal atresia and Hirschsprung disease and esophagus atresia in decreasing order<sup>12</sup>. The incidence of anorectal malformations was defined as 0.36%-2.7% in Down syndrome<sup>13</sup>. Intestinal malrotation is also high in Down syndrome with accompanying duodenal obstruction<sup>14</sup>. The incidence of major GI system abnormalities was higher (duodenal atresia, Hirschsprung's disease, and anal atresia) in our cohort compared with literature. In addition, we recorded one diaphragmatic hernia, one gastroesophageal reflux, one malrotation operation, one Meckel's diverticulum, and two urachal cyst operations in 218 patients. Although malrotation and diaphragmatic hernias are common in Down syndrome, Meckel's diverticulum and urachal cysts are very rare. Thus, they were not reported in series; only recorded in sporadic cases<sup>5,15-17</sup>. They are usually observed in other trisomies

**Table 5. Karyotype, major congenital malformation operation, and cardiac operation distributions and differences between maternal age below 35 and maternal age at 35 or higher age groups.**

|                                                        | Maternal age <35 yr | Maternal age ≥35 yr | Total      | p-value            |
|--------------------------------------------------------|---------------------|---------------------|------------|--------------------|
| <b>Karyotype, n (%)</b>                                |                     |                     |            |                    |
| Mosaics                                                | 2 (1.9)             | 3 (2.9)             | 5 (2.4)    |                    |
| Classical trisomy                                      | 99 (93.4)           | 99 (95.2)           | 198 (94.3) | 0.550 <sup>a</sup> |
| Robertsonian translocations                            | 4 (3.8)             | 1 (1.0)             | 5 (2.4)    |                    |
| Structural abnormalities                               | 1 (0.9)             | 1 (1.0)             | 2 (1.0)    |                    |
| <b>Major congenital malformation operations, n (%)</b> |                     |                     |            |                    |
| No                                                     | 70 (66)             | 69 (66.3)           | 139 (66.2) | 0.539 <sup>b</sup> |
| Yes                                                    | 36 (34)             | 35 (33.7)           | 71 (33.8)  |                    |
| <b>Cardiac operations, n (%)</b>                       |                     |                     |            |                    |
| No                                                     | 85 (80.2)           | 79 (76.0)           | 164 (78.1) | 0.283 <sup>b</sup> |
| Yes                                                    | 21 (19.8)           | 25 (24.0)           | 46 (21.9)  |                    |
| <b>GIS operations, n (%)</b>                           |                     |                     |            |                    |
| No                                                     | 96 (90.6)           | 100 (96.2)          | 196 (93.3) | 0.088 <sup>b</sup> |
| Yes                                                    | 10 (9.4)            | 4 (3.8)             | 14 (6.7)   |                    |
| <b>All operations, n (%)</b>                           |                     |                     |            |                    |
| No                                                     | 70 (66.0)           | 69 (66.3)           | 139 (66.2) | 0.539 <sup>b</sup> |
| Yes                                                    | 36 (34.0)           | 35 (33.7)           | 71 (33.8)  |                    |

<sup>a</sup>Chi-square likelihood ratio. <sup>b</sup>Fisher's Exact test, GIS: Gastrointestinal system

and/or with additional congenital malformations<sup>15,18,19</sup>. We may conclude that urachus cysts are more common than expected in Down syndrome in pediatric surgery practice.

While it has been reported that the incidence of umbilical hernia and undescended testes is high in Down syndrome, the interpretation of inguinal hernia is lacking<sup>4,5,14,20,21</sup>. In our cohort, the incidence of both umbilical hernias and inguinal hernias and also of cryptorchidism was rather high. Although some of the umbilical hernias regress spontaneously, they usually undergo surgical corrections for inguinal hernias and cryptorchidism, sometimes for both. In these children, these malformations are probably caused by loose connective tissue and decreased muscle tone.

Most of the children with Down syndrome experience surgical interventions for the head and neck area. We observed that the need for tonsillectomy, adenoidectomy, tympanostomy, and dacryocystorhinostomy for NLDS was quite high in our cohort. The incidence of dacryocystorhinostomy was similar to that reported series<sup>22,23</sup>. Although oral cavity anomalies, such as glossoptosis, are common in Down syndrome, tongue-tie was not mentioned as a common feature, but we recorded two tongue-ties requiring surgical intervention in our series. About 69%-76% of children with Down syndrome have obstructive sleep apnea; this is partly due to the flat facial structure and hypoplastic nasal bone, mandibular hypoplasia, and relative macroglossia. In addition, these children have additional immunological dysfunction and is prone to respiratory infections in infancy and school age<sup>24</sup>. Most children with Down syndrome have adenoid hypertrophy, tonsillar hypertrophy, and chronic serous otitis media due to recurrent infections. In these children, adenoidectomy and tonsillectomy is usually performed for the treatment of obstructive symptoms, but approximately 51% of preoperative symptoms regress<sup>25</sup>. The exact rate of otolaryngological surgery in children with Down is unknown, but considering the rate of obstructive symptoms, it should be high. While one of the highest number of surgeries in our series belonged to this group (n=12; 14.3%), it remains low compared with the above rate, probably due to the low mean age of our cohort (mean age at last examination, 40 months) (Table 4).

While the incidence of hip luxation in hospitalized children with Down syndrome was found to be 1.25%-7%, it should be less in general<sup>26</sup>. The mean age of acetabular operation for hip luxation in children with Down syndrome is 11.3±5.3 yr<sup>27</sup>. Although the mean age of our

cohort was low, the incidence of hip surgery was similar to the reported numbers (n=2, 0.9%) (Table 2).

Why are some babies with Down syndrome born with major malformations while others do well? And why do some children with Down syndrome need more hospitalizations and surgery for chronic conditions? It is likely related to multiple epigenetic factors involved in the expression of an overdose of many genes located on the extra chromosome 21. The main genomic determinants of phenotypic variability are transcription factors (e.g., RUNX1), noncoding regulatory RNAs, such as microRNAs and small nucleolar RNAs, and so forth, and lastly, content of CpG islands in the human chromosome 21<sup>28</sup>. Since the extra chromosome is maternal in most cases, we suppose that maternal factors, such as maternal age, may play a role in modifying the expression of these regulatory elements. In a recent report, the effect of maternal age on the genomic stability of the offspring was discussed; it was stated that as the primary oocytes get older, the methylation of cytosines and adenines in their genome increases as all aging cells. These methylated nucleotides play a role in increased gene expression, gene repression (silencing), and silencing of transposable elements<sup>29</sup>. Increased methylation of protein-coding genes and noncoding genes of regulatory elements may have a deleterious effect on the morphogenic genes and factors in the developing the embryo. This scenario is probably similar in the case of trisomic babies taking the extra chromosome 21 from the mother in most of the instances. In a study in which the records of 102,728 pregnancies were revised, it was determined that the incidence of congenital malformations (congenital heart defects, clubfoot, and diaphragmatic hernia) increased in the children of mothers over the age of 25, especially those over the age of 35<sup>8</sup>. There are conflicting data in the few studies investigated the effect of maternal age on the phenotype of Down syndrome. While in a study from the USA found no relation between the maternal age and the congenital malformations of Down syndrome, a study that scanned the Down syndrome registries in three European countries discovered that infants of women older than 30 yr were found to have a higher incidence of congenital heart defects, esophageal atresia, and anal atresia, and in another study, the young maternal age was related to oral defects<sup>30-32</sup>. Although our cohort number was high, the number of different malformations taken separately was not high enough for a satisfactory comparison. Perhaps this comparison of maternal age and malformation should be compared in a larger Down syndrome population, including prenatal abortions and neonatal deaths at more than one center.

## CONCLUSION

In conclusion, in addition to the congenital malformations, children with Down syndrome face many additional organ problems and have to undergo various interventions while growing up. Assuming that many problems are solved with minimal intervention with the development of technology, we think that the number in the literature has decreased, as in our cases. Still, the numbers are quite high compared with euploid cases. In this regard, it is of great importance that both pediatric and genetic physicians and branch physicians who follow Down syndrome are aware of the needs of the patients and additional problems that may affect their post-operation follow-up. Although advanced maternal age is associated with an increased incidence of Down syndrome at birth, we did not observe its effect on the incidence of malformations and the likelihood of surgery in patients with Down syndrome. Our study is one of the few studies investigating the effect of maternal age on the Down syndrome phenotype and indirectly on congenital malformations. In our opinion, as knowledge of the molecular aspects of gametogenesis related to the formation of congenital malformations and genetic disorders increases, it will be possible to prevent them before conception in the future.

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## Ethics

**Ethics Committee Approval:** This study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital (decision no: 2018/12/64).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

## Author Contributions

Surgical and Medical Practices: E.Y.G., A.G., Concept: E.Y.G., A.G., Design: E.Y.G., A.G., Data Collection and/or Processing: E.Y.G., A.G., Analysis and/or Interpretation: E.Y.G., Literature Search: E.Y.G., Writing: E.Y.G.

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