Pregnancy and delivery complications and treatment approach in attention deficit hyperactivity disorder

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Pregnancy, delivery complications and treatment approach were evaluated in 153 cases diagnosed with attention deficit hyperactivity disorder in the State Hospital of Antalya in the Child and Adolescent Psychiatry Polyclinic. Most of the cases had been delivered vaginally (74.5%). The most frequent delivery complication was asphyxia/hypoxia (15.6%). The agent most frequently preferred in the treatment regimen was methylphenidate (82.4%), which is a psychostimulant. The other drugs used were risperidone (29.4%), selective serotonin reuptake inhibitors (16.4%) and imipramine (4.6%). The most frequent side effect resulting from methylphenidate use was a decrease in appetite (34.9%). Attention deficit hyperactivity disorder often presents with comorbid disorders; in these cases, nonstimulant agents had to be added to methylphenidate for better treatment outcomes. Use of selective serotonin reuptake inhibitors in combined treatment and in cases with comorbidities is in agreement with the literature. Further studies of combined treatment regimens in attention deficit hyperactivity disorder are needed.

Key words: attention deficit hyperactivity disorder, methylphenidate, pregnancy/delivery complications.

Attention deficit hyperactivity disorder (ADHD) begins in early childhood, continues into adulthood and persists even into the following years. It is characterized by attention deficit, hyperactivity and impulsivity[1]. Although no single hypothesis is accepted for its etiology, most hypotheses have supporting evidence and emphasize brain dysfunction caused by genetic, partum or post–partum factors[2]. In case-control epidemiologic studies, pregnancy, partum, or neonatal complications are found to be more frequently related to environmental factors in children with ADHD than in healthy control cases. Although the intervening mechanism cannot be completely discerned, early traumas during a critical developmental phase are thought to have long-lasting effects on cognition and behavior[3].

Stimulants that have been used for more than 60 years as a treatment modality in ADHD are the first-rank drugs currently being used. They are the most commonly prescribed psychotropic medications in the United States, with an estimated of 2.7 million children and adolescents having received this treatment in 2002[4]. Methylphenidate use is thought to have increased by 2.5 times among children 5-14 years of age diagnosed with ADHD[5].

Short-lived side effects of stimulants are usually mild, and resolve upon 1-2 weeks of use. The most prevalent side effects are anorexia, irritability, and insomnia. Headache, abdominal pain, skin rash, and somnolence are seen in only 1% to 10% of cases. Nausea and vomiting can occur at the beginning of the treatment. Tactile hallucinations, toxic psychosis, pressured speech, anxiety, bone marrow suppression, and thrombocytopenia are seen, but very rarely[6]. Among children with ADHD, 30% do not benefit from or tolerate stimulants. In these children, tricyclic antidepressants have been used for a long time[1]. No consistent result has been obtained concerning use of selective serotonin reuptake

inhibitors (SSRIs) in the treatment of ADHD. Barrickman[7] has suggested that fluoxetine may be an effective alternative treatment for some cases of ADHD. However, Findling's study[8] indicated that ADHD symptoms do not regress with fluoxetine and sertraline. The Mental Health Institute has reported that SSRIs do not have a beneficial effect on ADHD symptoms, but can be an effective agent in comorbid cases[9].

Atypical antipsychotics are reported to be effective on temper outbursts and aggressive behaviors in ADHD[10]. No adverse effect emerged on cognitive and attention function in cases with ADHD comorbid with disruptive behavior disorders following risperidone treatment[11].

Although a history of delivery complication was not recorded in studies to date, in many ADHD children, perinatal factors in ADHD etiology continue to be an interesting subject[12]. In this study, we aimed to document, in addition to pregnancy and delivery complications, drug choice and side effects in 153 children with ADHD. Results are discussed in light of the present literature.

Material and Methods

One hundred fifty-three patients who attended the Child and Adolescent Psychiatry Polyclinic in the State Hospital of Antalya, Turkey between May 2006 and January 2007 and were diagnosed as ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria following clinical interviews by a child and adolescent psychiatrist with the child or adolescent and family were included in the study. The age of patients varied between 6 and 15 years, with a mean age of 9±1.98. Of the 153 patients, 116 (75.8%) were male and 37 (24.2%) female. The mean age of the female and male patients was 9±1.92 and 9±2.00 years, respectively. The diagnosis was supported by a screening and rating scale based on DSM-IV for attention deficit and disruptive behavior disorders completed by parents and teachers. Complications of delivery and pregnancy and delivery history were obtained from the parents and entered on a semi-structured data form prepared by the child and adolescent psychiatrist. The drug treatments used in patients with diagnosis of ADHD were determined, and the side effects and dosages of methylphenidate and risperidone were registered one month later in a semi-structured data form. Exclusion criteria were as follows: age below 6 years; substance or alcohol use in the last six months; trauma history leading to loss of consciousness; pervasive developmental disorders; chronic systemic disease; psychotic disorder; and child or parent not giving approval for participation in the study.

Data Collection Instruments

A semi-structured data form containing complications about delivery and pregnancy, the history of delivery of the child, and side effects and dosages of methylphenidate and risperidone was applied in all subjects.

The screening and rating scale based on DSM-IV for attention deficit and disruptive behavior disorders: This scale was developed by Turgay[13] for scanning disruptive behavior disorders. Ercan and colleagues[14] conducted the validity and reliability study in Turkey. This scale evaluated inattentiveness (9 items), hyperactivity (6 items), impulsivity (3 items), oppositional defiant disorder (8 items), and conduct disorder (15 items), for a total of 41 items[14]. Statistical analyses were performed with SPSS 11.5 for Windows.

Results

Vaginal deliveries were recorded in 74.5% of cases, while 39 cases were delivered by cesarean section (25.5%). Vacuum extraction was performed in 12 cases (7.8%). For 2 cases, labor was in breech presentation (1.3%). The most frequent delivery complication was asphyxia or hypoxia (15.6%). Abortus imminence (9.8%), preterm delivery (7.8%), preeclampsia (7.8%), drug use during pregnancy (4.5%), prepartum bleeding (3.9%), and Rh incompatibility (1.9%) were other complications documented, but no case of eclampsia was seen. History of delivery and complications of pregnancy and delivery experienced by children with ADHD are summarized in Table I.

With respect to treatment regimen, 82.4% of cases were treated with methylphenidate (n=126), 29.4% risperidone (n=45), 16.4% SSRIs (n=25), and 4.6% with imipramine (n=7) (these rates also include combined treatments). The agent most frequently preferred in the

Table I. History of Delivery, Pregnancy and Delivery Complications of Cases with Attention Deficit Hyperactivity Disorder

History of delivery, pregnancy and delivery complications	n	%
Vaginal delivery	114	74.5
Cesarean section	39	25.5
Asphyxia/hypoxia	24	15.6
Abortus imminence	15	9.8
Preterm delivery	12	7.8
Preeclampsia	12	7.8
Vacuum extraction	12	7.8
Drug use during pregnancy	7	4.5
Prepartum bleeding	6	3.9
Rh incompatibility	3	1.9
Breech presentation	2	1.3
Total	153	100

treatment regimen was methylphenidate, which is a psychostimulant. In 55.5% of cases (n=85), methylphenidate was used alone, while in 26.9% of cases (n=41), it was used in combination with other treatments. Side effects of methylphenidate were recorded in 51.6% (n=65) of cases, and no side effects in 48.4% (n=61). Methylphenidate treatment had to be discontinued in only 5.5% (n=7) of cases. Methylphenidate was used at a dose of 10-20 mg/day in 89.6% (n=113) of cases. The side effects leading to discontinuation of methylphenidate were weight loss, exacerbation of tics, irritability, hyperactivity, and papular rash. The second-line drug was risperidone, which was an atypical antipsychotic. Risperidone was frequently preferred in combined treatment (19.6%, n=30), while only 15 cases used risperidone alone (9.8%).

Selective serotonin reuptake inhibitors are the third-line drugs, and are used in combination. Fluoxetine (n=7) and sertraline (n=18) are preferred. The drug least preferred in combined treatment is imipramine: it is used with methylphenidate in only one case. Monotherapy (69.2%) was preferred over combined therapy (30.8%), and methylphenidate was the most frequently preferred monotherapy. Among combined treatments, methylphenidate and risperidone are the most frequently preferred drugs (n=21, 13.7%). Monotherapy and combined drug treatment regimens are shown in Table II.

Decrease in appetite was the most frequent side effect occurring with methylphenidate treatment (34.9%, n=44). Second- and third-rank side effects were insomnia, headache, and irritability, occurring in 15%, 13.4%, and 13.4% of cases, respectively. Skin rash was a rare side effect (0.7%, n=1); more than one side effect was seen in a given case. Side effects due to methylphenidate use are shown in Table III. Most of the cases treated with risperidone did not experience side effects (62%, n=28), but among them, sedation was the most common (28.8%, n=13). More than one side effect was detected in the same case. The dose of risperidone was 0.5-2 mg/day in 73.3% (n=33) of cases.

Table II. Monotherapy and Combined Drug Treatment Regimens

Drug Treatments	n	%
Methylphenidate	85	55.5
Risperidone	15	9.8
Imipramine	6	3.9
Methylphenidate + Risperidone	21	13.7
Methylphenidate + Selective serotonin reuptake inhibitors	16	10.5
Methylphenidate + Imipramine	1	0.7
Risperidone + Selective serotonin reuptake inhibitors	6	3.9
Methylphenidate + Risperidone + Selective serotonin reuptake inhibitors	3	2
Total	153	100

Table III. Side Effects due to Methylphenidate Use

Side Effects	n	%
Decreased appetite	44	34.9
Insomnia	19	15
Headache	17	13.4
Irritability	17	13.4
Weight loss	15	11.9
Sadness	10	7.9
Increased hyperactivity	9	7.1
Abdominal pain	9	7.1
Nausea	9	7.1
Somnolence	8	6.3
Dizziness	8	6.3
Exacerbation of tics	2	1.5
Social withdrawal	2	1.5
Skin rash	1	0.7

Discussion

Neurobiological risk factors, including perinatal obstetric complications or prematurity, can have a direct effect on cognitive development during the phases of rapid brain development and early phases of life. The brain regions related to executive functions are very sensitive to perinatal hypoxia[15]; accordingly, most pregnancy and delivery complications responsible for the development of ADHD are disorders leading to hypoxia[2]. The supporting data of our study detected asphyxia or hypoxia at a high level among complications. Chapieski[16] stated that preterm babies more frequently develop ADHD. Cherkes-Julkowski[17] compared preterm with term babies in a longitudinal study and found that preterm babies had more learning and language problems with attention deficit. In our study, preterm delivery was found to be the third-line delivery complication. Milberger and Chandola[18,19] found prepartum bleeding to be an important risk factor in ADHD; however, in our study, only a low rate of prepartum bleeding was found.

Ben Amor and colleagues[3] found a higher vacuum extraction rate in their healthy study group as compared with the ADHD group. A study conducted in Iceland found a statistically insignificant association between vacuum extraction and ADHD[20]. Korkman and colleagues[21] stated that a maternal history of preeclampsia was related to attention and visual motor development in children. In our study, vacuum extraction and preeclampsia were seen in 12 cases. Aysev and colleagues[22] reviewed the delivery history for 95 ADHD cases and found vaginal delivery at a high rate (81%), which is in agreement with our results.

In our study, most of the cases were delivered vaginally; a low rate of delivery and pregnancy complications was detected. Absence of a control group is a limiting aspect of our study, because it cannot be estimated whether or not pregnancy and delivery complications are risk factors for ADHD.

The most frequent drug used for ADHD treatment in our study was methylphenidate, which is in line with previous studies[23-26]. Kılıç and colleagues[27] found the rate of drug use to be 97.5% overall, while short-acting methylphenidate was used at a rate of 90%. In our study, all of the cases received a pharmacological treatment. Methylphenidate was used in 82.4% of cases, 68% of which was short-acting methylphenidate. The rate of short-acting methylphenidate use in our study was lower than the rate found in Kılıc's study. This reflects the fact that long-acting methylphenidate use is increasing today. In our study, long-acting methylphenidate was used at a rate of 14.4%.

Studies evaluating drug choice and stimulant use in ADHD in our country revealed that dramatic changes have taken place in the last 10 to 15 years. Öktem and Sonuvar[28] stated in 1993 that methylphenidate and imipramine were being used in the treatment of ADHD at rates of 2%-3% and 70%, respectively. A 1996 study examining the drug choice of doctors working in child and adolescent mental health reported that drug treatment was preferred in 80.4% of cases; antidepressants, especially imipramine, were found to be highly preferred. A study designed in a medical university found a 94% rate of drug treatment after one year, with methylphenidate the first-line drug at a rate of 49.6%[27]. When ADHD is diagnosed, methylphenidate usage is favored since positive results are attained within a short time, side effects are mild, drug cost is low, and it is easily accessible.

Short-lived side effects of stimulants are usually mild, and can be eliminated by changing the dosage or timing[6]. In the present study, side effects were seen in most cases (51.6%), but discontinuation of treatment was rarely seen (5.5%). Even though the degree of severity

of side effects was not measured, the low rate of discontinuation might reflect that they were tolerable. In studies outside Turkey, discontinuation of the drug because of side effects was found at a rate of 3.6% to 8.6%[29,30]. Thus, the discontinuation rate found in our study is supported by the literature.

In clinical trials, the most prevalent side effects of methylphenidate found were anorexia, sleep disturbances and irritability; headache, stomach ache, nausea, and vomiting also occur[31]. In our study, the most frequent side effect was a decrease in appetite, which is in agreement with the literature. Obsessive compulsive symptoms and withdrawal symptoms are other possible side effects[32]. We observed obsessive compulsive symptoms in one case and withdrawal symptoms in two cases in our study.

Dermatological side effects of methylphenidate are skin rash, urticaria, fever, arthralgia, and exfoliative dermatitis; hypersensitive reactions include erythema multiforme with histopathologically confirmed necrotizing vasculitis and thrombocytopenic purpura[33]. Confino-Cohen and Cohen[33,34] reported one case of maculopapular rash occurring following methylphenidate use and one case of drug eruption localized on the scrotum. Another study documented three cases treated with methylphenidate who developed skin rash[29]. In our study, one case developed a diffused pruritic maculopapular eruption because of methylphenidate use. Upon cessation of methylphenidate use and adding antihistaminic treatment, the maculopapular rash resolved.

Recent randomized controlled studies, however, have begun to suggest that stimulants can be safely and effectively prescribed in many ADHD patients with comorbid tic disorders[5]. Nolan and colleagues[35] did not report any exacerbation of tic in 19 children with ADHD with comorbid tic disorder. Law and Schachar[36] compared placebo and methylphenidate in 91 children with and without comorbid tic disorder and did not find any significant difference in exacerbation of tic. Findling and Lipkin[37,38] reported that 9% of cases treated with methylphenidate developed transient tics and 1% of cases developed chronic tic disorder. It has been reported that presence of tic is not a precise indication for cessation of stimulants, but the decision should be made according to severity of tics and degree of benefits from the drug. Some clinicians advise combination of stimulants and antipsychotics in ADHD with comorbid tic disorder. A second-generation antipsychotic, risperidone, which has favorable side effects, is also advised in these cases[5]. None of our cases developed tic; however, exacerbation of tic was seen in 2 out of 5 ADHD patients who had a history of tic disorder before initiation of the stimulant. Methylphenidate was discontinued in one case while risperidone was added in one.

Wilens and colleagues[39] reported the use of polypharmacy for the treatment of comorbid disorders and attained a synergistic effect. In our study, a combined treatment regimen was preferred in cases with a comorbid disorder. Although Guevara and colleagues[40] presented no detailed data about reliability and validity, nonstimulants were frequently added to stimulants in ADHD cases. In our study, nonstimulants, including atypical antipsychotic (risperidone), SSRIs (sertraline, fluoxetine), and a tricyclic antidepressant (imipramine), were added to the stimulant drugs. Turgay[41] stated that psychostimulants, tricyclic antidepressants including imipramine, SSRIs, and atypical antipsychotics like risperidone were beneficial in ADHD with comorbid disorders and conduct disorder. The treatment profile is similar with the treatments of this study.

In some controlled studies, antipsychotics with or without methylphenidate were found to be effective[42]. Risperidone was found to be the second-line drug preferred in our cases and was usually preferred in combined treatment. Most of the cases had no side effects. The most prevalent side effect was sedation. The treatment was discontinued due to sedation in two cases and weight gain in one case (6.6%). Due to the low rate of side effects and discontinuation, risperidone was considered to be well tolerated. Of cases treated with combined risperidone and methylphenidate, 95.2% had comorbidity. The most frequent comorbid disorder was oppositional defiant disorder (61.9%). Risperidone was found to be effective and safe in oppositional defiant disorder[11,43].

Monotherapy with SSRIs is not effective in ADHD, but can be combined with psychostimulants[8]. SSRIs were preferred only in combination

treatments in our study (16.3%), mostly with methylphenidate. In one study, fluoxetine and sertraline, the SSRIs prescribed in our study, were the most frequently preferred SSRIs found to be beneficial in ADHD with comorbid anxiety and depression[9]. The combination of SSRIs and methylphenidate was used in comorbid states in our study. The most frequent comorbid disorder was anxiety disorders (100%). In accord with the literature[40], this combination is preferred in ADHD when it is comorbid with internalizing disorders.

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