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Original Article

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Evaluation of fetomaternal outcomes and serum analytes in placenta previa and associated placenta accreta spectrum

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ABSTRACT

Aims: Evaluation of fetomaternal outcomes and serum analytes values in patients with placenta previa and associated placenta accreta spectrum (PAS).

Methods: The study comprised 160 patients, of whom 74 (46.3%) had placenta previa, 28 (17.5%) had PAS, and 58 (36.3%) were pregnant women in a healthy condition. The diagnosis was suspected by ultrasound examination and confirmed by the intraoperative findings and the pathology report. Demographic and obstetric characteristics data of the pregnant women, maternal and fetal outcomes, screening tests for the first and second trimester results of serum analysis were obtained retrospectively from the hospital records. The significance threshold was set at $p<0.05$ using the IBM SPSS.25 software.

Results: The mean age was significantly higher in the previa and PAS groups. The groups differed significantly in terms of the history of prior cesarean deliveries and gestational age at delivery. The PAS group had the lowest APGAR score and the lowest newborn weight (p<.001). Compared to the PAS group, the previa group's pregnancy associated plasma protein-A (PAPP-A) Mom value was considerably greater (p=.008). The alpha-fetoprotein (AFP) Mom value was significantly higher in the group of healthy pregnant women than in the group of previa (p=.015). Compared to the previa (p=.008) and PAS (p=.024) groups, the healthy pregnant group's Unconjugated Estriol-3 (UE3) Mom value was much higher.

Conclusion: Although the obstetric, fetal and maternal outcomes in our study were consistent with the literature, the serum analysis results were not.

Keywords: Placenta previa, PAS, PAPP-A, AFP, UE3

INTRODUCTION

Placenta previa refers to complete closure of the cervical os by the placenta.[1,3] The prevalence rate is 5.2/1000.[4] A number of adverse effects for both the mother and the fetus are linked to abnormal placental invasion, such as thrombophlebitis, septicemia, intrauterine growth restriction (intrauterine growth restriction), premature labor, prenatal and postnatal hemorrhage and malpresentation.[1,5] The placenta accreta spectrum (PAS) is used to describe abnormal invasion of the placenta. PAS includes placenta accreta (invasion to myometrium <50%), placenta increate (invasion to myometrium >50%), and placenta percreta (invasion to myometrium, uterine serosa, and neighboring organs).[6] PAS is defined in many guidelines in the literature.[7,9] The main risk factors associated with PAS include previous uterine surgery, curettage, placenta previa, advanced maternal age, multiple births and manual removal of the placenta.[10]

In patients with a history of prior cesarean deliveries, placenta previa is the most significant risk factor for PAS. Patients with placenta previa who have had one cesarean surgery have a 3% chance of developing PAS; however, the risk rises as more cesarean sections are performed.[11] The reported risk of PAS in patients with a history of a single cesarean section without placenta previa was 0.03%.[12] Jauniaux et al.[12] reported that the prevalence rate of PAS was 0.01%–1%. In addition to the demographic and obstetric risk factors, serum analyzes in the

first and second trimester of these patients can now provide information about abnormalities of placental invasion.[13,14]

This study aimed to evaluate serum analytes and fetomaternal outcomes in patients with placenta previa and associated PAS in our hospital.

METHODS

This study was carried on the Perinatology Clinic of Etlik Zübeyde Hanım Women's Health Care Training and Research Hospital between September 2019 and September 2022 by retrospective review of patient records. Approval was obtained from Etlik Zübeyde Hanım Women's Health Care Training and Research Hospital Non-interventional Clinical Researches Ethics Committee for the study (Date: 09.10.2024, Decision No: 2024/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 160 patients, including 74 (46.3%) with placenta previa, 28 (17.5%) with PAS, and 58 (36.3%) healthy pregnant women were included in the study. Upon suspected ultrasonographic signs indicative of the diagnosis, intraoperative results and pathology reports were used for the purposes of confirmation. Demographics (age and body-mass index (BMI)) and obstetric characteristics (gravida, parity, and previous history of cesarean section), maternal and fetal outcomes (hysterectomy, conservative methods, including Bacri balloon introduced after cesarean section, compression sutures, and uterine artery ligation) were used. Neonatal intensive care unit (NICU) and fetal outcomes of pregnant women included in the study were retrieved retrospectively from hospital records (**Table 1**). The diagnosis of PAS was based on the clinical staging system of intraoperative International Federation of Gynecology and Obstetrics (FIGO) and pathologic diagnosis.[7]

The serum analytes of the groups in the first and second trimester screening test are listed in **Table 2**. The values are given as multiples of the median (Mom) and comparison between groups.

Table 2. Comparison of first and second trimester biochemical markers between groups

	Previa (n=74, 46.3%)	PAS (n=28, 17.5%)	Healthy (n=58, 36.3%)	p value
PAPP-A Mom	.98 (.64-1.25)	.58 (.43-.85)	.92 (.57-1.13)	.010*
AFP Mom	.91 (.61-1.24)	1.10 (.57-2.27)	1.13 (.91-1.46)	.016*
FBhcg Mom	.91 (.67-1.51)	1.12 (.68-1.98)	.82 (.59-1.19)	.099
Bhcg Mom	.80 (.51-1.08)	.91 (.68-1.91)	.98 (.65-1.40)	.046*
UE3 Mom	.74 (.43-.99)	.69 (.52-.90)	.88 (.71-1.09)	.003*

Continuous variables median as shown IQR. Abbreviations: PAS: Placenta accreta spectrum, PAPP-A: Pregnancy-associated plasma protein A, AFP: Alfa-fetoprotein, FBhcg: Free beta human chorionic gonadotropin, Bhcg: Beta human chorionic gonadotropin, UE3: Unconjugated estriol-3

Statistical Analysis

Descriptive statistics for continuous variables are reported as median and interquartile range (IQR), whilst categorical variables are represented as frequency (n) and percentage (%). The Kolmogorov–Smirnov test was employed to evaluate the normality of data distribution. The Kruskal–Wallis test was employed to compare continuous variables across groups. Dunn's post-hoc test was utilized for pairwise comparisons when substantial differences were identified. The Chi-square test was employed to investigate the relationships between category variables. All statistical analyses were conducted using IBM SPSS Statistics version 25, with a p-value of <0.05 being statistically significant.

Table 1. Comparison of feto-maternal characteristics between groups

	Placenta previa (n=74, 46.3%)	PAS (n=28, 17.5%)	Healthy (n=58, 36.3%)	p value
Age (years)	32.00 (28.00-37.00)	33.00 (31.25-36.50)	29.00 (24.75-33.00)	.002*
Parity	1.00 (.00-2.00)	2.00 (1.00-3.00)	1.00 (.75-2.00)	.006*
Gravida	3.00 (1.00-4.00)	4.00 (2.25-5.00)	3.00 (2.00-3.00)	.011*
GW at delivery	35.00 (32.00-36.00)	34.00 (31.50-36.00)	38.00 (37.00-39.00)	<.001*
Previous C/S number	.00 (.00-.00)	2.00 (1.00-2.00)	.00 (.00-1.00)	<.001*
BMI (kg/m^{2})	27.00 (25.00-30.00)	28.00 (25.00-30.00)	28.00 (25.00-30.00)	.608
Placental localization				
Anterior	30 (40.5)	16 (57.1)	32 (55.2)	.154
Posterior	44 (59.5)	12 (42.9)	26 (44.8)	
Maternal outcome				<.001*
Histerectomy	0 (0.0)	11 (39.3)	1 (1.7)	
C/S	56 (75.7)	2 (7.1)	52 (89.7)	
Conservative method	18 (24.3)	15 (53.6)	5 (8.6)	
Transfusion				
Yes	22 (29.7)	21 (75.0)	3 (5.2)	<.001*
None	52 (70.3)	7 (25.0)	55 (94.8)	
Fetal outcome				
NICU	28 (37.8)	13 (46.4)	10 (17.2)	.008*
Apgar 5. Dk	9.00 (7.00-9.00)	8.00 (7.00-9.00)	9.00 (9.00-10.00)	<.001*
Newborn weight	2452.50 (1972.50-2816.25)	2322.50 (1920.00-2773.75)	3030.00 (2888.75-3355.00)	<.001*

Continuous variables median (IQR); categorical variables are given as n (%). Abbreviations: PAS: Placenta accreta spectrum, BMI: Body-mass index, GW: Gestational week, C/S: Caesarean section, NICU: Neonatal intensive care unit

RESULTS

Among the 160 pregnant women participating in the study, 74 (46.3%) were diagnosed with placenta previa, 28 (17.5%) with placental accreta spectrum (PAS), and 58 (36.3%) were categorized as the healthy group. Notable disparities were seen across the groups regarding age, parity, and gravida (p=.002, .006, .011, respectively; Kruskal–Wallis test). The Dunn post-hoc test indicated that the mean age of the control group was considerably lower than that of both the previa (p=.025) and PAS groups (p=.004). The parity and gravida values were markedly reduced in the previa group in comparison to the PAS group (p=.004 and p=.008, respectively, **Table 1**).

Anotable disparity existed between groups regarding gestational age (p<.001); the Dunn test indicated that the control group exhibited a significantly greater gestational age than both the previa and PAS groups (p<.001 for each comparison). The quantity of prior cesarean sections varied significantly (p<.001); the PAS group exhibited a markedly greater number of cesarean sections in comparison to both the previa and control groups (p<.001 for each comparison).

The healthy group exhibited a significantly greater birth weight than the previa and PAS groups (p<.001 for both comparisons; Dunn test). The 5-minute Apgar score was considerably elevated in the control group relative to the previa (p<.001) and PAS (p=.002) groups.

Substantial disparities were observed in maternal outcomes (p<.001). The cesarean section rate was minimal in the PAS group (7.1%), much lower than in the previa (75.7%) and control (89.7%) groups. Hysterectomy occurred most frequently in the PAS group (39.3%), although this finding was not statistically significant. Conservative procedures were utilized more often in the PAS group (53.6%) than in the previa (24.3%) and control groups (8.6%), although the difference lacked statistical significance.

The necessity for transfusion exhibited considerable variation among groups (p<.001). The transfusion rate in the control group (5.2%) was statistically significantly lower compared to the previa (29.7%) and PAS (75.0%) groups. The rate of neonatal admissions to the intensive care unit (ICU) was greater in the PAS group (46.4%) than in the control group (17.2%), with this difference being statistically significant (p=.008, **Table 1**).

Serum tests revealed significant variations in PAPP-A MoM values between groups (p=.010); Dunn's test indicated that the previa group exhibited considerably greater values than the PAS group (p=.008, **Table 2**).

AFP MoMreadings exhibited notable variations (p=.016); the control group demonstrated significantly elevated values compared to the previa group (p=.015). BhCG MoM values exhibited borderline significance between groups (p=.046); however, the Dunn test could not identify any significant differences in pairwise comparisons. UE3 MoMlevels exhibited significant differences (p=.003); the Dunn test revealed that the control group had markedly higher values than both the previa (p=.008) and PAS (p=.024) groups (**Table 2**).

DISCUSSION

This study compared risk factors associated with placenta previa, PAS and maternal-fetal outcomes. A number of risk factors for placenta previa were suggested by previous studies, including advanced maternal age (>35 years), multipartite, previous history of uterine surgery, history of placenta previa, assisted reproductive technology, and dilatation curettage.[14,17] In this study, the mean age was relevantly higher in the previa and PAS groups. With increasing age, damage to the vascular endothelia can occur, leading to insufficient development of the decidua and implantation of the placenta, which in turn leads to the development of PAS.[18] The number of previous cesarean section was higher in the PAS group. Previous studies have suggested that the main risk factors for PAS are placenta previa previous uterine surgery.[19] Cesarean section scars, curettage or previous uterine surgery damage the endometrial tissue and trophoblasts can grow abnormally in these areas.[20] Patients included in the previa and PAS groups delivered earlier than healthy pregnant women. Relevant guidelines currently recommend delivery between 36 0/7 and 37 0/7 weeks of gestation in cases of placenta previa.[21] The gestational age at delivery was earlier than the recommended gestational age due to emergency hemorrhagic presentation in certain patients included in the study. The recommended gestational age for planned cesarean section or hysterectomy in stable PAS cases was week 34 0/7-35 0/7; where an earlier gestational week may be recommended in cases such as persistent bleeding, premature rupture of membranes, and preeclampsia.[22] The PAS cases in this study were scheduled to deliver at the recommended week upon completion of antenatal steroid doses. Compared to the group of healthy pregnant women, the previa group had greater rates of hysterectomy and transfusion. The high rate of hysterectomies and blood transfusions in PAS cases was also shown in the study by Ogawa et al.[23] This suggests that the gynecologist may be less hesitant to perform a hysterectomy in cases of advanced age, multiparity and a history of cesarean sections. There was no significant difference between the anteriorly and posteriorly placenta. In the study by Fındık et al.,[24] hysterectomies and blood transfusions were observed more frequently in cases with an anterior placenta. In our study, there was no significant difference between anteriorly and posteriorly placenta. None of the patients with PAS were admitted to the adult intensive care unit. This may be attributed to planned delivery and the preparation of blood in advance. Newborn weight was lower in the previa and PAS groups because of the earlier delivery week. The results found in the comparison of serum analyzes did not correspond to the literature. Many studies in the literature have shown that the PAPP-A value in the first trimester and the screening test of serum analytes performed in the second trimester can predict abnormalities of the placenta.[25,26] Maternal serum analytes in first and second trimester screening tests can provide insights into various fetal or maternal disorders during other trimesters of pregnancy. Unexplained AFP values exceeding 2.5 Mom in the second trimester indicate conditions such as intrauterine death, intrauterine growth restriction, spontaneous abortion, oligohydramnios, gestational hypertension, and placental abruption; elevated human chorionic gonadotropin (HCG) levels (>2.0 Mom) may result in adverse pregnancy outcomes, including gestational hypertension and preterm birth.[28,29] Low UE3 levels have

been correlated with worse pregnancy outcomes.[28,29] Awareness of these concerns, including placental anomalies, is crucial to ensure that the clinical management and delivery of these pregnancies are managed by skilled teams in tertiary hospitals, therefore reducing maternal and fetal morbidity and mortality. Our study showed that the PAPP-A value was higher in the previa group. AFP and HCG levels measured in the second trimester were not elevated in the previa and placental invasion abnormalities groups.

Limitations

This study is limited by its nature as a single-center retrospective analysis. This situation restricts the establishment of a causal relationship. The other reason was the limited number of patients and the unavailability of serum analyses for certain individuals.

CONCLUSION

Early detecting of placenta previa instances facilitates the anticipation of potential hemorrhaging and the execution of requisite interventions; it guarantees that cases are referred to hospitals with the appropriate equipment.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from Etlik Zübeyde Hanım Women's Health Care Training and Research Hospital Non-interventional Clinical Researches Ethics Committee for the study (Date: 09.10.2024, Decision No: 2024/09).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Comparative study of metabolic syndrome and cardiovascular risk in women with and without polycystic ovary syndrome

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ABSTRACT

Aims: Polycystic ovary syndrome (PCOS) is associated with an increased risk of metabolic syndrome (MetS) and cardiovascular diseases (CVD). This study aimed to evaluate the prevalence of MetS and cardiovascular risk factors in women with and without PCOS to better understand the broader implications of the syndrome.

Methods: This comparative cross-sectional study included 400 women, aged 20 to 40 years, who were recruited from an outpatient clinic. Participants were divided into two groups: group I (200 women with PCOS, diagnosed according to the Rotterdam criteria) and group II (200 age-matched controls without PCOS). The data collected included body-mass index (BMI), fasting glucose, lipid profiles, blood pressure, and inflammatory markers (CRP and IL-6). MetS was defined using the NCEP ATP III criteria. Statistical analyses were performed to compare metabolic and cardiovascular markers between groups, with a significance level set at $p<0.05$.

Results: MetS prevalence was significantly higher in the PCOS group (60%) compared to controls (30%) ($p<0.01$). Insulin resistance was greater in the PCOS group, with a mean HOMA-IR of 3.2 versus 1.8 in controls ($p<0.001$), and fasting glucose levels were elevated (110 mg/dl vs. 95 mg/dl, $p<0.001$). Lipid profiles were more atherogenic in PCOS, with higher triglycerides (150 mg/dl vs. 100 mg/dl, $p<0.01$), higher LDL cholesterol (130 mg/dl vs. 110 mg/dl, $p<0.01$), and lower HDL cholesterol (40 mg/dl vs. 50 mg/dl, $p<0.05$). Blood pressure was also elevated in PCOS (systolic: 135 mmHg vs. 120 mmHg, $p<0.05$; diastolic: 85 mmHg vs. 75 mmHg, $p<0.05$). Inflammatory markers were significantly higher in PCOS, including CRP (4.2 mg/L vs. 2.1 mg/L) and IL-6 (6.0 pg/ml vs. 3.0 pg/ml) (both $p<0.01$).

Conclusion: Metabolic and cardiovascular risk factors are significantly more prevalent in women with PCOS. Early intervention, including management of insulin resistance, dyslipidemia, hypertension, and inflammation, is crucial to reducing cardiovascular morbidity and long-term health risks in this population.

Keywords: Polycystic ovary syndrome, metabolic syndrome, cardiovascular risk, insulin resistance, dyslipidemia

INTRODUCTION

The estimation of worldwide prevalence of polycystic ovary syndrome (PCOS), the predominant endocrine condition encountered among women of reproductive age, reaches 5-10%.[1] PCOS is defined by the presence of elevated androgen levels, irregular ovulation, and the morphological appearance of polycystic ovaries. It presents as a complex and multi-faceted health challenge with aspects going beyond gynecological concerns.[2] Metabolic syndrome (MetS) and cardiovascular diseases (CVD) are additional long-term morbidities for which women with PCOS have been shown to be at increased risk.[3] An association between PCOS and metabolic and cardiovascular risk factors has been rather well established, though the basic mechanisms underlying that association remain to be fully elucidated. In the face of the high prevalence of PCOS and its relations to metabolic and cardiovascular health risks, there is an urgent need to outline these associations to improve strategies of prevention, diagnosis, and management.

Recognized as a major risk factor for CVD, MetS consists of a group of interrelated conditions, namely insulin resistance, abdominal obesity, elevated blood pressure,

and dyslipidemia.[4] Women with PCOS seem particularly vulnerable for MetS, as several studies have reported higher MetS prevalence rates in PCOS patients when compared to the general population.[3,4] Studies have identified that women with PCOS have a two- to four-fold increased risk of MetS, independently of age and body-mass index (BMI).[5] The association between PCOS and MetS is further complicated by the high prevalence of insulin resistance in PCOS patients. Insulin resistance is present in 50-70% of women with PCOS irrespective of obesity and is felt to play a key role in the development of both MetS and CVD in the PCOS patients.[6]

Besides metabolic disturbances, dyslipidemia, manifested by high triglycerides, low high-density lipoprotein (HDL) cholesterol, and elevated low-density lipoprotein (LDL) cholesterol, is also commonly found among women with PCOS.[7] All these disturbances in the lipid profile perpetuate the risk of developing CVD by enhancing atherogenic changes which may eventually lead to arterial plaque formation.[8] Previous studies reported comparable lipid profiles in women with PCOS and specified that the management of disturbed lipid is the most important factor for the reduction of long-term cardiovascular risk in these patients.[9] Dyslipidemia, despite being well documented in PCOS, often remains poorly addressed in clinical practice due to lack of awareness about the long-term consequences.[8]

Other critical factors for CVD commonly seen in PCOS include hypertension. Studies reported higher blood pressure in PCOS women, suggesting possible chronic sympathetic activation and underlying endothelial dysfunction.[10] Hypertension is an established cause of cardiovascular morbidity, and its association with PCOS would suggest the indication for its management in this population.[4,10] In addition, there are new indications that PCOS may be associated with a chronic low-grade pro-inflammatory state, as supported indirectly by increased levels of inflammation markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) within women with PCOS.[11]

The present study, therefore, aims to present the overall comparative analysis of MetS prevalence and cardiovascular risk factors in women both with and without PCOS. In this regard, the investigation encompasses a wide variety of parameters for insulin resistance, lipid profile, blood pressure, and inflammation markers to clearly outline how these risk factors cluster in women with PCOS.

METHODS

Ethics

The study was conducted in accordance with the Declaration of Helsinki. Ethics Committee approval was granted by Bezmiâlem Vakıf University Non-interventional Researches Ethics Committee (Date: 31.12.2024, Decision No: 2024/431). As the study was retrospective in nature, it utilized pre-existing patient records, and no new interventions were made. Consequently, written informed consent was not required from the participants. However, all patient data were anonymized and de-identified to protect privacy and ensure confidentiality. Identifiable information was strictly excluded from the dataset, and the data were stored securely in compliance with applicable privacy regulations. The research adhered to ethical standards to ensure that no personal identifiers were disclosed at any stage of the study, maintaining the confidentiality and integrity of the participants' health information.

This was a cross-sectional comparative study conducted at an outpatient clinic, with the enrollment of 400 women between 20 and 40 years of age. Participants were divided into two groups: group I consisted of 200 women diagnosed with PCOS according to the Rotterdam criteria, while group II consisted of 200 age-matched controls without PCOS. Inclusion criteria ensured that the participants in both groups were comparable in age, minimizing the impact of age-related confounding factors on metabolic and cardiovascular outcomes.

Data Collection

Anthropometric and biochemical data were collected for each participant. Anthropometric measurements included BMI and waist circumference to assess obesity levels. Biochemical analyses included fasting glucose, a full lipid profile (triglycerides, HDL, and LDL cholesterol), blood pressure, and inflammatory markers (CRP and IL-6). Insulin resistance was evaluated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).

Metabolic Syndrome (MetS) Definition

MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. The diagnosis of MetS required the presence of at least three of the following five factors: abdominal obesity (waist circumference), hypertriglyceridemia, reduced HDL cholesterol, hypertension, and elevated fasting glucose.

Statistical Analysis

Comparisons of the prevalence of MetS and cardiovascular risk factors between the PCOS and control groups were made using statistical analyses. Mean differences in continuous variables like fasting glucose, triglycerides, and blood pressure were compared by independent t-tests. Categorical variables regarding the prevalence of MetS and insulin resistance were analyzed comparatively using Chi-square tests. On statistical significance, $p<0.05$ was considered and the results were stated as mean values with their standard deviations for continuous variables, while categorical data were expressed in percentages.

RESULTS

The study included a total of 400 women, aged 20 to 40 years, who were enrolled from an outpatient clinic. Participants were divided into two groups: group I consisted of 200 women diagnosed with PCOS based on the Rotterdam criteria, and group II consisted of 200 age-matched controls without PCOS. The two groups were comparable in age, which minimized potential confounding factors related to age when analyzing metabolic and cardiovascular outcomes.

MetS was significantly more common amongst women with PCOS compared with controls. In fact, MetS according to the NCEP ATP III criteria was present in 60% of women with PCOS as compared to 30% of controls ($p<0.01$). The main cardiovascular and metabolic parameters are summarized in **Table 1**, with significant differences found in insulin

Table 1. Cardiovascular and metabolic parameters

Parameter	PCOS group (mean±SD)	Control group (mean±SD)	p-value	Notes
MetS prevalence	60% (120/200)	30% (60/200)	<0.01	Proportion meeting NCEP ATP III criteria
HOMA-IR	3.2±1.0	1.8±0.6	<0.001	Elevated in PCOS group
Fasting glucose (mg/dl)	110±10	95±8	<0.001	Higher in PCOS group
Triglycerides (mg/dl)	150±20	100±15	<0.01	Higher in PCOS group
HDL cholesterol (mg/dl)	40±5	50±6	<0.05	Lower in PCOS group
LDL cholesterol (mg/dl)	130±10	110±8	<0.01	Higher in PCOS group
Systolic BP (mmHg)	135±10	120±8	<0.05	Higher in PCOS group
Diastolic BP (mmHg)	85±8	75±6	<0.05	Higher in PCOS group

PCOS: Polycystic ovary syndrome, SD: Standard deviation, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, MetS: Metabolic syndrome, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BP: Blood pressure

resistance, fasting glucose, lipid profile, and blood pressure between the two groups. The PCOS group consistently had an adverse profile on these measures indicative of increased predisposition to MetS and CVD.

Data in Table 1 show the clustering of metabolic risk factors in women with PCOS. An increased insulin resistance and fasting glucose would indicate a marked impairment in glucose metabolism, which increases the risk for type 2 diabetes. The adverse lipid profile, including higher levels of triglycerides and LDL cholesterol coupled with lower levels of HDL cholesterol, would suggest an atherogenic (artery-clogging) risk profile in the PCOS group.

Meanwhile, insulin resistance and fasting glucose did show a difference between the PCOS and controls. The mean value of HOMA-IR among women with PCOS was 3.2 (SD±1.0) as compared to 1.8 (SD±0.6) in controls (p<0.001). In a similar way, the level of fasting glucose was higher among the PCOS group, as it averaged at 110 mg/dl (SD±10) against that of controls at 95 mg/dl SD±8, (p<0.001). Blood pressure was also significantly higher among participants with PCOS. The average systolic blood pressure was 135 mmHg (SD±10) in subjects with PCOS compared to 120 mmHg SD±8 in the control group (p<0.05). The diastolic blood pressure was also similar: 85 mmHg (SD±8) for the PCOS group and 75 mmHg (SD±6) for controls (p<0.05) (Table 2).

Table 2. Insulin resistance, fasting glucose, and blood pressure parameters

Parameter	PCOS group (mean±SD)	Control group (mean±SD)	p-value
HOMA-IR	3.2± 1.0	1.8±0.6	<0.001
Fasting glucose (mg/dl)	110±10	95±8	<0.001
Systolic BP (mmHg)	135±10	120±8	<0.05
Diastolic BP (mmHg)	85±8	75±6	<0.05

PCOS: Polycystic ovary syndrome, SD: Standard deviation, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BP: Blood pressure

Significant dyslipidemia was noted in the PCOS group compared with controls. Mean triglyceride levels were 50% higher, on average, at 150 mg/dl (SD±20) compared with controls at 100 mg/dl (SD±15) (p<0.01). LDL cholesterol levels were also higher among women with PCOS, mean 130 mg/dl, (SD±10), versus controls, mean 110 mg/dl, SD±8 (p<0.01). On the other hand, HDL cholesterol, which is protective against CVD, was found to be lower in the PCOS group, with a mean of 40 mg/dl (SD±5) compared with 50 mg/dl (SD±6) in the control group (p<0.05) (Table 3).

Table 3. Lipid profile parameters

Lipid parameter	PCOS group (mean±SD)	Control group (mean±SD)	p-value
Triglycerides (mg/dl)	150±20	100±15	<0.01
HDL cholesterol (mg/dl)	40±5	50±6	<0.05
LDL cholesterol (mg/dl)	130±10	110±8	<0.01

PCOS: Polycystic ovary syndrome, SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

Chronic low-grade inflammation, as reflected by higher CRP and IL-6, was evident in the PCOS group. The level of CRP in women with PCOS was significantly higher, 4.2 mg/L ±1.0 SD, compared to controls, 2.1 mg/L ±0.8 SD (p<0.01). Similarly, IL-6 levels were elevated, with a mean value of 6.0 pg/ml ±1.5 SD in the PCOS group compared to 3.0 pg/ml ±1.2 SD in controls (p<0.01) (Table 4).

Table 4. Inflammatory markers parameters

Inflammatory marker	PCOS group (mean±SD)	Control group (mean±SD)	p-value
CRP (mg/L)	4.2±1.0	2.1±0.8	<0.01
IL-6 (pg/ml)	6.0±1.5	3.0±1.2	<0.01

PCOS: Polycystic ovary syndrome, SD: Standard deviation, CRP: C-reactive protein, IL-6: Interleukin-6

DISCUSSION

Such findings from this comparative study bring into focus the difference in metabolic and cardiovascular risks between women with and without PCOS, thereby shedding much light on the health consequences of PCOS. Indeed, the findings obtained indicated that women with PCOS did face notably higher risks for MetS and its associated cardiovascular conditions, including insulin resistance, dyslipidemia, hypertension, and chronic low-grade inflammation. These findings thus agree with and extend earlier studies that have emphasized the need for comprehensive care approaches in managing multifaceted risks associated with PCOS.[4,8,10,11]

The higher prevalence of MetS in our cohort of PCOS, as compared to controls, was 60% versus 30%, which confirms findings from similar studies in which a strong association between PCOS and MetS has been consistently reported. Indeed, large-scale studies such as those by Zaeemzadeh et

al.[12] showed that the prevalence of MetS in women with PCOS was high, indicating that women with the condition are more prone to metabolic abnormalities irrespective of age or BMI. Confirmation to this fact comes from Wekker et al.[9] during their meta-analysis, where they proved that the risk for MetS in women with PCOS is increased 2- to 4-fold compared with the general population. These findings confirm the results of our study and further underline the urgent need for screening and management of the components of MetS in women with PCOS.

The high insulin resistance and fasting glucose among PCOS patients in our study further strengthen the growing literature that identifies insulin resistance as a cardinal feature of PCOS. Indeed, our findings of an average HOMA-IR value of 3.2 among the PCOS group versus 1.8 among controls are in agreement with the consensus of earlier studies showing that insulin resistance among PCOS patients is disproportionately higher compared to age- and weight-matched controls, such as that indicated by Shirazi et al.[13] In addition, one study from Xu et al.[14] demonstrated that insulin resistance and impaired glucose tolerance in women with PCOS cut across all ethnic backgrounds, further solidifying these abnormalities as being intrinsic to PCOS, rather than representative of obesity or other environmental/external factors found in certain populations.

The high level of fasting glucose in our results signals a risk for type 2 diabetes in women with PCOS. The findings correspond with the work of Anagnostis et al.,[15] who note that women with PCOS have increased lifetime risk for type 2 diabetes, generally relating to the degree of insulin resistance. Collectively, these findings support the necessity of systematic study of glucose metabolism in women with PCOS for timely detection of insulin resistance and further reduction of risk according to the development of diabetes mellitus and its cardiovascular complications.

Our study showed significant lipid abnormalities in the PCOS group, since high levels of triglycerides and low HDL cholesterol with an increased LDL cholesterol level were observed. These data confirm the general dyslipidemic pattern reported in the changes associated with PCOS. For example, Guo et al.[8] performed a similar study on lipid abnormalities in a cohort of PCOS patients, since they reported higher levels of triglycerides and LDL and lower levels of HDL compared to controls. Moreover, the pattern of lipids present in our study-particularly the low HDL cholesterol-would be expected to be associated with an atherogenic profile that significantly raises cardiovascular risk.

In our study, HDL was lower and triglycerides higher, agreeing with Bizoń et al.[16] that these were common lipid disturbances in PCOS independent of BMI. This points to the fact that dyslipidemia in PCOS is most likely due to an inherent hormonal and metabolic disturbance characterizing the condition rather than merely being a function of weight. Therefore, these findings stress the need for lipid management in patients with PCOS either through dietary interventions or pharmacological treatments of dyslipidemia, which can effectively reduce cardiovascular risks.

The higher systolic and diastolic blood pressures of the PCOS group in our study agree with the increasing number of reports of the greater prevalence of hypertension among PCOS women. Zhang et al.[17] demonstrated similar elevations in blood pressure among PCOS patients, and a link was given to the elevated sympathetic tone and endothelial dysfunction characteristic of the condition. In another study, Joham et al.,[18] reported that in women with PCOS, hypertension was around 40% more prevalent than in age-matched controls, even after adjustment for BMI. The results of our study also bear significance, since the average systolic pressure stands at 135 mmHg in the PCOS group in contrast to 120 mmHg in controls and can be used for advocacy of regular monitoring of blood pressure in women diagnosed with PCOS. Among the well-recognized risk factors for cardiovascular morbidity, hypertension has been associated in PCOS, suggesting that early and frequent monitoring of blood pressure may be needed in such patients, along with practice of lifestyle modifications and pharmacological interventions which address this risk.

Our study also supports the hypothesis that chronic low-grade inflammation is a common feature of PCOS, as reflected in our study by higher levels of CRP and IL-6 in the PCOS cases. In fact, several studies on PCOS have documented raised levels of CRP and IL6, including studies by Rudnicka et al.,[11] which not only indicated that women with PCOS have higher levels compared to healthy controls for these inflammatory markers but also have reported this continuous increase in inflammatory markers. Chronic inflammation has been shown to further enhance insulin resistance, endothelial dysfunction, and other cardiovascular risk factors, thus suggesting a cyclical relationship that may increasingly deteriorate metabolic and cardiovascular outcomes with time in women with PCOS.[3,8,11] These results are in agreement with the findings of Khichar et al.,[19] who concluded that inflammatory markers such as CRP were significantly higher in women with PCOS as compared to controls, irrespective of obesity status, suggesting thereby that inflammation forms an intrinsic part of PCOS. It is believed that this inflammatory state contributes to the formation of atherosclerosis and other cardiovascular pathologies in patients with PCOS Abraham et al.[20] reinforcing the concept that anti-inflammatory treatments, such as lifestyle modifications and possibly pharmacological therapies, could be considered.

The results of this study bear considerable clinical significance for the management of women with PCOS. The high prevalence of MetS and high cardiovascular risk factors found in this population would suggest a comprehensive approach to screening and intervention. Early diagnosis of insulin resistance, dyslipidemia, hypertension, and inflammation in women with PCOS would definitely mitigate their risk for cardiovascular disease. Many risk factors tend to cluster, so a routine assessment of metabolic and cardiovascular markers should be considered standard care for the woman with PCOS.

Interventions for people with PCOS include lifestyle modification involving dietary habits, exercise, and body weight. Lifestyle modifications produced a minor weight

reduction that, however proved useful in improving insulin sensitivity and lowering blood pressure as well as normalization of lipid levels.[21] Insulin resistance is also treated using pharmacological means, such as metformin, which in turn might reduce metabolic and cardiovascular risks for PCOS patients.[22] Also, anti-inflammatory interventions-as in supplementation with omega-3 fatty acids or other anti-inflammatory agents-may help with the pro-inflammatory state commonly seen in women with PCOS.[23]

Limitations and Future Research Directions

Although this study comprehensively gives an overview of cardiovascular and metabolic risks associated with PCOS, certain limitations have to be considered. The first limitation is the cross-sectional study design, which restricts the ability to infer causality. The study provides valuable associations, but it cannot determine the directionality of these relationships. Longitudinal studies are needed in the future to assess the progression of metabolic and cardiovascular risk factors among women with PCOS and whether their trajectories can be altered through early interventions. Another limitation is the potential for selection bias due to the retrospective nature of the study, where participants were selected based on pre-existing medical records. This may affect the representativeness of the sample, limiting the generalizability of the findings. Additionally, incomplete data may have impacted the results, as certain variables, such as detailed demographic information, may not have been consistently documented in the records. Future studies should address these biases by utilizing more diverse and representative populations and ensuring more complete and accurate data collection.

The sample size, while adequate for detecting significant differences between groups, could be complemented by further studies involving larger cohorts to enhance the power and applicability of the results. In addition, future research should aim to clarify the mechanisms underlying the relationship between PCOS, inflammation, insulin resistance, and cardiovascular risk factors. Understanding these pathways in greater detail could lead to the development of targeted therapies that address the root causes of cardiovascular risk in women with PCOS, offering hope for improved clinical outcomes. Finally, studying the responses of this high-risk population to different treatment approaches—such as lifestyle interventions, pharmacological therapies, and anti-inflammatory treatments—could provide valuable insights into the most effective strategies for managing the metabolic and cardiovascular risks associated with PCOS.

CONCLUSION

In summary, this study confirms that MetS, insulin resistance, dyslipidemia, arterial hypertension, and chronic inflammation are significantly more prevalent in women with PCOS than in women without PCOS. These findings highlight the urgent need for regular cardiovascular and metabolic screening in women with PCOS to detect and address these risk factors early. Clinicians are encouraged to adopt comprehensive, multidisciplinary management approaches, which should focus on the early identification and management of metabolic and cardiovascular risks that often cluster together in this population. Lifestyle modifications, pharmacological interventions, and anti-inflammatory treatments may help mitigate these risks. Furthermore, future studies should focus on investigating targeted therapies and preventive strategies that could reduce the long-term cardiovascular morbidity and mortality associated with PCOS, ultimately improving the overall quality of life for affected women.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bezmiâlem Vakıf University Non-interventional Researches Ethics Committee study (Date: 31.12.2024, Decision No: 2024/431).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Use of multiplex polymerase chain reaction test in hospitalized newborns with acute respiratory tract infection: a randomized controlled trial

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ABSTRACT

Aims: We aimed to investigate whether the use of multiplex polymerase chain reaction (PCR) test reduced the duration of hospital stay, duration of antibiotic use and total hospital costs in neonates with acute respiratory tract infection (RTI).

Methods: This was a retrospective cross-sectional study including newborns with a diagnosis of RTI. We included two groups to compare the durations of antibiotic treatment, lengths of hospital stay, and total hospital costs. The first group, referred to as the "respiratory tract panel (RTP) group," consisted of our patients who underwent RTP testing. For comparison, a "non-RTP group" was created by simulating the same patients as if they had not undergone RTP testing based on the recommendations of the national neonatal society for managing similar cases.

Results: Among 76 neonates, 20 (26.3%) of the patients were diagnosed with viral RTI and 23 (30.3%) were diagnosed with bacterial RTI according to RTP. No causative agent in the etiology of RTI was detected in 33 (43.4%) newborns. No significant difference was found when the RTP group and the non-RTP group were compared in terms of duration of antibiotic use and length of hospital stay. Total hospital costs were higher in the RTP group compared to the non-RTP group (22.700 [15.890-26.105] TRY vs. 20.430 [13.620-23.835] TRY, p=0.009).

Conclusion: The use of multiplex PCR test did not have effect on the duration of antibiotic use and hospital stay in neonatal RTI. However, total hospital costs increased. Therefore, RTP test should be used selectively, especially in developing countries.

Keywords: Bacterial agents, hospital costs, neonates, respiratory tract infections, viruses

INTRODUCTION

Acute respiratory tract infection (RTI) in the infancy period is a significant cause of morbidity and mortality, and surviving patients may face problems such as recurrent wheezing and asthma in the long-term.[1-3] Newborns, especially premature babies, are more susceptible to infections, including RTI, because their immune systems are not yet fully mature.[3,4] Symptoms of RTI can vary widely, from mild symptoms such as rhinnorrhea, nasal congestion and cough to severe respiratory failure requiring mechanical ventilation and even extracorporeal membrane oxygenation.[3] On the other hand, it is difficult to predict how the disease will make progress in the neonatal period, and even nasal congestion, which seems to be a simple finding due to upper RTI, is an important problem for neonates as it may cause difficulty in sucking, feeding and sleeping.[3]

Neonatal RTI can mimic bacterial sepsis by causing temperature instability, neurological signs, apnea, gastroenteritis, skin lesions, etc. according to the underlying microbiological agent.[1,3,5-7] A respiratory tract virus was detected in 8% of high-risk infants who were evaluated for late-onset sepsis in a neonatal intensive care unit (NICU) and initiated on antibiotic treatment, and in 6% of sepsis evaluations overall.[7] In another study, the detection rate of respiratory tract viral infection in newborns with suspected nosocomial bacterial sepsis was found to be 10%.[5] It has also

been shown that premature newborns with virus detected in periodic respiratory tract panels (RTP) have longer hospital stays and mechanical ventilation requirements compared to those with negative RTPs, and bronchopulmonary dysplasia is more common in these newborns.[8]

Multiplex polymerase chain reaction (PCR) is a sensitive and specific test for revealing RTI agents from respiratory secretions, but the use of this test has not been shown to shorten the duration of hospitalization or to reduce the frequency of antibiotic usage or general hospital cost in the childhood period.[9] Although expensive, multiplex-PCR methods can test presence of many pathogens simultaneously in a single specimen in a short period of time with a confirmation rate of over 80% in children with RTI symptoms. However, the tests may not reflect the ability of the pathogens to multiply or infectivity as the results might be positive several days after the virus can no longer be isolated by culture.[9,10] As there is no consensus on when to use multiplex-PCR, it may be feasible to use this test only if the results can change the clinical course such as when deciding using antibiotics or when deciding hospitalization.[9] In newborns admitted to the NICU due to RTI, the effect of the multiplex PCR testing on the duration of hospital stay, duration of antibiotic use and total hospital costs is unknown. In this study, we aimed to investigate whether the use of multiplex PCR test reduced the duration of hospital stay, duration of antibiotic use and total hospital costs in neonates with RTI in a level II NICU in a developing country.

METHODS

This was a retrospective cross-sectional study. Newborns who were admitted to the NICU with a diagnosis of RTI between September 2023 and June 2024 were included in the study. Ethical approval for the study was obtained from the Şehit Prof. Dr. İlhan Varank Training and Research Hospital Clinical Researches Ethics Committee (Date: 19.08.2024, Decision No: 2024/237). The study was completed in accordance with the Declaration of Helsinki as revised in 2013. Since the unit where the study was conducted was a level II NICU, newborns requiring invasive mechanical ventilation due to respiratory failure were referred to a level III NICU and were excluded from the study. Another exclusion criteria was the presence of major congenital anomalies and/or congenital heart disease. Since there was no delivery room in the center where the study was conducted, all patients were sent to our unit by a ground ambulance from other hospitals with the diagnosis of RTI. Among the patients hospitalized due to RTI, those with respiratory failure, auscultation findings (wheezing, rales, rhonchus) and appearance compatible with bronchiolitis (flattening of the ribs, increased aeration, perihilar fullness) or pneumonia (consolidation, infiltration) on the chest radiograph were diagnosed with lower RTI.[3] Upper RTI was defined as the presence of respiratory symptoms such as rhinnorrhea, nasal congestion, cough and sneezing without signs of lower RTI.

Respiratory Tract Infection Management and Follow-up Policy

Due to the fear of rapid deterioration, we monitored the patients with any signs of RTI in the neonatal period in the NICU for observation for at least 48 hours, even if only upper RTI signs were present. RTP was studied in all newborns who were admitted to our unit due to RTI findings within the first 24 hours of admission, and the results were obtained within 6 hours. The specimens were obtained by sterile flexible swabs which were inserted in each nostril and posterior nasopharynx, and a RTP was sent using a viral nucleic acid buffer transfer tube (vNAT®). This panel tests for 24 respiratory pathogens using the real-time multiplex PCR method, including *Mycoplasma pneumoniae, Bordatella pertussis*, Respiratory syncytial virus A/B (RSV), Parainfluenza virus types 1-4, Influenza A and B, Human metapneumovirus, Coronavirus (types OC43, 229E, NL63, and HKU1), Adenovirus, Human bocavirus, Human parechovirus, *Haemophilus influenzae, Legionella pneumophila, Streptococcus pneumoniae*, Rhinovirus/Enterovirus, and SARS-CoV-2.

In the presence of RTI, antibiotic treatment of the patients with viral agents detected in the RTP was discontinued, and antibiotic treatment of the patients with bacterial agents was decided according to the agent detected. If antibiotic treatment had not been started, the treatment decision was made according to the RTP results. The treatment of the patients whose RTP showed no causative agent despite RTI findings was planned by the consultant neonatologist according to the national neonatal society quideline.

All patients diagnosed with RTI underwent nasal irrigation with physiological saline whenever necessary. The patients, who were diagnosed with lower RTI, were administered 2 ml inhaled hypertonic saline 4-8 times a day, depending on the patient's condition. Inhaled salbutamol treatment was given to selected subjects whose auscultation findings worsened under inhaled hypertonic treatment.[11]

Respiratory failure was defined as presence of ongoing signs of respiratory distress and associated acidosis (pH<7.25), hypercarbia (partial pressure of arterial carbon dioxide [pCO_2] >60 to 65 mmHg), and hypoxemia (fraction of inspired oxygen [FIO_2]>40%). Intubation was reserved for neonates with respiratory failure and severe apnea on maximal nasal intermittent positive pressure ventilation (positive end-expiratory pressure ≥8 cm H_2O and positive inspiratory pressure ≥25 cm H_2O) support.[12] The newborns, who required intubation, were transferred to a level III NICU by ground ambulance.

The national guideline on neonatal infections-diagnosis and treatment for sepsis evaluation was used to create a second group for comparing the outcomes of our patients.[13] The first group, referred to as the "RTP group," consisted of our patients who underwent RTP testing upon admission. For this group, the data on the duration of antibiotic treatment, length of hospital stay, and total hospital costs were collected retrospectively. For comparison, a "non-RTP group" was created by simulating the same patients as if they had not undergone RTP testing. In the non-RTP group, the duration of antibiotic treatment, length of hospital stay, and total hospital costs were estimated based on the recommendations of the national neonatal society for managing similar cases. The outcomes for the RTP and non-RTP groups were then compared. According to the national neonatal society's guidelines, neonates with lower RTI were assumed to recieve

seven days of antibiotic therapy with a minimum hospital stay of seven days, and the total cost was calculated accordingly.

Statistical Analysis

The Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Data were assessed for normality using histogram plots and the Shapiro-Wilk test. Variables with a normal distribution were expressed as means and standard deviations (SD), while non-normally distributed variables were reported as medians and interquartile ranges (IQR) (25th and 75th percentiles). Parametric variables were compared using the Student's t-test, whereas nonparametric variables were analyzed with the Mann-Whitney U test. Categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. Both statistically significant and nonsignificant values were presented with their corresponding 95% confidence intervals. A p-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

During the study period, 79 neonates were eligible for enrollment, three neonates were excluded from the study as two of them needed intubation and one was diagnosed with atrioventricular septal defect in the follow-up, and 76 neonates were analyzed. The median gestational age of the neonates and the postnatal age on admission were 39 (38-40) week and 18 (13-24.2) day, respectively. The mean weight of the neonates on admission were 3187±519 grams. Two (2.5%) patients needed non-invasive ventilation support and five (6.3%) needed oxygen support. Thirty-two (42.1%) of the patients had upper RTI and 44 (57.9%) had lower RTI. No growth was detected in any blood culture, and all patients were discharged with recovery. Demographic and clinical characteristics, and laboratory results are summarized in Table 1.

Table 1. Demographic and clinical characteristics, and laboratory results (n=76)

Demographic characteristics	
Female[a]	29 (38.2)
Cesarean section[a]	42 (55.3)
Gestational age, w[b]	39 (38-40)
Birth weight, g[c]	3187±519
Postnatal age on admission, day[b]	18 (13-24.2)
Clinical characteristics	
Upper RTI/lower RTI[a]	32 (42.1)/44 (57.9)
Duration of antibiotic treatment[b]	5 (3-7)
Length of hospital stay[b]	7 (5-10)
Laboratory results during sepsis	
White blood cell,/μL[b]	10.280 (8.512-13.070)
Neutrophil,/μL[b]	3.090 (2.355-5.243)
Lymphocyte,/μL[b]	5.130 (4.065-6.395)
C-reactive protein, mg/l[b]	1.64 (0.60-8.42)
Procalcitonin, μg/l[b]	0.13 (0.10-0.22)

a: Number (percentage), b: Median (interquartile range), c: Mean±standard deviation, RTI: Respiratory tract infection

According to RTP, 20 (26.3%) of the patients were diagnosed with viral RTI and 23 (30.3%) were diagnosed with bacterial RTI. No causative agent in the etiology of RTI was detected in the RTP in 33 (43.4%) patients. The most common viral agent detected in RTP was RSV (n, %=9, 21) and the most common bacterial agent was *Streptococcus pneumoniae* (n, %=3, 30.2), both causing primarily lower RTI. The causative agents of RTI detected on RTP are summarized in Table 2.

Table 2. Respiratory tract infection agents detected on respiratory tract panel (n=43)

Viral agents (n=20)	**Upper RTI (n, %=7, 16.3)**	**Lower RTI (n, %=13, 30.2)**
Respiratory syncytial virus	2 (4.7)	7 (16.3)
Influenza virus type B	1 (2.3)	1 (2.3)
Human bocavirus	2 (4.7)	0 (0.0)
Coronavirus	0 (0.0)	4 (9.3)
Enterovirus	1 (2.3)	1 (2.3)
Adenovirus	1 (2.3)	0 (0.0)
Bacterial agents (n=23)	**Upper RTI (n, %=7, 16.3)**	**Lower RTI (n, %=16, 37.3)**
Streptococcus pneumoniae	5 (11.6)	8 (18.6)
Hemophilus influenza	2 (4.7)	6 (14.0)
Bordetella pertussis	0 (0.0)	2 (4.7)

RTI: Respiratory tract infection

The platelet count was found to be lower in viral RTI compared to in bacterial RTI (p=0.040), but platelet counts were within the normal range in both bacterial and viral RTI. Duration of antibiotic treatment and length of hospital stay were longer in bacterial RTI compared to viral RTI (p=<0.001, 0.027, respectively). Comparison of laboratory and clinical findings according to the underlying microorganisms are summarized in Table 3.

Table 3. Comparison of laboratory and clinical findings according to the underlying microorganisms (n=43)

Variables	**Viral**	**Bacterial**	**p value**
White blood cell,/μL[c]	11.579±3.50	12.053±4.10	0.688[*]
Neutrophil,/μL[c]	4.096±2.24	4.601±3.09	0.819[**]
Lymphocyte,/μL[c]	5.566±2.02	5.701±2.96	0.511[**]
Hemoglobin, g/dl[c]	14.45±2.43	13.66±2.03	0.257[*]
Platelet,/μL[c]	359.895±140.93	459.609±159.50	**0.040**[*]
C-reactive protein, mg/l[b]	1.59 (0.84-2.93)	1.54 (0.60-8.22)	0.883[**]
Procalcitonin, μg/l[b]	0.13 (0.10-0.19)	0.13 (0.08-0.19)	0.494[**]
Upper RTI/lower RTI[a]	7 (16.3)/13 (30.2)	7 (16.3)/16 (37.2)	0.750[***]
Fever, yes[a]	9 (20.9)	12 (27.9)	0.639[***]
Duration of antibiotic treatment[b]	4.50 (0-5)	7 (6-10)	**<0.001**[**]
Length of hospital stay[b]	7.00 (4.75-8.50)	10.00 (7.00-10.50)	**0.027**[**]

a: Number (percentage), b: Median (interquartile range), c: Mean±standard deviation, RTI: Respiratory tract infection, p values marked with corresponding symbols are calculated with (*) the Student t-test, (**) the Mann-Whitney U test, (***) the Chi-square test, and (****) the Fisher's exact test. Statistically significant p values are marked as bold.

No significant difference was found when the RTP group and the non-RTP group were compared in terms of antibiotic

treatment duration and length of hospital stay. On the other hand, total hospital costs were higher in the RTP group compared to the non-RTP group (22.700 [15.890-26.105] TRY vs 20.430 [13.620-23.835] TRY, p= 0.009) (**Table 4**).

Table 4. Comparison of durations of antibiotic treatment, lengths of hospital stay, and total hospital costs between the RTP and non-RTP groups (n=76)

Variables	RTP group	Non-RTP group	p value*
Duration of antibiotic treatment, day	5 (3-7)	7 (0-7)	0.217
Length of hospital stay, day	7 (5-10)	7 (7-7)	0.294
Total hospital cost, TRY	22.700 (15.890-26.105)	20.430 (13.620- 23.835)	**0.009**

RTP: Respiratory tract panel, TRY: Turkish lira, * Mann-Whitney U test. Statistically significant p values are marked as bold.

DISCUSSION

In our study, which we conducted to determine whether the use of multiplex PCR test affected the duration of antibiotic use, length of hospital stay and total hospital costs in neonatal RTI, we found that there was no significant difference in duration of antibiotic treatment and hospital stay between the RTP group and the non-RTP group, however total hospital costs were higher in the RTP group compared to the non-RTP group. Only a limited number of studies have examined the costs and antibiotic usage associated with multiplex-PCR for respiratory pathogens, and so far, no significant benefit has been demonstrated for this diagnostic technique in children without risk factors, and no validated algorithms currently exist for implementing this approach in clinical practice, even in children.[9]

Since we could not detect a viral or a bacterial agent in RTP in 43.4% of our patients, the fact that treatment decisions were made according to the recommendations of the national neonatology society may be the reason why we found the hospital cost to be higher in the RTP group compared to the non-RTP group with no difference in duration of antibiotic treatment and length of hospital stay. The other fact that the multiplex PCR we use in our unit is a very expensive kit to detect too many RTI agents may be another reason for the higher cost. However, it can be mentioned that the RTP test, which is an expensive test for developing countries, may increase total hospital costs without benefiting important clinical outcomes such as antibiotic use and hospital stay, and that this test should be used very selectively in centers with limited resources. The main value of multiplex PCR testing in children with RTI is to differentiate between viral and bacterial infections, guiding decisions on further investigations and antibiotic use. Despite advances in testing, its clinical utility and specific indications remain under-discussed.[14,15] Respiratory panel testing is crucial when results can guide clinical management, particularly in febrile infants under three months, immunocompromised patients, those at risk of influenza complications, and intensive care unit-admitted children.[14,15]

As expected, the durations of antibiotic treatment and hospitalization in bacterial RTI were longer compared to viral RTI, but the newborns diagnosed with viral RTI also recieved antibiotics for a median of 4.5 days. This may be because we are afraid to monitor newborns, who are a fragile population, without antibiotics, at least for a while, in the presence of accompanying clinical sepsis findings such as fever and respiratory distress and/or laboratory sepsis findings such as elevated C-reactive protein and procalcitonin. In a study of 334 NICU-admitted neonates, PCR detection of respiratory pathogens in nasopharyngeal aspirates was 10.2%, with Parainfluenza-1, human rhinovirus, parainfluenza-3, and RSV identified in decreasing frequency.[16] The main risks for detection of a respiratory patogen were increased age and rhinorrhea among those neonatal medium care unit newborns.[17] Similar to our findings, however, the clinicians were blinded to the RTP results, the frequency of antibiotic use and length of hospital stay were similar between those with pathogens detected in the respiratory tract and those without, and so the effect of the knowledge of respiratory viruses being present in respiratory samples of newborns on clinical outcomes is still in question.[16]

In the neonatal period, routine laboratory tests, such as white blood cell, C-reactive protein etc. were found to be incapable to differentiate viral infections from bacterial infections, and newborns should be evaluated for respiratory pathogens in the presence of RTI signs.[5,6] When respiratory virus surveillance was performed in the NICU, a RTI agent was detected in half of the premature newborns even when they were asymptomatic or minimally symptomatic, and the presence of viral nucleic acids in nasopharyngeal secretions was associated with many adverse outcomes.[8] Although it does not seem right to limit the use of tests that can be used for RTI surveillance to microorganisms with specific treatment in developed countries and to selected patient groups in developing countries, it would be economically reasonable.

To our knowledge, this is the first study to evaluate the effect of multiplex PCR use in neonatal RTI on the duration of antibiotic treatment, length of hospital stay, and hospital costs in a NICU in a developing country. The fact that the use of multiplex PCR increases hospital costs without reducing the duration of antibiotic use and hospital stay suggests that it would be reasonable to use cheaper kits that are limited to viruses that may affect the treatment when detected, such as influenza virus, and to the most common bacterial agents, in newborns with signs and symptoms of RTI. It is important to organize the treatment and follow-up of all newborns diagnosed with RTI and monitored in the NICU, regardless of the RTI agent, by taking respiratory tract isolation measures. Similar to the literature, the most frequent viral RTI agent detected in our study was RSV, and it is known that RSV infection is the leading cause of hospitalization due to a severe course of RTI in infants younger than 6 months.[18]

Limitations

The main limitation of our study was the absence of a real control group. As, RTP test was a routine test for neonates with RTI in our unit, it was not possible to create a non-RTP group for real. The other limitations were the cross-sectional retrospective design of the study and small number of newborns included in the study. The final limitation was that the multiplex PCR kit we used in our hospital was intended

to detect a large number of RTI agents and their detection in RTP would have no effect other than increasing the cost, because most of these agents do not have specific treatment.

CONCLUSION

As a result, the use of multiplex PCR test did not affect the duration of antibiotic use and length of hospital stay in neonatal RTI. On the other hand, total hospital costs were higher in the RTP group compared to the non-RTP group. The RTP test, which is an expensive test for developing countries, seems to increase total hospital costs without benefiting important clinical outcomes such as antibiotic use and hospital stay, and this test should be used very selectively in developing countries with limited resources. Prospective studies that include more patients with a real control group may help investigate the true impact of using RTP testing on patient outcomes and hospital costs.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study was obtained from the Şehit Prof. Dr. İlhan Varank Training and Research Hospital Clinical Researches Ethics Committee (Date: 19.08.2024, Decision No: 2024/237).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Human papillomavirus vaccines in obstetrics and pediatrics: a comprehensive review

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ABSTRACT

This review highlights the epidemiological significance, immunological function, and economic feasibility of Human papillomavirus (HPV) immunization, emphasizing both its benefits and challenges. Addressing vaccine hesitancy, ensuring equitable access, and expanding vaccination coverage for both genders are crucial to maximizing public health benefits. HPV is a highly prevalent infection with significant implications for global public health, particularly in obstetric and pediatric populations. Persistent infection with high-risk HPV genotypes, such as HPV-16 and HPV-18, is a leading cause of cervical cancer, a major contributor to cancer-related mortality worldwide. Beyond cervical malignancies, HPV is etiologically linked to anal, vulvar, vaginal, penile, and oropharyngeal carcinomas. Additionally, it is responsible for benign but distressing conditions such as genital warts, imposing substantial psychosocial and economic burdens. Prophylactic HPV vaccines have significantly improved the prevention of HPV-associated diseases. The currently available bivalent, quadrivalent, and nonavalent vaccines target high-risk oncogenic HPV types and provide near-complete protection against vaccine-included genotypes. These vaccines function by eliciting a robust immune response, effectively neutralizing HPV before it establishes an infection. However, despite their well-documented benefits, challenges such as vaccine hesitancy, misinformation, economic barriers, and global disparities in vaccine access persist. This review provides a comprehensive analysis of HPV immunization within obstetrics and pediatrics, emphasizing its epidemiological impact, immunological mechanisms, efficacy, safety, and implementation strategies. Furthermore, we explore existing barriers to vaccine uptake, disparities in global access, and potential future advancements, including next-generation vaccines and therapeutic interventions. Addressing these challenges through targeted public health initiatives, healthcare provider education, and equitable vaccine distribution strategies is essential to maximizing the public health impact of HPV immunization and reducing the global burden of diseases associated with HPV.

Keywords: Human papillomavirus, HPV, HPV vaccines, cervical cancer prevention, vaccine efficacy and safety, global vaccine access

INTRODUCTION

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections worldwide, affecting individuals of all genders and age groups. Persistent infection with high-risk HPV types, particularly HPV-16 and HPV-18, is the primary etiological factor for cervical cancer, which remains the leading cause of cancer-related mortality in women globally. HPV is also implicated in other anogenital malignancies, including vulvar, vaginal, and anal cancers, as well as a growing proportion of oropharyngeal cancers. In addition to malignancies, HPV causes benign conditions such as genital warts, which impose significant psychosocial and economic burdens on affected individuals.[1]

The development and widespread availability of prophylactic HPV vaccines represent a major advance in public health. These vaccines, particularly the quadrivalent and nonavalent formulations, provide near-complete protection against the most oncogenic HPV types. By preventing persistent HPV infection, vaccination effectively reduces the incidence of cervical intraepithelial neoplasia, cervical cancer, and

other diseases associated with HPV. Yet extensive evidence demonstrating their safety and efficacy, global vaccine uptake remains inadequate. Multifactorial barriers including socio-cultural stigma, misinformation, cost, and disparities in healthcare infrastructure continue to hinder equitable access and acceptance of the vaccine in many regions.[2]

This review provides a comprehensive analysis of HPV immunization within the fields of both obstetrics and pediatrics, focusing on its role in reducing disease burden, improving reproductive health, and preventing HPV-related conditions in adolescents. It also explores challenges to implementation and highlights prospective advancements, such as next-generation vaccines and therapeutic interventions, that aim to mitigate the global impact of diseases associated with HPV in future.

METHODS

This review was conducted through a comprehensive analysis of peer-reviewed studies, systematic reviews, and meta-analyses published in the past two decades. A systematic literature search was performed using databases such as PubMed, Scopus, and Web of Science, focusing on HPV immunization in obstetrics and pediatrics. Selection criteria included studies on vaccine efficacy, safety, immunological mechanisms, public health implementation strategies, and obstacles to vaccine supply. Key articles were reviewed for relevance, with an emphasis on recent high-impact research.

HPV AND ITS IMPACT ON WOMEN'S HEALTH

HPV is recognized as a significant oncogenic virus and the primary causative agent of cervical cancer, responsible for nearly 99% of cases globally.[3] Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality among women, particularly in low- and middle-income countries where access to preventive healthcare is often limited. Beyond cervical neoplasia, HPV is strongly associated with other malignancies, including cancers of the vulva, vagina, anus, and oropharynx. These non-cervical HPV-associated cancers are becoming increasingly prevalent, particularly among women who lack access to HPV immunization or regular screening programs.[4]

In addition to its oncogenic potential, HPV infections are a significant cause of benign conditions such as persistent genital warts. Although they are non-life-threatening, these warts carry substantial psychosocial consequences, including stigma, embarrassment, and reduced quality of life for affected individuals.[5] Furthermore, the management and treatment of these benign conditions impose an economic burden on healthcare systems worldwide.

The morbidity and mortality associated with diseases associated with HPV underscore the urgent need for effective prophylactic strategies. HPV immunization has emerged as a transformative public health measure. Clinical trials and real-world studies have consistently demonstrated the vaccines' efficacy in preventing high-risk HPV infections and reducing the prevalence of cervical precancerous lesions and invasive cancers. Vaccinated populations have shown a marked decline in cervical abnormalities, genital warts, and even HPV prevalence at the community level, indicating the potential for herd immunity when vaccine coverage is high.[6]

Moreover, as the incidence of non-cervical HPV-associated cancers rises, the broader protective effects of HPV immunization become increasingly evident. These findings reinforce the importance of widespread vaccination efforts to improve women's health outcomes and reduce the global burden of diseases associated with HPV.

HPV VACCINATION IN OBSTETRICS

The role of HPV immunization in obstetrics is critical, given its potential to prevent infections that could negatively impact pregnancy outcomes. In women of reproductive age, persistent HPV infections are associated with an increased risk of adverse obstetric events, including preterm labor, low birth weight, premature rupture of membranes, and even miscarriage. Research indicates that the presence of high-risk HPV types during pregnancy may contribute to localized inflammation and structural changes in the cervix, increasing the likelihood of complications.[7]

HPV immunization prior to conception has been shown to have no adverse effects on fertility or pregnancy outcomes. While clinical trials and observational studies affirm the safety and efficacy of vaccines in non-pregnant women, limited data exist regarding their administration during pregnancy. As a precautionary measure, HPV vaccines are not recommended for use during pregnancy. If vaccination occurs inadvertently during pregnancy, remaining doses should be deferred until after delivery.[8] However, no evidence currently suggests teratogenic effects or adverse fetal outcomes resulting from accidental vaccination.

Preconception vaccination is particularly crucial for women planning to conceive, as it not only reduces the risk of cervical precancerous lesions and cancer but also lowers the likelihood of HPV-related complications during pregnancy. Obstetric healthcare providers have a pivotal role in advocating for HPV immunization among their patients. By educating women on the long-term health benefits of immunization, clinicians can address vaccine hesitancy and misconceptions, particularly those surrounding fertility and pregnancy safety.[9]

Furthermore, integrating HPV immunization counseling into routine obstetric care, including prenatal visits, provides an ideal opportunity to increase vaccine awareness and uptake. This proactive approach ensures that women receive adequate protection against HPV infections, ultimately contributing to better maternal and neonatal health outcomes.[10]

HPV VACCINATION IN PEDIATRICS

HPV immunization during early adolescence is a cornerstone of effective disease prevention strategies. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend routine HPV immunization for both females and males between the ages of 9 and 14, ideally before the initiation of sexual activity. Administering the vaccine at this age not only ensures that

individuals are protected prior to potential exposure but also takes advantage of the robust immunogenic response elicited in younger recipients.[11] Studies show that the immune response to HPV immunization is significantly stronger in pre-adolescents compared to older adolescents or adults, resulting in higher levels of long-term protection.[12]

Although HPV has traditionally been associated with cervical cancer in women, its impact on males is also significant. HPV is linked to various cancers in males, including oropharyngeal, anal, and penile cancers. Immunizing boys is therefore critical for reducing overall HPV transmission within the population and providing direct protection against HPV-associated malignancies in males.[13] This gender-neutral vaccination strategy enhances herd immunity, ultimately benefiting the entire population.

Pediatric healthcare providers play a pivotal role in advocating for HPV immunization. By educating parents on the vaccine's safety, efficacy, and benefits, they can address common misconceptions and hesitancy. Misunderstandings, such as concerns about vaccine-related adverse effects or the misbelief that vaccination encourages early sexual activity, remain significant barriers to vaccine uptake. Transparent communication from trusted healthcare professionals is the key to overcome these challenges.

School-based vaccination programs have emerged as one of the most effective approaches to increasing coverage rates among adolescents. These programs eliminate logistical barriers, such as transportation difficulties and lack of access to healthcare facilities, and provide a structured framework for timely vaccine delivery. Implementing such initiatives on a broader scale could substantially increase global HPV immunization rates, ensuring better protection for future generations.[14]

A recent study found that patients who research vaccination issues on the Internet are likely to encounter sophisticated anti-vaccination Web sites.[15] In addition, press coverage of vaccination also can, at times, have an anti-immunization slant.[16] However, when media reporting on medical issues is balanced and accurate, it can be an excellent source of corrective information for patients.[17] Providers should be prepared to direct patients to accurate news and Web-based information about immunization in general and HPV infection and immunization in particular.

EFFICACY AND SAFETY OF HPV VACCINES

Extensive clinical trials and real-world studies provide compelling evidence of the high efficacy of HPV vaccines in preventing HPV-related infections and associated malignancies.[18] The quadrivalent and nonavalent HPV vaccines, in particular, have demonstrated nearly 100% protection against the high-risk oncogenic HPV types responsible for the majority of cervical, vaginal, vulvar, and anal cancers.[19] These vaccines are also highly effective in preventing high-grade cervical intraepithelial neoplasia (CIN2+), a well-recognized precursor to invasive cervical cancer. By interrupting the progression from persistent HPV infection to malignancy, HPV immunization has the potential to drastically reduce cervical cancer incidence globally, especially in populations with high vaccine coverage.

Moreover, population-level studies have documented significant reductions in the prevalence of genital warts and cervical abnormalities among vaccinated cohorts. For instance, countries with robust national HPV immunization programs, such as Australia, have reported declines in genital warts of up to 90% among young women and men within a decade of vaccine implementation. This highlights the profound impact of HPV vaccines not only on individual health but also on public health outcomes through herd immunity.[20]

The safety profile of HPV vaccines has been rigorously evaluated in both pre-licensure clinical trials and post-licensure surveillance. Data from these studies demonstrate no significant increase in the risk of severe adverse events compared to other routinely administered vaccines.[21] The most commonly reported side effects are minor and transient, including localized pain, swelling, redness at the injection site, and mild fever.[22] Importantly, long-term safety studies have further confirmed that HPV vaccines are not associated with increased risks of autoimmune disorders, infertility, or adverse neurological outcomes. These findings have been consistently upheld across diverse populations and age groups, underscoring the vaccines' safety and reliability.[23]

Despite their proven efficacy and safety, addressing vaccine hesitancy remains a critical challenge. Proactive communication strategies emphasizing the vaccines' benefits and robust safety profile are essential for increasing acceptance and achieving higher global vaccination rates. This will further solidify HPV immunization as a cornerstone of cancer prevention worldwide.

Challenges and barriers to HPV vaccine uptake cost-effectiveness analysis studies indicate that HPV immunization is a highly cost-efficient intervention in preventing HPV-related cancers. Long-term healthcare savings and economic benefits should be emphasized to support widespread vaccine adoption. Economic evaluations indicate that HPV vaccination is highly cost-effective, preventing costly treatments for HPV-related cancers and associated healthcare burdens. Expanding the discussion on long-term cost-benefit analyses would strengthen the manuscript.[24]

Although the benefits of HPV immunization are well established, its global coverage remains suboptimal.

Misinformation, amplified by social media and anti-vaccine movements, exacerbates these challenges. Misleading narratives that question vaccine efficacy or propagate false claims about long-term side effects contribute to hesitancy and refusal. Cultural and religious beliefs also play a role, particularly in conservative societies where discussing sexually transmitted infections is a taboo. These societal norms can hinder educational campaigns and limit open discussions about the importance of HPV immunization.[25]

Economic constraints present another significant barrier, particularly in low-and middle-income countries. The cost of

HPV vaccines can be prohibitive for families and healthcare systems in resource-limited settings. While programs such as Gavi, the Vaccine Alliance, have made significant strides in reducing vaccine costs, gaps in funding and infrastructure persist. Disparities in healthcare access, including a lack of trained healthcare providers and vaccination facilities in rural and underserved areas, further exacerbate inequalities in coverage.[26]

Addressing these challenges requires a multifaceted approach. Public awareness campaigns that provide clear, evidence-based information about the benefits and safety of HPV vaccines are essential. These campaigns should leverage trusted community figures, such as healthcare providers, religious leaders, and educators, to dispel myths and promote acceptance. Integrating HPV immunization into routine school-based immunization programs has proven effective improving coverage, as it reduces logistical barriers and ensures widespread access.

In addition to outreach efforts, financial barriers must be addressed through sustained investments in immunization programs. Subsidizing vaccine costs and strengthening healthcare infrastructure in resource-limited settings are critical steps toward equitable vaccine distribution. Collaborations with global health organizations, such as the WHO and Gavi, can help bridge funding gaps and support vaccine delivery in underserved regions.[27]

Ultimately, overcoming these barriers will require coordinated efforts among governments, healthcare providers, and international organizations. A unified strategy that combines education, advocacy, and resource allocation has the potential to significantly increase HPV immunization rates, reduce the global burden of HPV-associated diseases, and advance health equity.[28]

GLOBAL HPV VACCINATION POLICIES AND FUTURE PERSPECTIVES

HPV immunization has been a cornerstone of cancer prevention efforts worldwide, with numerous countries achieving significant progress by integrating HPV vaccines into their national immunization programs. This strategy has been particularly successful in reducing the prevalence of diseases associated with HPV, including cervical cancer, genital warts, and other HPV-associated malignancies.[29]

Australia is often regarded as a global leader in HPV immunization. Its comprehensive school-based vaccination program, introduced in 2007, has resulted in vaccination rates exceeding 80% among adolescents. Within a decade of implementation, Australia reported a marked reduction in the prevalence of HPV infections and related diseases, including a dramatic decrease in cervical intraepithelial neoplasia and genital warts. These outcomes highlight the effectiveness of universal vaccination programs in achieving population-level benefits and advancing towards the elimination of cervical cancer as a public health issue.[20]

In low-income settings, Rwanda has emerged as a success story for HPV immunization. Through strong political commitment, strategic partnerships with global organizations like Gavi, and community-based outreach, Rwanda achieved vaccination coverage of over 90% in eligible girls. This achievement demonstrates the potential for resource-limited countries to overcome barriers and implement successful vaccination programs when supported by strong governance and adequate resources.[30]

Despite these successes, significant challenges remain. Global disparities in vaccine access, particularly in low- and middle-income countries, hinder progress toward widespread HPV eradication. High vaccine costs, limited healthcare infrastructure, and logistical barriers to vaccine distribution are persistent issues. Addressing these inequities requires sustained investments, international collaborations, and targeted efforts to improve healthcare delivery systems. Organizations like the WHO and Gavi play critical roles in subsidizing vaccine costs and supporting vaccination initiatives in underserved regions.[31]

Future advancements in HPV prevention hold great promise. Ongoing research into next-generation HPV vaccines aims to enhance their efficacy, extend protection to additional HPV types, and reduce dosing schedules to improve accessibility. Moreover, the development of therapeutic vaccines targeting existing HPV infections represents a groundbreaking approach to managing persistent infections and preventing progression to malignancy. Research into booster doses is also critical to determine the duration of immunity and ensure long-term protection.

Integrating HPV immunization with other adolescent health initiatives, such as routine immunizations and sexual health education, could further streamline vaccine delivery and improve coverage rates. Public awareness campaigns addressing vaccine hesitancy and misinformation remain vital for increasing acceptance and achieving higher uptake. By addressing these challenges and leveraging innovative solutions, the global community can make significant strides toward the ultimate goal of eradicating diseases associated with HPV and advancing public health equity.[32]

CONCLUSION

It is crucial for obstetric and pediatric health, effectively preventing cervical cancer, genital warts, and HPV-related malignancies.

Despite the substantial progress achieved through HPV immunization programs, several barriers continue to hinder widespread vaccine uptake. Vaccine hesitancy, driven by misinformation, cultural misconceptions, and concerns about vaccine safety, remains a significant challenge. These issues are further exacerbated by inequities in healthcare access, particularly in low-and middle-income countries where the economic burden of vaccination and inadequate infrastructure limit vaccine distribution. Addressing these challenges requires comprehensive and coordinated efforts that include public education campaigns, policy interventions, and financial support for vaccination programs.

Strengthening global immunization efforts is critical to maximizing the public health impact of HPV immunization. Investments in healthcare infrastructure, innovative vaccine

delivery models, and international collaborations are essential to achieving equitable access. Moreover, advancing research on next-generation vaccines and therapeutic options holds promise for improving efficacy, extending protection to additional HPV types, and addressing existing infections.

The eradication of diseases associated with HPV is an attainable goal with sustained commitment from healthcare providers, policymakers, and community leaders. Their collaboration will be instrumental in overcoming barriers, enhancing vaccine coverage, and fostering public trust. By prioritizing HPV immunization as a global health initiative, significant strides can be made in reducing HPV-associated morbidity and mortality, thereby improving the quality of life for millions worldwide. Achieving this vision will require persistent efforts over the coming decades but promises substantial rewards for future generations.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Acute abdomen caused by multisystemic inflammatory syndrome after COVID-19 in two pediatric patients

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ABSTRACT

During the COVID-19 pandemic, a complex disease presentation known as multisystemic inflammatory syndrome (MIS-C) has been identified in children. This inflammatory condition, which affects multiple organs, poses significant challenges for pediatric surgeons, especially when acute abdominal symptoms are present. This article aims to share the experiences with, aged 11 and 4.5 years, who presented with similar difficulties in our clinic.

Keywords: COVID-19, multisystemic inflammatory syndrome, children

INTRODUCTION

COVID-19 generally causes mild symptoms in children, commonly presenting as respiratory tract infections.[1,2] However, it can manifest in various forms, from mild upper respiratory tract symptoms to more severe conditions such as multisystemic inflammatory syndrome in children (MIS-C).[1,2] Clinical conditions more severe than simple respiratory issues can also occur, and complications or serious clinical processes may arise in pediatric patients.[2,3]

Treatment of MIS-C includes steroids, immunomodulation, immunoglobulin, and aspirin among other therapies.[3] This treatment process can be significantly different depending on whether surgery is required.[3] Therefore, pediatric surgeons must remain cautious when managing these patients, considering the possibility of MIS-C, even when symptoms resemble surgical conditions.

This study presents two cases of pediatric patients with COVID-19 who developed MIS-C, presenting with acute abdominal pain.

CASE 1

An 11-year-old male patient, initially treated for earache and fever at an outside facility, was referred to our clinic with a preliminary diagnosis of acute abdomen. His symptoms persisted, and he developed abdominal pain. Redness in his eyes was also noted in his history. Upon examination, his temperature was 39°C, pulse rate 120/min, respiration 22/min, and there was significant tenderness in the right upper quadrant of the abdomen. Laboratory findings were as follows: leukocytes 5470/µL, urea 68.48 mg/dl, creatinine 1.24 mg/dl, sodium 125 mEq/L, chloride 93.6 mEq/L, ALT 53.6 U/L, AST 50.2 U/L, total bilirubin 2.98 mg/dl, direct bilirubin 2.069 mg/dl, CRP 258 mg/L, fibrinogen 447 mg/dl, albumin 27.3 g/L, procalcitonin 40.54 ng/ml, D-dimer 5.33 µg/ml. Abdominal ultrasound was unremarkable. We began intensive intravenous hydration and administered broad-spectrum antibiotics, as tomography showed suspicious opacity at the distal end of the common bile duct. The patient was hospitalized with a preliminary diagnosis of cholelithiasis and acute cholangitis and underwent magnetic resonance imaging (MRI) cholangiography. Intrahepatic and extrahepatic bile ducts appeared normal, and a 5 mm stone was identified in the gallbladder.

On the third day of hospitalization, pain in the right upper quadrant resolved, but rebound tenderness appeared in the right lower quadrant. Since the evolving clinical condition suggested acute appendicitis, a diagnostic laparoscopy was performed due to the evolving clinical situation. Intraoperatively, the appendix vermiformis was found, appeared slightly inflamed, and approximately 2 liters of serofibrinous fluid were noted in the abdomen. We performed an appendectomy and biopsied the peritoneal and omentum. The biopsy revealed no evidence of granulomatous

disease. Postoperatively, the patient developed rashes, tachycardia, edema in the hands and feet, and conjunctivitis. PCR and antibody tests for COVID-19 and MIS-C were negative. A consultation with pediatric cardiology identified perimyocarditis, pericardial effusion, and echogenicity in the coronary arteries, consistent with Kawasaki disease. The patient was diagnosed as MIS-C and transferred to pediatric infectious diseases for further management. Follow-up care was planned after discharge.

CASE 2

A 4.5-year-old male patient, with a history of fever and abdominal pain for three days, was referred with an ultrasound showing a 7.5 mm appendicitis. The patient also tested positive for COVID-19. On examination, the general condition was moderate, temperature 38.4°C, pulse 120/min, respiration 23/min, and there was diffuse tenderness in the abdomen. Laboratory findings included leukocytes 23.000/µL, neutrophils 20.000/µL, and CRP 115 mg/L. The patient was hospitalized for observation due to acute abdomen and COVID-19 infection. The control ultrasonography measured free fluid in the retrocecal region and an appendix size of approximately 8 mm. As the symptoms did not improve on the third day of hospitalization, a laparoscopic appendectomy was performed with a preliminary diagnosis of acute appendicitis. Intraoperatively, the appendix was perforated, and a localized abscess was found. Broad-spectrum antibiotics were started, and the patient was discharged on the sixth postoperative day in good condition.

DISCUSSION

The symptoms of MIS- resemble those of Kawasaki syndrome, Toxic Shock syndrome, or Macrophage activation syndrome.[4] In MIS-C, the exaggerated immune response occurs, typically 2–4 weeks after a COVID-19 infection, causing vasculitis and potentially damaging organs such as the gastrointestinal tract, myocardium, coronary arteries, skin, brain, kidneys, and lungs.[1,2] Gastrointestinal symptoms may persist persist longer than in adults.[3] It is believed that viral excretion in feces lasts longer in children, contributing to prolonged gastrointestinal symptoms.[3] A critical indicator for diagnosing MIS-C is a positive COVID-19 test 2–6 weeks prior to symptom onset.[3,4] Elevated levels of CRP, D-dimer, IL-6, procalcitonin, ferritin, and lactate dehydrogenase, along with persistent fever and signs of systemic inflammation, are commonly observed.[2] The CDC recommends diagnosing MIS-C in cases of fever lasting more than 24 hours, systemic organ involvement, and positive inflammatory markers.[3]

Abdominal pain and other gastrointestinal symptoms are common in MIS-C, making the diagnosis challenging and treatment complex.[1] In the study by Rouva et al.,[1] various diagnoses were observed in patients, including mesenteric adenitis, paralytic ileus, ascites, appendicitis, terminal ileitis, and ileocolitis. In our experience, one patient was initially thought to have cholecystitis, while the other presented with appendicitis, complicating the diagnosis due to the patient's concurrent COVID-19 positivity.

The most common problem in MIS-C cases is inflammatory bowel disease.[3] This rate is around 75%.[3] It most commonly manifests itself with abdominal pain.[3] The probability of other diseases and gastrointestinal complaints is around 25%.[3] There are also cases involving the liver and pancreas.[3] In addition to abdominal pain, specific complaints such as vomiting and diarrhea may be present and may be confused with diseases that cause acute abdomen, especially acute appendicitis.[1] In our experiences, we thought one of our patients might have cholecystitis, but the complaints, especially abdominal pain, changed its features. In the second case, appendicitis was considered, but since the patient was simultaneously COVID-positive, there was hesitation as to whether we were challenged with a MIS-C picture.

The broad spectrum of MIS-C symptoms can delay diagnosis. A study involving 55 patients reported that the time to diagnosis ranged from 3 to 8 days.[3,4] In our patients, this period was approximately 3±1 days.

CONCLUSION

In cases of abdominal pain associated with COVID-19 infection, the differential diagnosis of acute abdomen becomes difficult. In patients presenting with systemic disease findings and worsening abdominal pain, the possibility of MIS-C should not be ignored. Early recognition of this condition and planning appropriate treatment and surgery are essential to minimize morbidity. When deciding on conservative or surgical treatment, the surgeon's experience is as crucial as the patient's clinical and laboratory findings.

ETHICAL DECLARATIONS

Informed Consent
Parents of all patients signed a free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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