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Chapter 1

VARICOCELE INCIDENCE IN INFERTILE COUPLES ADMITTED TO A GYNAECOLOGY CLINIC

Özgül ÖZGAN ÇELİKEL¹

Osman GÜL

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End the accepted definition on infertility over the years; failure of pregnancy to occur despite reproductive age couples having unprotected sexual intercourse three or four times a week for at least one year, or it is also inability to maintain pregnancy. Epidemiological data indicates that approximately 10%–15% of all couples experience difficulty in conceiving. According to a study conducted by the World Health Organisation (WHO) in developed countries, the underlying causes infertility in infertile couples are only male-associated in 37% cases, male- and female-associated in 8% cases and only female-associated in 35% cases. In addition, the underlying cause remained unknown in 5% cases, and 15% cases were able to conceive during the course of the study (Unuane D& et al.2011)

Varicocele, the abnormal dilatation of the veins in the panpiniform plexus and presence of reflux flow, is the most common cause of male infertility and is treatable (Arcangelo B& et al 2019) . It is often seen on the left side. The exact underlying cause of varicocele-induced infertility is still unknown (Shiraishi K& et al.2012). However, several pathophysiological mechanisms have been elucidated. The most widely accepted mechanism suggests that the increase in scrotal heat and decrease in androgen synthesis causes varicocele-induced infertility. Increasing temperature reportedly causes DNA polymerase enzyme inactivation and spermatogenetic testicular dysfunction (Durairajanayagam D& et al.2015).

The study aimed to evaluate the varicocele incidence in infertile couples and to determine its relationship with semen parameters and its effects on infertility.

MATERIAL METHODS

Married couples admitted to the Gynaecology and Obstetrics Clinic and diagnosed with infertility between 15 December, 2018 and 15 June, 2019 were included in the study. Age, gravida and infertility duration, body mass index, smoking habitus, chronic drug use, systemic disease, primer or seconder infertility were recorded for all the patients. Those with chronic drug use and systemic disease were excluded from the study. 222 of 254 excluded from the study. Their spouses were referred to the urology clinic to undergo spermiogram examination and varicocele evaluation. Age and infertility duration of all the males were also recorded.

Varicocele examination was conducted in the outpatient clinic using the Valsalva manoeuvre in standing and supine positions at optimal room temperature. All included participants underwent physical examination and testicular Doppler ultrasonography (USG). Participants in whom varicocele was not detected on physical examination and Doppler USG were included in the non-varicocele group; those in whom varicocele was detected on physical examination as well as Doppler USG were included

in the clinical varicocele (CV) group and those in whom varicocele was identified only on Doppler USG were included in the subclinical varicocele (SV) group (Manesh K D& et al.2020).

Doppler Ultrasonography: When the participant was in the supine position, a towel was used to provide support under the scrotum, a warm gel was applied to the scrotum and a high frequency linear transducer (<7.5 MHz) was used to perform USG.

Semen Analysis: All semen parameters of the participants were obtained after 3–5 days of sexual abstinence. Semen samples were analysed twice, and the average of the two results was evaluated. Semen parameters were evaluated based on the criteria set by the WHO. Sperm concentration (million/mL), percentages of total motile sperm count and normal sperm morphology were evaluated. Threshold values for abnormal semen parameters were <15 million/mL for sperm concentration, 40% for total motility, 32% for progressive motility and <4% for normal sperm morphology (It is available at: <http://www.who.int/iris//10665/44261>).

Statistics

The study comprised 222 male participants classified into the following three groups: those in whom varicocele was not detected on physical examination and Doppler USG (non-varicocele group; n = 134), those in whom varicocele was identified on physical examination and Doppler USG (CV group, n = 51) and those in whom varicocele was identified only on Doppler USG (SV group, n = 37). All statistical analyses were performed using IBM SPSS (Statistical Package for Social Sciences) Statistics 23 software package. Normality assumptions for numerical variables were examined using the Shapiro–Wilk normality test and the variables did not have normal distribution. Non-parametric statistical methods were used. The relationships between two independent categorical variables were analysed using the Chi-square test. In case expected value assumption was not obtained via Chi-square test, the results of the Fisher exact test were used. Differences between more than two independent variables were examined by the Kruskal–Wallis test. The relationships between two independent numerical variables were examined by the Spearman’s Rho coefficient. The threshold for statistical significance was 0.05.

2018/63 ministerial ethics committee approval was obtained from Yildirim Beyazıt University Yenimahalle Training and Research Hospital.

RESULTS

The mean age of males and females was similar between groups. Infertility duration, semen volume, sperm concentration, total motile sperm count, progressive motile sperm count and Kruger values were not

significantly different between groups ($p > 0.05$) (table 1). Epididymal cysts were identified in 11 participants. In addition, two participants had undergone surgery for varicocele and one participant had undergone surgery for testicular tumour.

Table I: Differences of Parameters According to Groups

	Control (n=134)	Clinic Varicocele (n=51)	Subclinic Varicocele (n=37)	Statistis	P
Primer Infertil Male Number (%)	97 (79,1)	35(92,6)	27(64,7)	5,179*	0,075
Sekonder Infertil Male Number(%)	37(20,9)	16(7,4)	10(35,3)	5,179*	0,075
Unilateral Varicocele Number(%)	0(0)	22(81,5)	14(82,4)	0,000*	1,000
Bilateral Varicocele Number(%)	0(0)	5(18,5)	3(17,6)		
Female Age (year) Median (Min-Max)	31(20-43)	31(23-43)	29(22-37)	1,708 ^b	0,191
Male Age (Year) Median (Min-Max)	33(22-53)	32(25-45)	32(27-51)	0,029 ^b	0,865
Infertility Period(Year) Median (Min-Max)	2(1-20)	2(1-10)	2(1-6)	0,249 ^b	0,618
Semen volüm(ml) Median (Min-Max)	2,7(1,5-5)	2,7(1,5-5)	3(2-5)	1,285 ^b	0,257
Sperm Consantrasyon (x10⁶) Median (Min-Max)	27,5(15-56)	25(3-41)	25(7-45)	0,561 ^b	0,454
Total Sperm Motility (%) Median (Min-Max)	45(2-64)	43(2-54)	45(23-52)	0,990 ^b	0,320
Progresif Sperm Motility (%) Median (Min-Max)	35,5(23-51)	34(0-42)	34(21-42)	0,326 ^b	0,568
Kruger (%) Median (Min-Max)	8(3-13)	7(0-13)	8(5-13)	0,388 ^b	0,533
BMI(gr/cm²)	18(15-30)	21(17-28)	22(16-31)	0,322 ^b	0,423
Sigara içen (5-10 adet/gün)	21	9	4	0,234	0,033

^a : Ki Kare Analizi , ^b : Kruskal Wallis; * : Fisher's Exact

BMI (body mass index gr/cm²)

Table II: Investigation of the Relationship Between Semen Parameters and Age and Infertility Duration of Couples

	Control(n=134)			Clinic Varicocele (n=51)			Subclinic Vericocele (n=37)		
	Female Age	Male Age	Infertility Period (year)	Female Age	Male Age	Infertility Period(year)	Female Age	Male Age	Infertility Period
Semen Volüm (ml)	r 0,049	0,089	0,113	0,054	0,282	0,176	0,421	0,326	-0,060
	p 0,570	0,305	0,197	0,789	0,154	0,380	0,092	0,202	0,819
Sperm Consantrasyon (x10⁶)	r -0,065	-0,044	-0,008	0,097	0,001	-0,007	-0,030	0,141	0,181
	p 0,457	0,614	0,931	0,629	0,998	0,973	0,908	0,590	0,487

Total Sperm Motility (%)	r	0,095	0,151	0,063	0,077	0,091	-0,005	-0,193	-0,154	-0,016
	p	0,275	0,081	0,469	0,703	0,650	0,979	0,457	0,555	0,952
Progresif Sperm Motility(%)	r	0,105	0,124	0,144	0,321	0,114	-0,096	-0,037	0,077	0,158
	p	0,229	0,155	0,099	0,102	0,572	0,635	0,889	0,768	0,544
Kruger (%)	r	0,103	0,073	0,064	-0,015	0,223	-0,156	0,085	0,173	0,348
	p	0,237	0,405	0,462	0,943	0,264	0,438	0,746	0,507	0,172

r:Spearman's Rho correlation coefficient

Table 2 presents the relationship between the age of males and females, infertility duration and semen parameters. No correlation was observed between semen parameters, age of males and females and infertility duration ($p < 0.05$).

DISCUSSION

Epidemiologically, varicocele is common (Damsgaard J& et al.2016). Its incidence varies between 15%–20% in healthy males (Lundy SD&Sabanegh ES 2017; Karina da Silva M& et al. 2021) and it usually develops during adolescence. Varicocele incidence is reportedly high with 35% of primary infertile males and approximately 45%–81% of secondary infertile males (Matthew A& et al.2011). In our study on infertile couples admitted to the gynaecology clinic, the varicocele incidence was 26.77% ($n = 51$). The mean age was similar between the groups. Varicocele was identified in approximately 19.67 % of primary infertile males and in nearly 4.37% of secondary infertile males. Varicocele incidence in primary infertile males was higher than that in secondary infertile males.

Although varicocele was defined 2000 years ago, it still remains a multi-faceted disease that may lead to biological issues such as infertility, hypogonadism and chronic orchidovia. The underlying mechanisms are not yet well understood and probably include hypoxia, oxidative stress, hyperthermia, anatomical aberrations and genetic causes. Although its incidence is high among asymptomatic fertile males, it is the most common treatable cause of male infertility (Justin J& et al.2011).

Studies indicate that CV is associated with impaired semen parameters and male factor infertility. Increased probability of conception is possible when varicolectomy is combined with assisted reproductive techniques such as intrauterine insemination , in vitro fertilisation and intracytoplasmic sperm injection (Kohn TP& et al.2017). In a study on males with CV, varicolectomy reportedly increased the live birth rate (Kirby EW& et al.2016). In our study, the CV rate was 17.49% ($n = 37$). Total motile sperm count in the CV group was below normal ($p < 0.05$).

In a retrospective study conducted in 2012 in 172 male patients, sperm motility and viability was significantly lower in all patients with unilateral or bilateral varicocele than in healthy volunteers ($p < 0.05$). Additionally, there was no significant difference with respect to sperm concentration, motility or viability between patients with unilateral and bilateral varicocele ($p > 0.05$) (Xue J & et al.2012). Unilateral or bilateral varicocele incidence in the CV and SV groups in our study was also similar ($p > 0.05$). Furthermore, semen volume, sperm concentration, total motile sperm count, progressive motile sperm count and Kruger values were found to be similar between non-varicocele, CV and SV groups ($p > 0.05$, table I).

Although it is established that SVs have clinically significant effects on semen parameters (Daria M& et al.2021), it is unclear whether these effects are as significant as the effects of CV (Olivier C& et al.2021). Keskin et al. retrospectively evaluated 294 patients aged 18–37 years admitted to the urology clinic for infertility. They obtained the average of semen parameters that were analysed at two different times, and found that the semen parameters in patients with CV were significantly lower than in those without varicocele. Semen parameters in patients with SV did not differ between those with CV and those without varicocele (Keskin M &Kısa E 2019).

The SV ratio in our study was 9.26% ($n = 37$). The SV group had normal sperm concentration, total motile sperm count, progressive motile sperm count and Kruger values; however, these values were lower than those in the non-varicocele group. The results were not significant ($p > 0.05$).

With respect to the relationship between semen parameters and ages of those diagnosed with SV, Chen et al. reported no significant difference in semen parameters of sub-fertile SV patients under and over 50 years of age (Chen SS. 2017). In our study, the ages were similar between the groups. Male and female ages were not associated with semen parameters in both CV and SV groups ($p < 0.05$) (table II). Regardless of age, patients with SV reportedly have a lower chance at fertility than patients with CV (. Chen SS 2012). Another study reported SV can progress to CV in 28% of adolescents within four years. Research emphasises that SV should be considered as the first step in CV development (Patricia S C & et al.2021).

Postoperative semen parameters after varicocelectomy in patients with SV were reportedly either mildly improved or did not change at all. In addition, the conception rates did not increase (Seo JT& et al.2010). In contrast, Seo et al. reported that patients with SV who underwent microscopic varicocelectomy had statistically higher natural conception rates than those patients who underwent empirical and follow-up treatment (Ubaldo C& et al.2015).

CONCLUSION

The evaluation of spouses of the patients admitted to the gynaecology clinic revealed that 17.48% had CV and 9.28% had SV. Varicocele had no significant effect on sperm parameters. In addition, although SV had a negative effect on sperm concentration, total motile sperm count, progressive motile sperm count and Kruger values, this effect was not significant when compared to those without varicocele. Considering that SV may be a pre-CV condition, may affect semen parameters as reported by some studies and varicocelectomy for CV may increase live birth rates, we concluded that it is important for the spouse of every female admitted for primary or secondary infertility to undergo varicocele examination at a urology clinic.

REFERENCES

- Unuane D, Tournaye H, Velkeniers B, Poppe K. (2011). Endocrine disorders & . Best Pract Res Clin Endocrinol Metab;25:861-73.
- Arcangelo B, Alessio M, Elisa M, Settimio D, Dorian B, Chiara C, Felice F, Sandro F (2019). Front Endocrinol (Lausanne); 10: 164
- Shiraishi K, Matsuyama H, Takihara H. (2012). Pathophysiology of varicocele in male infertility in the era of assisted reproductive technology. Int J Urol;19:538–50.
- Durairajanayagam D, Agarwal A, Ong C (2015). Causes, effects and molecular mechanisms of testicular heat stress. Reprod Biomed Online;30:14-27.
- Manesh K ,Panner S, Luna S, Ashok A. (2020). Functional Analysis of Differentially Expressed Acetylated Spermatozoal Proteins in Infertile Men with Unilateral and Bilateral Varicocele. Int J Mol Sci; 21: 3155.
- Damsgaard J, Joensen U.N, Carlsen E, Erenpreiss J, Jensen M.B, Matulevicius V (2016). Varicocele is associated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. Eur Urol;70:1019–1029.
- Lundy SD, Sabanegh ES (2017).Varicocele management for infertility and pain: A systematic review. Arab J Urol;11:157-170.
- Karina da Silva M, Maria Eduarda Gomes de Sena Melo Mariz, Esther Alice Dantas de Araújo, Gabriel Ribeiro de Souza, Karinna Veríssimo Meira Taveira, Danielle Barbosa Morais (2021). Factors related to infertility in Brazil and their relationship with success rates after assisted reproduction treatment: an integrative review. JBRA Assist Reprod; 25: 136–149
- Matthew A, Will M.D, Jason Swain Ph.D, Mikkel Fode M.D, Jens Sonksen M.D, Gregory M. at al. (2011). The great debate: varicocele treatment and impact on fertility. Fertility and Sterility ;99:841-852
- Justin J, NorkD., Jonathan H, Berger M.D, Donald S, Crain M.D.et al.(2014). Youth varicocele and varicocele treatment: a meta-analysis of semen outcomes. Fertility and Sterility; 102:381-387.
- Kohn TP, Kohn JR, Pastuszak AW (2017). Varicocelectomy before assisted reproductive technology: are outcomes improved? Fertil Steril;108:385-391.
- Kirby EW, Wiener LE, Rajanahally S, Crowell K, Coward RM (2016). Undergoing varicocele repair before assisted reproduction improves pregnancy rate and live birth rate in azoospermic and oligospermic men with a varicocele: a systematic review and meta-analysis. Fertil Steril;106:1338-1343.
- Xue J, Yang J, Yan J, Jiang X, He LY, Wu T et al. Abnormalities of the testes and semen parameters in clinical varicocele (2012). Nan Fang Yi Ke Da Xue Xue Bao;32:439-42.

- Daria M, Giorgia S, Jessica D, Beatrice M, Alessia N, Gaetano De Feo, et. al.(2021). Improvement of sperm morphology after surgical varicocele repair. *Andrology*; 9: 1176–1184
- Olivier C, Patricia F, Carole P, Kévin G, Pierre-Olivier C, et.al (2021). Relevant Biological Effects of Varicocele Embolization with N-Butyl Cyanoacrylate Glue on Semen Parameters in Infertile Men . *Biomedicines*; 9: 1423
- Keskin M , K1sa E (2019). Investigation of the effects of subclinical varicocele on semen parameters. *Androl Bul*;21:6–9
- Chen SS (2017). Significant predictive factors for subfertility in patients with subclinical varicocele. *Andrologia*;49:12781.
- Chen SS (2012). Differences in the clinical characteristics between young and elderly men with varicocele. *Int J Androl*;35:695–9.
- Patricia S C, Richard N Y, Harriet J P, Matthew A M, Xiaoran L, Alyssia V, David A D (2021). Clinical outcome of pediatric and young adult subclinical varicoceles: a single-institution experience. *Asian J Androl*; 23: 611–615
- Seo JT, Kim KT, Moon MH, Kim WT (2010). The significance of microsurgical varicolectomy in the treatment of subclinical varicocele. *Fertil Steril*;93:1907–10.
- Ubaldo C, Massimo P, Giovanni M (2015). Reassessing the Role of Subclinical Varicocele in Infertile Men With Impaired Semen Quality: A Prospective Study. *Urology*;85:826-830

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Chapter 2

GYNECOLOGICAL LAPAROSCOPY IN MARES

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Introduction

When the technological developments in the medical world are examined, it is seen that there have been radical changes in the understanding of surgery in the last 30 years. The idea of imaging organs and tissues (endoscopy) without opening body cavities has attracted the attention of physicians since the beginning of the history of medicine.

Laparoscopic imaging, one of the subunits of endoscopy, is a technique that allows surgical applications in the diagnosis and treatment phase of many genital diseases without the need for laparotomy. While it was preferred only for diagnosis and simple applications twenty years ago, the indications of laparoscopic surgery have increased greatly today.

Laparoscopy applications in our country have been performed since the late 1960s and early 1970s. Laparoscopy, which initially found use in human medicine, has recently found application in veterinary medicine with increasing frequency. Laparoscopy in mares started to be practiced in the 1970s and has been routinely used in ovariectomy, cryptorchidectomy, ovariohysterectomy, diagnostic abdominal examinations and many other reproductive applications in the last 40 years. It is thought that it can shed light on many reproductive situations in the future.

Laparoscopy Definition

Endoscopy is the process of examining the internal organs with a bendable tube-shaped instrument that has a special light source and allows to take images through the camera at the end. When we examine the term laparoscopy, which is a subclass of this application, it is seen that laparo means the soft area between the hip bone and the costal bones in ancient Greek, and skopie means examination. Today, laparoscopy is a diagnosis and treatment method used for operation and examination on the intra-abdominal organs through a small incision in the abdominal wall, after the process of introducing air into the peritoneal cavity (Conley and Lee, 2012).

Instruments Used in Laparoscopic Applications

Telescope (laparoscope): Telescope is the name given to a lighted device inserted through the abdominal wall for examination and surgery by seeing the abdominal cavity and abdominal organs. The diameter of telescopes varies between 2 and 12 mm, but the ones with 5 and 10 mm diameters are most commonly used (Tok, 2008; Fakraden, 2013).

Camera and monitors: *Cameras to the operator;* Provides intra-abdominal imaging in surgical applications. Before the camera is placed in the abdominal cavity, it is connected to the telescope and the brightness is

adjusted (Fakraden, 2013). There are many different monitor types for the minimally invasive method. Video monitors are 13-19 inches in diameter and are available in cathode ray tube (CRT) and liquid crystal diode (LCD) variants (Tok, 2008; Hendrickson, 2012).

Light sources: During laparoscopy applications, the operator must use the light source to obtain intra-abdominal images. The quality of the light depends on the lamp used. Often halogen and xenon cold light sources are used. During the procedure, the end of the light cable should not touch the patient and the drapes, otherwise it may cause serious burns (Tok, 2008; Hendrickson, 2012).

Insufflation system: In order to create minimal damage during laparoscopic application, the operator has to create an inter-tissue space, this process is called pneumoperitoneum. Insufflation system is needed to create pneumoperitoneum. Frequently, CO₂ gas is used for insufflation through a veress needle (Tok, 2008).

Trocar: In the minimally invasive technique, it allows the instruments to be directed into the peritoneal cavity without losing intra-abdominal pressure. The diameters of the trocars vary between 2 and 20 mm and their lengths vary between 5-15 cm (Tok, 2008).

Hand instruments: Laparoscopic instruments; It can be examined in 2 parts as hand tools and hemostasis tools. Hand tools; holders (grasper, klinch, babcock etc.), dissectors, scissors, retractors, Hook and aspiration-irrigation systems (Tate et al., 2012).

Ligation and Hemostasis Techniques in Laparoscopic Applications

Effective ligation and hemostasis of intra-abdominal structures during laparoscopic applications is a critical point. Difficulties such as two-dimensional vision and strength of the body wall have led to the development of many different techniques to achieve hemostasis and ligation (Cokelaere et al., 2005).

Suture ligation: Suture ligation was one of the first techniques developed for intra-abdominal ligation and hemostasis, and is the most cost-effective hemostasis technique used throughout laparoscopic surgery. Unlike other methods of hemostasis, the technique requires the use of suture ligation (Hendrickson, 2012). Suture ligation, which was first used for castration in horses, was also used in the ligation procedure to place the descending testicle back into the abdomen (Wilson et al., 1996). A few researchers; used suture ligation to provide hemostasis and create ligation during ovariectomy in mares (Boure et al., 1997).

Polyamide tie-rap: Commercially, white colored polyamide tie-rap is

used in mesovarium ligation (Cokelaere et al., 2005). In a study conducted on mares, laparoscopic ovariectomy cases using tie-clip were found to be technically easy, inexpensive and safe. Although adhesion was observed between the mesenterium and the left ligature residue in two mares, but no signs of adhesion were detected, the researchers removed the tissue residue by reoperating because of the risk of adhesion in one of them (Cokelaere et al., 2005).

Monopolar and bipolar electrosurgery instruments: Monopolar and bipolar electrosurgery; In addition to adhesions, ovariectomy provides convenience for hemostasis in the abdominal cavity in cases of descending testis and cryptorchidism (Hanrath and Rodgerson, 2002; Smith and Mair, 2008). Monopolar electrosurgery; It is widely used in human laparoscopy applications (Fischer, 2002). bipolar electrosurgery; It is a technique performed by means of instruments fixed in the desired place in the tissue, since there is an electric current only between its two ends. The bipolar technique is safer than the monopolar technique, due to the leakage energy affecting other tissues and reducing the damage of abnormal current to the collateral tissues (Rodgerson et al., 2001; Hanrath and Rodgerson, 2002). In a study on bipolar and monopolar electrosurgical forceps in mares; 2 of 23 mares were euthanized after the operation for unknown reasons, and moderate colic was found in 1 mare within 24 hours after the operation. No long-term complications were observed in 21 mares within 6-24 months after the operation (Rodgerson et al., 2001).

Vascular occlusion devices (radiofrequency): Due to the small vessel diameter in monopolar and bipolar applications, devices with different electrosurgery principles have been developed. These devices are known as vascular occlusion devices (LigaSure, Endo GIA, etc.) and use radio frequency energy when compared to other electrosurgical techniques in terms of coagulation (Hendrickson, 2012). The LigaSure device is widely used in horses. This device; It is designed to withstand three times the normal blood pressure and is suitable for vessel diameters over 7 mm. Cutters often contain sharp blades and can thus be used for sequential cutting and coagulation without tool changing and removal (Hendrickson, 2012). LigaSure device; used and device for ovarian isolation, hemostasis and extraction; It has been determined that it provides an extremely safe, effective, fast and sufficient hemostasis (Beccati et al., 2011). The use of vascular closure device in horses; It has also been used for the extraction of normal ovaries as well as granulosa cell tumors. In most cases, complete hemostasis was achieved without bleeding at any stage of the procedures and complications were not reported (De Bont et al., 2010).

Ultrasonic cutting and coagulation devices: Ultrasonic cutting and coagulation devices safely send sound waves onto tissues. Sound waves

of high power level and intensity; It performs dissection, coagulation and cutting of tissues. In the double-sided laparoscopic ovariectomy study using a harmonic blade known as ultrasonic surgery units; Hemostasis of ovarian pedicles was achieved in all mares. The cutting process for ovarian pedicles took approximately 28 minutes. Post-operative complications; transient fever, mild subcutaneous emphysema and incisional seroma formation. adhesion formation, bleeding and generalized peritonitis were not encountered (Düsterdieck et al., 2003).

Stapling devices: Surgical stapling devices; It was developed because it allows easy and safe hemostasis in the amputation of abdominal structures. Endoscopic stable devices have been successfully used for amputation and ligation of normal ovaries in 10 mares undergoing laparoscopic ovariectomy (Van Hoogmoed and Galuppo, 2005).

Surgical lasers: Laser surgery; It is the process of applying various heat-generating substances under the image of light. The laser beam is made up of photons. Commonly, laser mediums contain CO₂ in veterinary medicine (Hendrickson, 2012). In a study, they used endoscopic stapling devices and lasers in unilateral ovariectomy applications in normal mares and stated that the mares returned to their normal activities within two weeks after the operation and no complications occurred (Palmer, 1993).

Laparoscopy Sites in Mares

In horses, the abdomen is divided into two main sections, left posterior and right posterior. These regions are also divided into lower and upper parts within themselves (Alsafy et al., 2013). The position of the patient during laparoscopy is very important. The intestines, especially the colon and caecum, cover a large area in adult horses, so only the upper parts of the abdomen are displayed more clearly and the deep tissues are viewed in poor quality. If the tissues to be examined are in the dorso-abdominal region, the patient should be treated on an standing basis. If the relevant tissues cover the right or left side, the mare should be laid on its side (Hendrickson, 2012). The main application area for flank laparoscopy; They are the points bounded by the last rib, tuber coxa and transversal processes of the vertebrae. The iliac artery and vein, which are located near the dorsal edge of the internal abdominal muscle, are the vessels to be considered (Hendrickson, 2008).

On the left side of the standing laparoscopic imaging; stomach, diaphragm, spleen, kidney, small colon, mesocolon, small intestines, left ovary, left cornu uteri, urinary bladder. In the right approach; duodenum, ventral band of the cecum, small colon, mesocolon, small intestine, right ovary, right cornu uteri and urinary bladder are possible structures (Galuppo et al., 1995).

In imaging of ventro-abdominal organs, it would be more accurate to lay the mare in the supine position (Hendrickson, 2012). Laparoscopy area suitable for this position; are the points bounded by the umbilicus, xiphoid cartilage and inguinal canals. Deep and superficial epigastric arteries and veins located at the edge of the rectus abdominalis muscle are a point to be considered during the application. In the dorsal supine position; liver, diaphragm, urinary bladder, spleen, small intestines, cecum and upper part of the colon can be seen. Hind abdomen at its best; Although it can be observed in the trendelenburg position called the head down, tail up stance, the anterior abdomen is best seen; can be seen in the reverse trendelenburg position with head up and tail down (Galuppo et al., 1996; Boure et al., 1997).

Anesthesia Techniques Used

Sedation: Standing laparoscopy with a combination of sedation and local anesthesia may not be suitable for every horse. In patient selection, animals that can stand still should be selected (Hendrickson, 2012). Alpha-2 agonists and opioids are widely used drugs for sedation. These are made as combinations of xylazine (0.5-1 mg/kg) and butarphanol (0.02 mg/kg) or detomidine (2-10 mcg/kg) and butarphanol (0.02 mg/kg). Generally, many operators have chosen to create long-term sedation with a single-dose intravenous injection rather than prolonged consecutive injections. For this purpose, the use of alpha-2 agonists as lower epidural as well as infusion has been successful (Van Dijk et al., 2003).

Epidural anesthesia: In standing laparoscopy applications in horses, xylazine (0.18mg/kg) is administered epidurally into the S5-C1 or C1-C2 space to ensure the insensitivity of the posterior part of the body (Skarda and Muir, 1994). Detomidine is used epidurally at a dose of 40-60 mcg/kg, while the maintenance dose is 60 mcg/kg. However, it is not recommended to use more than 40 mcg/kg in surgical applications, since ataxia is observed in some horses after administration (Wuttern et al., 1998). It has been determined in studies that there is no need for additional applications because this method provides a significant amount of sedation (Hendrickson, 2012).

Continuous infusion anesthesia: Reliable sedation was provided in the medetomidine-morphine combination used for this purpose, and no adverse changes were observed in respiratory-cardiac functions (Solano et al., 2009). For a similar purpose, butarphanol can be used in addition to the continuous infusion of 20 mcg of detomidine in 1 liter of FTS (Hendrickson, 2008). It should be noted that the epidural anesthesia method produces better sedation compared to continuous infusion, especially the pain during removal of the left ovary was higher in the infusion group, but it

should be noted that continuous infusion is also easier to use and is better tolerated by the horse (Virgin et al., 2010).

Local anesthesia applications: It should be noted that during standing surgery, patients can often move during the application, since they are only under sedation and maintain skin sensitivity (Walmsley, 1999). Therefore, additional use of local anesthesia is inevitable. For local anesthesia of the abdominal wall and skin, local anesthetic can be given in the form of an inverted “L” in the flank region or anesthetic can be dripped into each portal entrance. Researchers administer 2% lidocaine to each entry point using a 20 gauge (1.5 inch) needle. In portal area anesthesia, the formation of ridges on the skin is important. If the skin incision is far from the anesthesia site, the patient will feel pain and additional lidocaine will be needed. However, the critical dose in horses has not been determined precisely. Some researchers recommend not to exceed 200 ml for every 500 kg (Hendrickson, 2012). During intra-abdominal operations such as cryptorchidectomy and ovariectomy, the movements of horses may not be adequately reduced despite being limited by sedation. Researchers recommended the use of 2% lidocaine into the mesovarium and mesorchium before ligation and amputation. In many studies; Instillation of local anesthetic into these areas limited movement during the application in horses (Farstvedt and Hendrickson, 2005; Joyce and Hendrickson, 2006).

Gynecological Laparoscopy Application Techniques

Standing laparoscopy: Cessation of feed intake 12-24 hours before laparoscopy in horses significantly reduces the volume of intestinal contents and improves the quality of vision during the application (Fischer, 1991). The hair of the flank area is cut and prepared aseptically for application. In cases planned for research purposes, it is recommended to prepare both flank areas for the operation. The sedation should be predetermined to suit the operator's preference. Single-dose intravenous, intravenous continuous infusion, lower epidural as well as intravenous sedation or lower epidural anesthesia using detomidine are among the applications (Farstvedt and Hendrickson, 2005; Joyce and Hendrickson, 2006). Standing laparoscopic applications; while sedation and local anesthesia are required, general anesthesia is required in the supine position (Lee and Hendrickson, 2008). Local anesthesia of the flank region; 2% lidocaine or 2% mepivacaine in the skin and muscle layer is formed in an inverted ‘L’ shape, between 40-60 ml or more recently, by applying 10-15 ml of local anesthesia only to the entry points and to each point. Researchers have recommended the use of an 8 mm diameter mare urinary catheter or a 10 mm diameter and 20 cm long blind trocar at entry into the peritoneal cavity to deliver CO₂ prior to trocar placement. A small incision is made in the skin in the flank region, which is the lowest level of the tuber coxa and the midpoint of the last rib

and tuber coxa. Another entry technique is to enter with a cannula in a controlled manner. The presence of the catheter entry into the peritoneal cavity can be determined by the sound of air entering the abdomen and the negative pressure created (Hendrickson, 2012). Three holes are created for tool entry; one based on the midpoint of the last rib and the tuber-coxa and the other based on the alignment of the tuber-coxa; 10 cm in front of the first cannula and the last cannula is placed 5-10 cm below the first cannula (Alsafy et al., 2013).

Laparoscopy in the inpatient: In cases where it is not possible to perform standing, laparoscopy can be performed from the lateral or median region, depending on the location of the tissue to be examined. A flank is preferred in lateral applications. Preoperative preparations are similar in the inpatient. Pre-operative preparation is similar to the standing application. It is anesthetized by placing it in the lateral supine position on the desired side in the abdominal region. The hairs in the flank area are shaved and prepared aseptically. Pneumoperitoneum is similar to the application to the flank region of the standing, this approach allows only the upper part of the abdominal region to be reached and is generally advantageous in cases of enlarged granulosa cell tumors (Hendrickson, 2012). In the laparoscopic approach to be performed from the median line, it is important to fast before the operation to reduce the intestinal volume. Thanks to this application, it will be easier to reach the dorsal abdominal structures (Ragle et al., 1998). After the patient is anesthetized, it is placed on his back. In the animal placed in the Trendelenburg position (removal of the back of the body); research applications and manipulations in the posterior abdomen are easier, on the contrary, lifting the anterior part of the body has made manipulations and researches in the anterior abdomen easier. In either case, it should be attached to the table to reduce the possibility of the patient slipping on the table. Although the asepsis of the region and the placement of the cervix depends on the operation area, it should also include the navel, inguinal and xiphoid regions. In practice, CO₂ is injected into the abdomen at a pressure of 10-15 mmHg via a Veress needle, mammary cannula or laparoscopic trocar. When the abdomen is swollen, the veress needle or mammary cannula is removed, the skin incision is widened to the size of the telescope cannula, and the cannula is placed on the body wall with a blunt obturator. Other cannulas can be placed under direct vision. Some surgeons prefer to insert a spinal needle prior to cannula placement to determine the exact entry points of additional cannulas (Donaldson et al., 1998; Canola et al., 2011).

Colpotomy: Laparoscopically assisted colpotomy, which is a hand-assisted technique applied through a small incision on the vaginal wall; It was developed as an alternative to serous fluid accumulation, impaired

aesthetic appearance and delayed healing complications following large flank incisions (Smith and Devine, 2013) and was first used in ovariectomy applications in mares by M. Charlier (1850) and later Williams (1903). Colpotomy was initially preferred for the extraction of ovaries or small granulosa cell tumors with a diameter of 8-10 cm (Tate et al., 2012). The colpotomy technique requires two operators, the first creating the colpotomy and using the crushing chain, while the other manipulating the laparoscope. The operation begins with a 1 cm incision at the midpoint of the flank, and then an equine laparoscopic trocar with a diameter of 10 mm is inserted into the abdominal region. A laparoscope with a diameter of 10 mm and a size of 33 cm with a 30 degree angle is directed into the abdomen with the screen and video camera associated with the recording, and 15 mmHg CO₂ is introduced into the abdomen. A flow of 20 L per minute is maintained. Abdominal internal organs, especially left ovary and mesovarium are determined. An incision is made through the skin and subcutaneous tissues 2 cm caudal and ventral to this incision. The 4 mm diameter cannula containing the injection needle is advanced blindly through the abdominal muscles and into the abdomen parallel to the laparoscope. The mesovarium is entered with a needle and 10-15 ml of mepivacaine is injected into the mesovarium. The other surgeon makes a 3-5 cm colpotomy lateral to the cervix at the 2 o'clock position from the right anterior angle of the fornix. After the scalpel is removed, the hand is re-inserted into the vagina with the help of the index finger and advanced in the abdomen (Smith and Devine, 2013).

Clinical Applications in Gynecological Laparoscopy

When laparoscopic applications for reproductive purposes are examined in mares, it is possible to say that there are various indications. These include elective and curative sterilization operations, extirpation of ovarian and uterine benign and malignant tumors, especially granulosa theca cell tumors and leiomyomas, massaging fetuses, reproductive colic, treatment of sexual behavior disorders, initiation of estrus by chemical means, and definitive diagnosis in various infertility cases. sampling and various examinations.

Ovariectomy operations: Through to laparoscopic ovariectomy operations, it was observed that the field of view increased, the risk of abdominal contamination and bleeding decreased, ease of hemostasis, and improvement in postoperative wound quality (Hoogmoed and Galuppo, 2005; Alsafy et al., 2013, Kambayashi et al., 2014). Ovariectomy in mares; It can be created in the standing position through a flank incision or under general anesthesia with a median, paramedian, and flank approach (Tate et al., 2012). The approach to be made is determined according to the ovary size, mare size and temperament, available personnel, facilities, surgical instruments and

operator selection (Murphy et al., 2005; Goodin et al., 2011). Application in trendelenburg position with dorsal supine can be recommended for aggressive horses. In order to move the abdominal organs forward and away from the uterus and ovaries, it is recommended to tilt the applied table at least 30 degrees to the side (Ragle, 2000). When bilateral ovariectomy is performed, both flank areas should be prepared for the operation. Six cannulas are required for this application. Before amputation, 10-15 ml of local anesthetic should be infiltrated into the mesovarium (Farstvedt and Hendrickson, 2005). Suture ligation (Boure et al., 1997; Hendrickson, 2006), vessel occlusion devices (Düsterdieck et al., 2003; Alldredge, 2004; Van Hoogmoed and Galuppo, 2005), electrosurgery (Rodgerson et al., 2001; Smith and Mair, 2008), laser (Palmer, 1993), and polyamide tie-rap (Cokelaere and Martens, 2005) can be used. After amputation of the ovaries, the right ovary; the small colon is passed under the left side of the abdomen and both ovaries are removed through the enlarged lower flank incision. It should not be forgotten that there is a risk of ovaries falling into the abdomen after amputation in young mares (Shoemaker et al., 2004). Despite this risk, not removing the ovaries after cutting the ovarian pedicles can be considered as an alternative option. It was observed that no complications were encountered within 10 weeks when the ovaries were left in the abdomen (Shoemaker et al., 2004). An important indication of laparoscopic ovariectomy in mares is ovarian granulosa cell tumors. Colpotomy technique from the median line, flank and vaginal wall can be used for ovariectomy in these cases. Generally, the median line is used for ovaries larger than 15 cm, while flank and colpotomy may be preferred for small ovaries (Murphy et al., 2005). In granulosa cell tumor operations, only the affected ovarian side should be prepared (Ragle et al., 1996). LigaSure devices are recommended as it may be difficult to use suture ligation in enlarged GTC cases. In general, the use of suture ligation in ovaries with a diameter of 18 cm, and the use of a LigaSure device in cases with a diameter of 25 cm and above are recommended. If cystic areas are seen in the ultrasonography of the tumor, the cystic fluids were drained by means of absorbent devices with injection needles in order to reduce the size of the ovary (Hendrickson, 2012). In order to remove large ovaries; a plastic bag was inserted through the hole and the ovaries in this bag could be divided into two or more parts and removed through the small abdominal incision. In this way, the need for large incisions and general anesthesia was eliminated (De Bont et al., 2010). Researchers have focused on the use of hand-assisted laparoscopy for ovariectomy. While a larger incision is required for this technique, the incision required for removal of the ovaries is much smaller than this. For this reason, this technique is a correct application especially in granulosa cell tumors and may be technically easier than the direct laparoscopic approach (Rodgerson et al., 2002).

Applications in the oviduct: Mare's oviduct; since it is both a carrier and a secretory function, it has reproductive importance in early pregnancy. Diagnosis and treatment of diseases of the region are quite challenging and options are limited. Findings obtained in transrectal palpation and ultrasonographic evaluations may leave the physician undecided. Today, flank laparoscopy is used in the treatment of oviduct pathologies, in the intrafallopian transplantation of oocytes or embryos in the standing/inpatient. It may be possible to wash and catheterize the oviduct under sedation. Transvaginal laparoscopic approach is not suitable for this procedure in mares, and only lateral applications should be preferred (Köllmann et al., 2011).

Ovariohysterectomy operations: Ovariohysterectomy operations are not common in mares and donkeys, but they are a radical treatment method for uterine diseases that do not respond to medical treatment. Its main indications are pyometra and uterine proliferation due to infection. It can also be preferred in tumors of the uterus. Laparoscopic ovariohysterectomy is performed for delayed uterine torsion in mares. In vascular ligation, devices such as LigaSure provide fast and safe healing due to the tension it creates in the uterus and ovary. However, laparoscopic method will not be the right option in cases where the uterus is excessively tense and filled with fluid, and in pathologies in the caudal uterus segment (Santschi, 2014). In mares, chronic metritis can be successfully healed by laparotomy and hand-assisted laparoscopy (Scharner et al., 2009). In another example: A 13-year-old mare was diagnosed with post-abortion endometritis, but in the period when she was resistant to medical applications, echogenic fluid accumulation and fetal remains were found in the infected uterus in ultrasonography. In addition to these, a mass of 5-6 cm in diameter was detected at the tip of the cornu. In its treatment, the mass was removed by laparoscopic ovariohysterectomy, and leiomyoma and leiomyosarcoma areas in some areas were determined in its histopathology (Heijltjes et al., 2009).

Uterine tumors: Evaluation of primary mass and metastatic lesions, diagnosis and biopsy of small-scale metastatic lesions (0.5 cm or less) that cannot be easily detected by other methods are possible with laparoscopy (Monnet and Twedt, 2003; Twedt and Monnet, 2005). Benign tumors of the uterus in mares and other species are among the causes of infertility. Leiomyomas are among the most common uterine tumors of mares and are solitary or multiple, often small and stalked formations. Large or invasive tumors can be removed by paramedian, midline complete or partial ovariohysterectomy in anesthetized mares (Gablehouse et al., 2009). In the treatment of uterine leiomyomas in the mare, unilateral ovariectomy and partial hysterectomy with hand-assisted ambulatory

laparoscopy have been reported (Gablehouse et al., 2009). In another case report, uterine leiomyoma with a diameter of 15 cm in rectal palpation and ultrasonic examinations was removed by hand-assisted laparoscopy-assisted ovariectomy. However, postoperative complications such as pain, tachycardia, and wound infection have been reported (Muurlink et al., 2008). Similarly, it has been reported that no complications were encountered in a mare who underwent laparoscopic assisted vaginal ovariohysterectomy for ovariectomy and removal of a 9 cm diameter mass in the left cornea. Researchers reported that outpatient laparoscopic assisted vaginal ovariohysterectomy is a viable alternative to the traditional ovariohysterectomy technique (Gablehouse et al., 2009).

Difficulties and Complications Encountered in Gynecological Laparoscopy

In laparoscopic surgery, which is preferred due to its many advantages, the problems that may be encountered during the application should not be forgotten and appropriate precautions should be taken. The need for accurate simulation of tissues and organs displayed on a two-dimensional screen by the physician and specialized hand-eye coordination is at the forefront of these challenges. Depth perception has been difficult to understand when working on two-dimensional maternal. Creating depth perception with telescope movement accompanied by correct manipulations will be the right approach in this case. In this sense, the camera operator was needed and it fulfills the task of moving the telescope away from the area of other instruments directed into the abdominal cavity and helps to ensure its movement at the same speed as the instruments used. This harmony ensures a balanced coordination between the surgeon and the assistant. It should not be forgotten that physicians need to do a lot of practice in the formation of laparoscopic competence (Hendrickson, 2012).

However, the resistance of the abdominal wall to manipulations significantly affects the success of the physician. In order to reduce the resistance of the wall, the operator and assistant should move the telescopic tool in the opposite direction with the active hand. If a large amount of instrument is in the abdominal cavity, the telescopic tip should be moved more slowly. Conversely, if a small amount of instrument is inserted into the abdominal cavity, the hand must be moved a greater amount to ensure minimal movement of the telescope tip. Many companies have developed instruments that simply move inside the abdomen, seeing that intra-abdominal manipulation of instruments is associated with difficulty in application. In this way, various manipulations, suturing and hemostasis are performed more easily (Hendrickson, 2012).

Major complications after laparoscopy include intraoperative bleeding (especially from paralumbal incision) and mild post-operative pain. Mild pain can be seen in mares after diagonal paramedian, laparoscopic and colpotomy ovariectomies. However, it has also been reported that bleeding occurs as a result of trauma to the forearm of the iliac artery (Goodin et al., 2011). In laparoscopic ovariectomy applications in supine mares, care should be taken in trocar placement. Complications that may be encountered in standing laparoscopy applications occur during cannula insertion or ventilation. These complications are peritoneal separation, injuries to the spleen or kidney, intestinal perforation, and rupture of the iliac artery (Desmaizieres et al., 2003). The most important first rule in standing laparoscopic ovariectomy applications is to ensure that the patient can stand under sedation throughout the operation. In addition, the possibility of falling into the abdominal cavity after cutting the ovary should not be forgotten. Finding and removing the ovary in the abdomen is possible with laparoscopic instruments. However, in some cases it may be necessary to enlarge the incision to manually locate and remove the ovary. In some cases, large follicles in the ovaries make it difficult to be taken out, and it may be necessary to drain the follicles in the abdomen and reduce their size (Lee and Hendrickson 2008). After laparoscopy, infection at the incision site, loss of appetite, opening of the ligature thrown into the mesovarium, postoperative tachycardia and high fever can be counted among other complications (Kamm and Hendrickson, 2007). Perforation of the intestine and spleen during cannula placement, and retroperitoneal air accumulation due to faulty working angle are among the secondary complications (Madron et al., 2012).

REFERENCES

- Allredge JG, Hendrickson DA. (2004). Use of high-power ultrasonic shears for laparoscopic ovariectomy in mares. *Journal of the American Veterinary Medical Association*, 225(10), 1578-80.
- Alsafy MAM, El-Kammar MH, Kassem MM, El-Gendy SAA, El-Khamary AN. (2013). Laparoscopic anatomy of the abdomen and laparoscopic ligating loops, electrocoagulation, and a novel modified electroligation ovariectomy in standing mares. *Journal of Equine Veterinary Science*, 33, 912-23.
- Beccati F, Pepe M, Gialletti R, Cercone M, Bazzica C, Nannarone S. (2011). Is there a statistical correlation between ultrasonographic findings and definitive diagnosis in horses with acute abdominal pain. *Equine Veterinary Journal*, 43(39), 98-105.
- Boure L, Marcoux M, Laverty S. (1997). Paralumbal fossa laparoscopic ovariectomy in horses with use of endoloop ligatures. *Veterinary Surgery*, 26(6), 478-83.
- Canola PA, Perotta JH, Laskoski LM, et al. (2011). Effect of passive pneumoperitoneum on oesophageal pressure, cardiovascular parameters and blood gas analysis in horses. *Equine Veterinary Journal*, 43(4), 446-50.
- Cokelaere SM, Martens AMJG, Wiemer P. (2005). Laparoscopic ovariectomy in mares using a polyamide tie-rap. *Veterinary Surgery*, 34(6), 651-6.
- Conley SP, Lee BR. (2012). Patient Preparation and Operating Room Set-up for Laparoscopic and Robotic Surgery. *Smith's Textbook of Endourology*, 783-92.
- De Bont MP, Wilderjans H, Simon O. (2010). Standing laparoscopic ovariectomy technique with intraabdominal dissection for removal of large pathologic ovaries in mares. *Veterinary Surgery*, 39(6), 737-41.
- De Bont MP, Wilderjans H, Simon O. (2010). Standing laparoscopic ovariectomy technique with intraabdominal dissection for removal of large pathologic ovaries in mares. *Veterinary Surgery*, 39(6), 0000737-41.
- Desmaizieres L, Martinot S, Lepage MO, Bareiss E, Cadore J. (2003). Complication associated with cannula insertion techniques used for laparoscopy in standing horse. *Veterinary Surgery*, 32, 501-6.
- Donaldson LL, Trostle SS, White NA. (1998). Cardiopulmonary changes associated with abdominal insufflation of carbon dioxide in mechanically ventilated, dorsally recumbent, halothane anaesthetised horses. *Equine Veterinary Journal*, 30(2), 144-51.
- Düsterdieck KF, Pleasant RS, Lanz OI, Saunders G, Howard RD. (2003). Evaluation of the harmonic scalpel for laparoscopic bilateral ovariectomy in standing horses. *Veterinary Surgery*, 32, 242-50.
- Fakraden AH. (2013). Retrospective analysis of fifteen hundred gynecological laparoscopy cases. Master thesis. Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey.

- Farstvedt EG, Hendrickson DA. (2005). Intraoperative pain responses following intraovarian versus mesovarian injection of lidocaine in mares undergoing laparoscopic ovariectomy. *Journal of the American Veterinary Medical Association*, 227(4), 593-6.
- Fischer AT. (1991). Standing laparoscopic surgery. *The Veterinary Clinics of North America*, 7(3), 641-7.
- Fischer AT. (2002). Electrosurgery in laparoscopy. In: Fischer AT (eds), *Equine diagnostic and surgical laparoscopy*. Philadelphia: WB Saunders, 79-82.
- Gablehouse KB, Cary J, Farnsworth K, Ragle CA. (2009). Standing laparoscopic-assisted vaginal ovariohysterectomy in a mare. *Equine Veterinary Education*, 21(6), 303-6.
- Galuppo LD, Snyder JR, Pascoe JR, Stover SM, Morgan R. (1996). Laparoscopic anatomy of the abdomen in dorsally recumbent horses. *American Journal of Veterinary Research*, 57(6), 923-31.
- Galuppo LD, Snyder JR, Pascoe JR. (1995). Laparoscopic anatomy of the equine abdomen. *American Journal of Veterinary Research*, 56(4), 518-31.
- Goodin JT, Rodgerson DH, Gomez JH. (2011). Standing hand-assisted laparoscopic ovariectomy in 65 mares. *Veterinary Surgery*, 40, 90-2.
- Hanrath M, Rodgerson DH. (2002). Laparoscopic cryptorchidectomy using electrosurgical instrumentation in standing horse. *Veterinary Surgery*, 31(2), 117-24.
- Heijltjes JM, Rijkenhuizen ABM, Hendriks WK, Stout TAE. (2009). Removal by laparoscopic partial ovariohysterectomy of a uterine leiomyoma assumed to have caused fetal death in a mare. *Equine Veterinary Education*, 21(4), 198-203.
- Hendrickson DA. (2006). Electrosurgery as an adjunct to minimally invasive procedures. In: Wilson DG (eds), *Recent advance in laparoscopy and thoracoscopy*. Ithaca: International Veterinary Information Service; <http://www.ivis.org/>
- Hendrickson DA. (2008). Complications of laparoscopic surgery. *The Veterinary Clinics of North America*, 24(3), 557-71.
- Hendrickson DA. (2012). A review of equine laparoscopy. *Veterinary Science*, 2012, 1-32.
- Hoogmoed LM, Galuppo LD. (2005). Laparoscopic ovariectomy using the endo-gia stapling device and endo-catch pouches and evaluation of analgesic efficacy of epidural morphine sulfate in 10 mares. *Veterinary Surgery*, 34, 646-50.
- Joyce J, Hendrickson DA. (2006). Comparison of intraoperative pain responses following intratesticular or mesorchial injection of lidocaine in standing horses undergoing laparoscopic cryptorchidectomy. *Journal of the American Veterinary Medical Association*, 229(11), 1779-83.

- Kambayashi Y, Tsuzuki N, Seo J, Yamaga T, Tanabe T, Uchiyama H, Sasaki N. (2014). Evaluation of single-incision laparoscopic ovariectomy in standing mares. *Journal of Equine Veterinary Science*, 34, 446-50.
- Kamm JL, Hendrickson DA. (2007). Clients' perspectives on the effects of laparoscopic ovariectomy on equine behaviour and medical problems. *Journal of Equine Veterinary Science*, 27, 435-7.
- Köllmann M, Rötting A, Heberling A, Sieme H. (2011). Laparoscopic techniques for investigating the equine ovidukt. *Equine Veterinary Journal*, 43(1), 106-11.
- Lee M, Hendrickson DA. (2008). A review of equine standing laparoscopic ovariectomy. *Journal of Equine Veterinary Science*, 28(2), 105-11.
- Madron MS, Caston SS, Tracey AK, Kersh KD. (2012). Instrument associated complication of a laparoscopic ovariectomy. *Equine Veterinary Education*, 24(7), 325-30.
- Monnet E, Twedt DC. (2003). Laparoscopy. *The Veterinary Clinic of North America*, 33, 1147-63.
- Murphy J, Hendrickson DA, Hendrix S. (2005). Right flank laparoscopic ovariectomy of a regressing granulosa thecal cell tumor of a pregnant mare: a case review. *Journal of Equine Veterinary Science*, 25(7), 309-11.
- Murphy J, Hendrickson DA, Hendrix S. (2005). Right flank laparoscopic ovariectomy of a regressing granulosa thecal cell tumor of a pregnant mare: a case review. *Journal of Equine Veterinary Science*, 25(7), 309-11.
- Muurlink T, Walmsley J, Whitton C. (2008). Successful laparoscopic surgery for a uterine leiomyoma in a mare. *Equine Veterinary Education*, 20(10), 508-11.
- Palmer SE. (1993). Standing laparoscopic laser technique for ovariectomy in five mares. *Journal of the American Veterinary Medical Association*, 203(2), 279-83.
- Ragle CA, Southwood LL, Hopper SA, Buote PL. (1996). Laparoscopic ovariectomy in two horses with granulosa cell tumors. *Journal of the American Veterinary Medical Association*, 209(6), 1121-4.
- Ragle CA, Southwood LL, Howlett MR. (1998). Ventral abdominal approach for laparoscopic cryptorchidectomy in horses. *Veterinary Surgery*, 27(2), 138-42.
- Ragle CA. (2000). Dorsally recumbent female equine urogenital endoscopic surgery. *The Veterinary Clinics of North America*, 16(2), 317-28.
- Rodgerson DH, Belknap JK, Wilson DA. (2001). Laparoscopic ovariectomy using sequential electrocoagulation and sharp transection of the equine mesovarium. *Veterinary Surgery*, 30(6), 572-9.
- Rodgerson DH, Brown MP, Watt BC, Keoughan CG, Hanrath M. (2002). Hand-assisted laparoscopic technique for removal of ovarian tumors in

- standing mare. *Journal of the American Veterinary Medical Association*, 220(10), 1503-7.
- Santschi EM. (2014). Laparoscopic ovariohysterectomy in the equine; an elusive goal. *Equine Veterinary Education*, 26(2), 79-80.
- Scharner D, Crzbowski M, Brehm W. (2009). Laparoscopic ovariohysterectomy in a mare with chronic pyometra. *Praktische Tierarzt*, 90(4), 328-33.
- Shoemaker RW, Read EK, Duke T, Wilson DG. (2004). An alternative to laparoscopic ovariectomy in juvenile horses. *Canadian Journal of Veterinary Research*, 68(1), 27-32.
- Smith LJ, Mair TS. (2008). Unilateral and bilateral laparoscopic ovariectomy. *Veterinary Record*, 163(10), 297-300.
- Smith SE, Devine DV. (2013). Hand-assisted laparoscopic ovariectomy and colpotomy in standing mares. *Veterinary Surgery*, 42, 586-590.
- Solano AM, Valverde A, Desrochers A, Nykamp S, Boure LP. (2009). Behavioural and cardiorespiratory effects of a constant rate infusion of medetomidine and morphine for sedation during standing laparoscopy in horses. *Equine Veterinary Journal*, 41(2), 153-9.
- Tate LP, Fogle CA, Bailey CS, Tate KB, Davis JW. (2012). Laparoscopic-assisted colpotomy for ovariectomy in the mares. *Veterinary Surgery*, 41, 625-8.
- Tok A. (2008). Retroperineoscopy indications, technique and complications. Master thesis. Haseki Training and Research Hospital, urology clinic, Istanbul, Turkey.
- Twedt DC, Monnet E. (2005). Laparoscopy: Technique and Clinical Experience. In: McCarthy (eds), *Veterinary Endoscopy for the Small Animal Practitioner*. St Louis: Elsevier Saunders, 357-385.
- Van Dijk P, Lankveld DP, rijken huizen AB, Jonker FH. (2003). Hormonal, metabolic and physiological effects of laparoscopic surgery using a detomidine-buprenorphine combination in standing horses. *Veterinary Anaesthesia and Analgesia*, 30(2), 72-80.
- Van Hoogmoed LM, Galuppo LD. (2005). Laroscopic ovariectomy using the endo-GIA stapling device and endo-catch pouches and evaluation of analgesic efficacy of epidural morphine sulfate in 10 mares. *Veterinary Surgery*, 34(6), 646-50.
- Virgin J, Hendrickson D, Wallis T, Rao S. (2010). Comparison of intraoperative behavioral and hormonal responses to noxious stimuli between mares sedated with caudal epidural detomidine hydrochloride or a continuous intravenous infusion of detomidine hydrochloride for standing laparoscopic ovariectomy. *Veterinary Surgery*, 39(6), 754-60.
- Walmsley JP. (1999). The Sir Frederick Hobday memorial lecture: review of equine laparoscopy and an analysis of 158 laparoscopies in the horse. *Equine Veterinary Journal*, 31(6), 456-64.

- Wilson DG, Hendrickson DA, Cooley AJ, Degrave-Madigan E. (1996). Laparoscopic methods for castration of equids. *Journal of the American Veterinary Medical Association*, 209(1), 112-4.
- Wittern C, Hendrickson DA, Trumble T, Wagner A. (1998). Complications associated with administration of detomidine into the caudal epidural space in a horse. *Journal of the American Veterinary Medical Association*, 213(4), 516-8.

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Chapter 3

THE RELATIONSHIP BETWEEN COVID-19 AND VITAMIN C

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THE RELATIONSHIP BETWEEN COVID-19 AND VITAMIN C

COVID-19 was first detected in China and has spread rapidly, making it a global public health issue. The World Health Organization (WHO) and the International Committee on Virus Taxonomy (ICTV) identified this virus as the cause of SARS-CoV-2 disease (Tsang, 2021).

Although the first source of transmission of SARS-CoV-2 is not known exactly, it is known that the way of transmission from person to person is through the respiratory and/or contact way of the person carrying the virus (Acet Öztürk, 2020; Özer ve Özcan, 2020; Şirin ve Özkan, 2020). Symptoms such as fever, weakness, fatigue, cough and shortness of breath seen in many viral infections may also be observed during COVID-19. Gastrointestinal system (GIS) symptoms (nausea, vomiting, diarrhoea) may also be observed, but their incidence is lower than others (Chams, 2020). Patients can be asymptomatic and life-threatening.

When examining the pathophysiology of COVID-19, oxidative stress can cause damage to organs and vessels and inhibit the immune system. This makes it essential to strengthen the immune system (Vollbracht, 2021). During Covid-19 disease, the immune system is the most affected after the respiratory system. Chemokines, systemic interleukins and Tumor Necrosis Factor- α (TNF- α) level rise, causing CRS (Cytokine Release Syndrome) to develop. Because of the oxidative stress that develops, inflammation increases and coagulation can develop in the venous and arterial circulation (Infusino, 2020).

Anti-inflammatory, antioxidant, antiviral, antimicrobial and immunostimulant nutraceutical supplements, such as vitamin C, are believed to have potential therapeutic benefits in the treatment of COVID-19.

C Vitamin

Vitamin C, also called ascorbic acid, is one of the water-soluble vitamins (Miura 2021). It has a low molecular weight, simple and diol structure. Its diol structure gives it the quality of being the main electron donor and ensures that the activity of Fe²⁺ and collagen hydroxylase enzyme fully functional (Du, 2012). It helps prevent vascular damage through its anti-inflammatory effect and plays a role in regulating coagulopathy from septicemia (Shrestha, 2021). It also supports the immune system by improving chemotaxis, producing host defense peptides, inhibiting bacterial replication, stimulating interferon formation, modulating T-cells, and fighting neutrophilic bacteria.

Vitamin C acts as a cofactor for mono and dioxygenase enzymes, and also has pleiotropic effects. That way;

- Detoxify reactive nitrogen and oxygen species (Heruye 2022). Thus, it ensures the removal of free radicals from the body, and restores cellular antioxidants such as α -tocopherol and tetrahydrobiopterin to the body. In addition, xanthine oxidase, unbound nitric oxide synthase (NOS), NADPH oxidase and exogenous oxidant radical species formed by mitochondrial metabolism from the body (Marik, 2018)

- It decreases leukocyte density and inhibits the TNF- α -induced intracellular adhesion molecule (ICAM) and has a healing effect.

- Assists with tissue repair.

- Increases susceptibility to catecholamine.

- Prevents depletion of eNOs and decomposes eNOS. As a result of these properties, it protects against pathological vasoconstriction and reduces endothelial permeability.

- It strengthens the endothelial barrier by inhibiting apoptosis in endothelial progenitor cells (Spoelstra-de Man, 2018)

Humans cannot produce vitamin C in their bodies due to the mutation of the GULO genes and, for this reason, must be taken in the diet (van Gorkom, 2019).

Daily vitamin C needs vary with body weight, gender, age, lifestyle, smoking or not, level of physical activity, and the presence of chronic diseases. The recommended daily dose of vitamin C; 15 mg/day for 1-4 years old, 25 mg/day for 4-8 years old, 90 mg/day for adult women, 75 mg/day for adult men, 80-85 mg/day during pregnancy, 115-120 mg/day during breastfeeding is the day (Monsen, 2000). Oral intake of vitamin C above 200 mg/day, decreases bioavailability and absorption, and increases excretion of vitamin C into the urine. Intravenous administration of vitamin C increases bioavailability by eliminating absorption in the gastrointestinal tract and increasing plasma levels (Ohno 2009). Gastrointestinal effects such as nausea and diarrhea may occur with enteral administration of 3-4 g/day. Intravenous vitamin C supplementation has no contraindications and no signs of toxicity appear until 6 g/day parenterally (Holford, 2020).

Vitamin C deficiency; Weakness, fatigue, depression and scurvy can occur, making these people more vulnerable to infections than others. In the case of hypovitaminosis, it affects the synthesis of collagen from lysine and proline hydroxylation (Knight 2016).

COVID-19 AND VITAMIN C

The cause of the greatest damage to the body in COVID-19 is the development of inflammatory cytokine storm. This condition, which increases free radicals, induces vascular leakage and exudates, triggers the formation of proteases (Wu, 2020). It has been determined that ascorbic acid will work prophylactically, especially during the destruction of the lung caused by the cytokine storm of COVID-19, with its immunomodulatory property and its effect on reducing tissue-organ damage. In addition, it has been stated that vitamin C supplementation given to patients with pneumonia may reduce the length of hospital stay, improve respiratory complications, and microthrombus and coagulopathy (Carr, 2020b; Colunga, 2020). In a study conducted; It has been determined that when 1000 mg of vitamin C is used daily, it increases peripheral blood mononuclear cells (PBMC), IL-10 cells (anti-inflammatory cytokines) in the immune system, and thus inflammation is kept under control (Shakoor, 2021).

In treating COVID-19, the combination of vitamin C and methylprednisolone has been demonstrated to improve the effect of vitamin C. The MATH+ Protocol has been published by the FLCCC (Front Line Covid-19 Critical Care Alliance). In this protocol; Using Methylprednisol, Ascorbic Acid, Thiamine (B1) and Heparin, in the treatment written as +; It has been emphasized that supplements such as magnesium, vitamin D, zinc, ivermectin, melatonin can be added. In a study, mortality declined four times in patients treated with MATH (Turkia, 2020).

Vitamin C, an alternative therapeutic agent, has also been found to reduce the mortality rate in sepsis patients in the intensive care unit (Li, 2021).

In the studies carried out; In COVID-19 patients given intravenous vitamin C, compared to other patients; It has been determined that the need for bronchodilators, the incidence of thrombosis, mortality and the need for mechanical ventilators have decreased (Coppock, 2022; Al Suleiman, 2021; Rawat, 2021).

As a result, vitamin C; It is promising for the treatment of COVID-19 due to its low cost, the ability to tolerate even high doses easily and the absence of serious side effects, as well as reducing oxidative stress, antiviral, antimicrobial and anti-inflammatory effects. Low-dose oral prophylaxis for 1-2 days in patients with mild symptoms or high-dose IV administration in patients with severe treatment may be beneficial (Feyaerts, 2020).

REFERENCES

- Acet Öztürk, NA., Aydın Güçlü, Ö., Görek Dilektaşlı, A. (2020). Covid-19 ve Akciğerler. İçinde Heper. C (Ed.), Bursa Tabip Odası Sürekli Tıp Eğitimi Pandemi Kitabı. Bursa: Bursa Tabip Odası Yayınları: 158-161.
- Al Sulaiman, K., Aljuhani, O., Saleh, K. B., Badreldin, H. A., Al Harthi, A., Alenazi, M., Alharbi, A., Algarni, R., Al Harbi, S., Alhammad, A. M., Vishwakarma, R., & Aldekhyl, S. (2021). Ascorbic acid as an adjunctive therapy in critically ill patients with COVID-19: a propensity score matched study. *Scientific reports*, 11(1), 17648.
- Carr, A. C., & Rowe, S. (2020b). The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19. *Nutrients*, 12(11), 3286.
- Colunga Biancatelli, R., Berrill, M., Catravas, J. D., & Marik, P. E. (2020). Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). *Frontiers in immunology*, 11, 1451.
- Coppock, D., Violet, P. C., Vasquez, G., Belden, K., Foster, M., Mullin, B., Levine, M. (2022). Pharmacologic Ascorbic Acid as Early Therapy for Hospitalized Patients with COVID-19: A Randomized Clinical Trial. *Life*, 12(3), 453.
- Du, J., Cullen, J. J., & Buettner, G. R. (2012). Ascorbic acid: chemistry, biology and the treatment of cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, 1826(2), 443-457.
- Feyaerts, A. F., & Luyten, W. (2020). Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? *Nutrition (Burbank, Los Angeles County, Calif.)*, 79-80, 110948.
- Heruye, S. H., Warren, T. J., Kostansek Iv, J. A., Draves, S. B., Matthews, S. A., West, P. J. et al. (2022). Ascorbic Acid Reduces Neurotransmission, Synaptic Plasticity, and Spontaneous Hippocampal Rhythms in In Vitro Slices. *Nutrients*, 14(3), 613.
- Holford, P., Carr, A. C., Jovic, T. H., Ali, S. R., Whitaker, I. S., Marik, P. E., & Smith, A. D. (2020). Vitamin C-An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19. *Nutrients*, 12(12), 3760.
- Infusino, F., Marazzato, M., Mancone, M., Fedele, F., Mastroianni, C. M., Severino, P., d’Ettore, G. (2020). Diet supplementation, probiotics, and nutraceuticals in SARS-CoV-2 infection: a scoping review. *Nutrients*, 12(6), 1718.
- Knight, J., Madduma-Liyanage, K., Mobley, J. A., Assimios, D. G., & Holmes, R. P. (2016). Ascorbic acid intake and oxalate synthesis. *Urolithiasis*, 44(4), 289–297.

- Li, R., Guo, C., Li, Y., Qin, Z., & Huang, W. (2021). Therapeutic targets and signaling mechanisms of vitamin C activity against sepsis: a bioinformatics study. *Briefings in bioinformatics*, 22(3).
- Marik P. E. (2018). Hydrocortisone, Ascorbic Acid and Thiamine (HAT Therapy) for the Treatment of Sepsis. Focus on Ascorbic Acid. *Nutrients*, 10(11), 1762.
- Miura, K., Matsuno, H., Iwaoka, Y., Ito, H., & Tai, A. (2021). Antiallergic Activity of 6-Deoxy-2-O-methyl-6-(N-hexadecanoyl) amino-l-ascorbic Acid. *Molecules*, 26(15), 4684.
- Monsen, E. R. (2000). Dietary reference intakes for the antioxidant nutrients: vitamin C, vitamin E, selenium, and carotenoids. *Journal of the Academy of Nutrition and Dietetics*, 100(6), 637.
- Ohno, S., Ohno, Y., Suzuki, N., Soma, G. I., & Inoue, M. (2009). High-dose vitamin C (ascorbic acid) therapy in the treatment of patients with advanced cancer. *Anticancer research*, 29(3), 809-815.
- Özer, Z. Y., Özcan, S. (2020). Birinci Basamak Sağlık Hizmetlerinde COVID-19 Enfeksiyonu: Korunma ve Kontrol Önerileri. *Arşiv Kaynak Tarama Dergisi*, 29(Özel Sayı), 67-72.
- Rawat, D., Roy, A., Maitra, S., Gulati, A., Khanna, P., & Baidya, D. K. (2021). Vitamin C and COVID-19 treatment: A systematic review and meta-analysis of randomized controlled trials. *Diabetes & metabolic syndrome*, 15(6), 102324.
- Shakoor, H., Feehan, J., Al Dhaheri, A. S., Ali, H. I., Platat, C., Ismail, L. C., et al. (2021). Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas*, 143, 1–9.
- Shrestha, D. B., Budhathoki, P., Sedhai, Y. R., Mandal, S. K., Shikhrakar, S., Karki, S. et al. (2021). Vitamin C in Critically Ill Patients: An Updated Systematic Review and Meta-Analysis. *Nutrients*, 13(10), 3564.
- Spoelstra-de Man, A., Elbers, P., & Oudemans-Van Straaten, H. M. (2018). Vitamin C: should we supplement? *Current opinion in critical care*, 24(4), 248–255.
- Şirin, H., Özkan, S. (2020). Dünyada ve Türkiye’de COVID-19 Epidemiyolojisi. *Kulak Burun Boğaz ve Baş Boyun Cerrahisi Dergisi*, 28, 6-13.
- Tsang, H. F., Chan, L. W. C., Cho, W. C. S., Yu, A. C. S., Yim, A. K. Y., Chan, A. K. C., Wong, S. C. C. (2021). An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies. *Expert review of anti-infective therapy*, 19(7), 877-888.
- Turkia M. (2020). The History of Methylprednisolone, Ascorbic Acid, Thiamine, and Heparin Protocol and I-MASK+ Ivermectin Protocol for COVID-19. *Cureus*, 12(12), e12403.

- van Gorkom, G., Lookermans, E. L., Van Elssen, C., & Bos, G. (2019). The Effect of Vitamin C (Ascorbic Acid) in the Treatment of Patients with Cancer: A Systematic Review. *Nutrients*, 11(5), 977.
- Vollbracht, C., Kraft, K. (2021). Feasibility of vitamin C in the treatment of post viral fatigue with focus on long COVID, based on a systematic review of IV vitamin C on fatigue. *Nutrients*, 13(4), 1154.
- Wu J. (2020). Tackle the free radicals damage in COVID-19. *Nitric oxide : biology and chemistry*, 102, 39–41.

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Chapter 4

LINKING EVIDENCE TO ACTION: INTEGRATION OF EVIDENCE-BASED PRACTICE IN PEDIATRIC NURSING

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INTRODUCTION

In recent years, delivery of evidence-based practice is regarded as the most effective approach, which can lead to improve patient outcomes and clinical decisions, yet implementation of EBP among nurses is a challenge in many places all over the world. Most nursing care are not evidence based they deliver care based on work experiences, information from colleagues rather than utilizing evidence-based knowledge. A gap exists between the research and practice in nursing care, consequently patient often do not receive the optimal nursing care.

DEFINITION OF EVIDENCE BASED PRACTICE

EVIDENCE-BASED PRACTICE emerged from Florence Nightingale in the 1800s, medical doctor practice in the 1970s, and nursing as a career in the late 1990s. It started as a strategy to enhance outcomes for patients who had exposure to poor and unhygienic settings, and as a strategy to enhance outcomes for patients who had exposure to deliver safe and competent care (Mackey & Bassendowski, 2017).

The goal of evidence-based nursing, is to increase patient safety, save healthcare costs, and ultimately offer a framework that supports clinical judgment in patient-specific circumstances. (Beyea & Slattery, 2013). In order to make clinical decisions, healthcare professionals apply evidence in conjunction with their experience. (Balakas & Smith, 2016). It involves using the best available evidence in clinical practice (Fiset et al., 2017). An approach to problem-solving in nursing known as evidence-based practice (EBP) involves nurse practitioners continue to pose clinically critical questions, evidence that is obtained from research, interpreting, appraising and synthesizing evidence is combined with healthcare professional, patient experiences and expertise to improve nursing care practice (Chiwaula et al., 2018). EBP in nursing is a method that nurses use to make clinical decisions that incorporates the best available research information, their clinical skills, patient preferences, and practice guidelines (Farokhzadian et al., 2015). It is regarded as the foundation for responding to clinical questions by assessing the situation and using the best available information about the patient unit and professional practices. It involves combining the patient's values with particular clinical situations that are supported by scientific data (Shafiei et al., 2014). The nursing profession can reduce the theory to practice gap, according to the International Council of Nurses (ICN), by using evidence-based practice (Mackey & Bassendowski, 2017).

SEVEN STEPS OF EBP IN NURSING

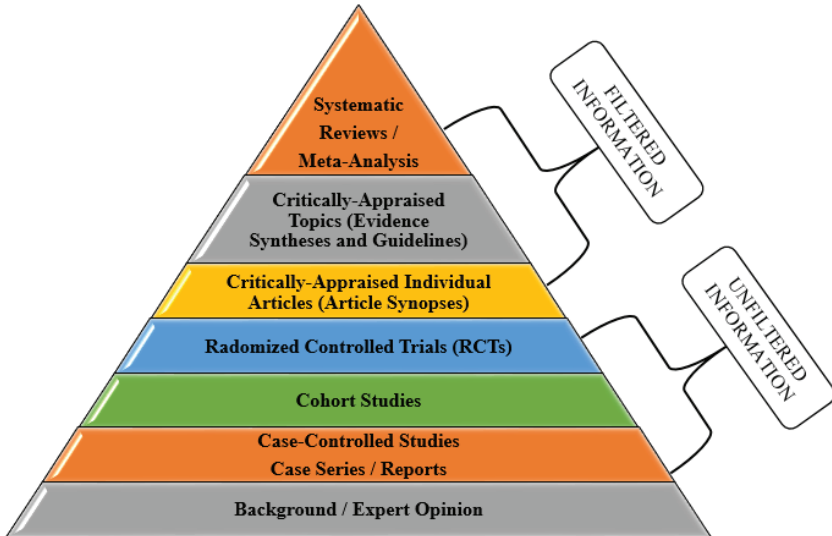
The systematic EBP process, which consists of seven steps, offers a framework for supporting the best clinical judgments, ensuring the

greatest patient outcomes and enhancing healthcare. (Melnyk et al., 2014).

1. Creating an atmosphere and culture of EBP; cultivating an inquiry-based mindset;
2. Ask the PICO(T) question (**P**atient/**P**opulation, **I**ntervention, **C**omparison intervention or group, **O**utcome and **T**ime)
3. Search for the best evidence
4. Evaluate the evidence critically.
5. Gather the data with clinical knowledge and patient preferences.
6. Evaluate the outcomes of EBP practice change to make the optimal healthcare judgment.
7. Disseminate the findings

HIERARCHY OF EVIDENCE

It begins with the least dependable (base) and moving up to the most reliable, the nursing research pyramid, also known as the nursing research hierarchy of evidence, displays scientific methods in a visual and logical way (apex). The pyramid shows both qualitative and quantitative approaches (Ingham-Broomfield, 2016).



1.1 At the base of the pyramid background information (level 7)

- It is the least reliable evidence, that is formed from ideas, opinions and editorials. It can also be from practices, traditions and customs.
- Unscientific report and observation.

1.2 A case-controlled studies/ case series/case report (Level 6)

- It is an in-depth study of an individual unit.
- It combines both qualitative and quantitative data.
- In this level, either subjects have the disease or condition being studied (cases) or they don't (control).
- Much more trustworthy, however recall bias is still a possibility, and information that is gathered retrospectively may have an impact on the quality.

1.3 Cohort studies (Level 5)

- In the study participants are divided into groups based on their level of exposure to risk factors, and they are then monitored over time to look for any potential signs of disease.
- It is known as a longitudinal observational study
- It can be prospective or retrospective.
- Increasing reliability.
- Observational studies are excellent at providing answers to prognosis, diagnosis, frequency, and etiology-related concerns, but they fall short on investigating the effect of an intervention.

1.4 Random Control Trials (Level 4)

- A participant is randomly assigned to one of two or more groups, and each group receives a specific intervention in this experimental study design.
- The effects of the interventions are measure at the end of the trial.
- It is highly reliable/Gold standard.
- Compared to cohort studies, random controlled trials are higher on the pyramid because they can measure the effects of intervention.

1.5 Critically-Appraised Individual Articles (Level 3)

- It is utilized to evaluate the outcomes as evidence of the effectiveness of a research study.
- An expert sums up an article in a synthesis, highlighting its strengths.
- Increasing the outcome reliability of outcome.

- The reliability is less than topics that have been critically appraised because there is less evidence in individual articles than there is in a synthesis of a topic combining multiple studies.

1.6 Critically Appraised Topics (Level 2)

- Multiple research studies are evaluated and synthesized.
- It requires classifying a number of related studies, analysing and interpreting their results, and then putting the summary of the results into a single assertion.

- It is highly reliable.

- In order to synthesize research articles, a number of related studies must first be categorized, their findings must then be analysed and interpreted, and finally their conclusions must be summarized into logical assertions.

- The validity may be undermined by a potential lack of consistency.

1.7 Systematic reviews and Meta-analysis (Level 1)

- A systematic review entails finding, evaluating, choosing, and synthesizing all high-quality research findings before examining the existing literature on a specific topic.

- The outcomes of all quantitative investigations are combined in meta-analysis into a single statistical analysis of outcomes.

- Highest Reliability.

- Systematic reviews and meta-analyses are recognized internationally as of primary research on clinical policy and in evidence-based practice.

MODELS OF EBP IN NURSING

In a review study, Camargo et al., (2017) identified 16 models that are used in the nursing practice between 1970 and 2015. According to a study of 127 nurses in the United States, the “Iowa model of evidence-based practice” (60%), “the John Hopkins Nursing Evidence-Based Practice Model” (19%), and “the Advancing Research and Clinical Practice through Close Collaboration Model” were the three most frequently used EBP models (6.7%) (Speroni et al., 2020).

a. Stetler Model of Research Utilization (Individual Scientific approach)

Synthesis of Step:

1. Identify the goals of the literature review.

2. To critically assess the research results
3. Evaluating the relationship between research findings and clinical practice
4. Decide what to do or what not to do
5. Explain and defend the procedures involved in implementing the new approach, and conduct a thorough evaluation.

b. Conduct and Utilization of Research in Nursing (CURN) (Individual, Organizational Scientific evidence)

Synthesis of Step:

1. Apprehension regarding modifications to nursing practice
2. Investigate and analyze issues with patient care
3. Search for solutions
4. Choose a viable solution
5. Test the proposed solution or conduct experiments
6. Repeat the steps if the solution is not satisfactory after evaluating it.

c. Quality Assurance Model Using Research (QAMUR) Organizational Scientific evidence

Synthesis of Step

1. Identify problem by asking questions
2. Search for solution, examine, and appraise the literature by conducting research
3. Plan to change
4. Implement new ideas as protocols, procedures and policies.
5. Evaluate the expected outcomes

d. Establish an improved care guidelines Iowa Model (Organizational scientific evidence)

Synthesis of Step

1. Determine critical problems and create research questions.
2. Identify the severity of the problem with the organization's top priority.
3. Choose keywords to use in your search for evidence, then critically analyse and synthesise it.

4. Ascertain whether the evidence is sufficient; if not, carry out a search.

5. Conduct a pilot study to alter the practice if the evidence is sufficient and the changes are appropriate.

6. Analyse pilot outcomes, share findings, and implement change into practice.

e. Ottawa Model of Research Use (OMRU) Individual Organizational scientific evidence

Synthesis of Step

1. Find the necessary resources and those with the power to give the change process legitimately.

2. Clearly state the concept or innovation that has to be applied.

3. Determine who can adopt innovation, what obstacles would stand in the way, and what facilities might be implemented.

4. Choose techniques to educate individuals involved about the importance of innovation and its spread throughout the organization until it reaches direct patient care.

5. Analyze the results, then disseminate them.

f. Promoting Action on Research Implementation in Health Services Framework (PARHIS). Organizational Scientific evidence

Synthesis of Step

1. Utilize facts and reports from the institution, clinical experience, patient experiences, and scientific research to support your claims.

2. Utilize innovation to improve organizational culture by assisting leadership and examining procedures.

3. Bring in professionals whose knowledge and abilities can assist changing practice in accordance with the evidence.

g. The Rosswurm and Larrabee Model (Individual best scientific evidence)

Synthesis of Step

1. Determine the necessity for a change in practice

2. Analyze the situation with outcome variables

3. Summarize the strongest scientific evidence i.e., systematic analysis and taking into account the implementation's viability, benefits, and risks

4. Create a strategy for changing the practice that includes the required resources.

5. Change implementation and evaluation

6. Integrate and sustain change processes in your work by reporting results to strategic experts

7. Observe implementation.

h. Advancing Research and Clinical Practice Through Close Collaboration (ARCC)

Synthesis of Step

1. Recognize organizational culture and change readiness

2. Determine the organization's EBP implementation's strengths and challenges.

3. Determine the organization's experts who will work with the support teams in the clinical units to aid in the execution of the EBP.

4. Apply the research in practice, then assess the outcomes.

1. Johns Hopkins Nursing Evidence based Practice Model (JHNEBP) (Individual Scientific and non-scientific approach)

Synthesis of Step

1. Choose a practice-related topic, and then formulate the research question using words that are appropriate for the scientific process.

2. Identify, appraise, organize, and classify the various levels of evidence

3. Making decisions based on "non-scientific" facts such as financial information, professional expertise, and patient preferences

4. Determine whether the evidence can be applied, create an action plan for its application, make the change, evaluate the results, and report the findings.

j. Model in an Academic Medical Center (Individual Organizational Scientific evidence)

Synthesis of Step

1. Create a clinical question.

2. Use systematic review of experimental study to search out the best evidence.

3. Examine the evidence critically

4. incorporate evidence into your practice
5. Report the findings.

k. The Tyler Collaborative Model (Organizational Scientific and Non-Scientific Evidence)

Synthesis of Step

1. Establishing a foundation for collaboration among strategic leaders to accept change by recognizing organizational forces that can effect change.

2. Diagnose the problems and identify places where EBP should be used.

3. Obtaining resources: determining the financial and personnel needs for the execution of change

4. Engage nursing assistants to find EBP-based answers to their demands (organize working group)

5. Select a solution: thorough evaluation of scientific output

6. Implement the evidence via a pilot study to obtain approval and supporters and allows them to assess the attention paid to the adoption of the evidence relative to their non-adoption.

7. Control: Integrate evidence into practices and regulations of the organization

8. Prepare reports that analyze the organization's results by comparing them to the evidence incorporated into daily practice

l. Academic Center for Evidence-Based Practice (ACE) (Individual Scientific Evidence)

Synthesis of Steps

1. In order to generate new knowledge, one must conduct rigorous reviews of numerous source studies (taking into account their various designs).

2. Create a document or instruction guide to put the research into action

3. Integrate knowledge into practice by controlling organizational and individual change

4. Analyze the effects of the practice changes and the improvement in care quality.

m. The Colorado Model (Individual Organizational Scientific and Non-Scientific Evidence)

Synthesis of Steps

1. Determine the factors that encourage organizational change.
2. Using the PICO approach, develop a clinical question.
3. Analyze the patient's values and preferences
4. Determine the patient's needs
5. If the hospital has an institutional EBP protocol, look for scientific data in accordance with that protocol. Otherwise, conduct a thorough literature study.
6. Use evidence from alternative sources, such as infection control data, cost-effectiveness analyses, and clinical expertise, in the lack of scientific evidence.
7. Summarize the data taking into account their classification
8. Apply them in accordance with the patient's circumstances and decisions
9. Analyze the outcomes

n. The Multisystem Model of Knowledge Integration and Translation (MKIT) (Organizational Scientific and Non-Scientific Evidence)

Synthesis of Steps

1. Promote the development of relevant research in practice
2. Search, critically evaluate, and synthesize the data about transformational leadership in organizations through the action of nurses who have an expertise in the practice.
3. Encourage the application of evidence by organizing activities for nursing assistants and nurse researchers.
4. Assemble normative papers (protocols and clinical guidelines), incorporate evidence into the work process, plan a pilot study with the assistance of specialized nurses
5. Track the outcomes of the implementation; to spread the results of implementation

o. The Research Appreciation, Accessibility and Application Model (RAAAM) (Organizational Scientific and Non-Scientific Evidence)

Synthesis of Steps

1. Partner with research institute and hospitals to contribute to research project.

2. Through a group of committees utilize research findings to improve the practice guidelines.

3. Apply research (model sustainability is ensured by integrating research development into the function of nurses in the hospital context) (disseminating and reporting EBP outcomes by developing a communication strategies)

p. The Clinical Scholar Model (Individual Organizational Scientific and Non-Scientific Evidence)

Synthesis of Steps

1. Determine the best periods to introduce change within an organization.

2. An evaluation of both internal evidence as data and external evidence as search result

3. Make a plan for implementing the evidence based on the scientific validity.

4. Conduct a search if they are not valid enough.

5. To apply them, acquire the results in context, and simulate its use using various methods

6. Reporting the findings to the organization's internal and external audience.

KNOWLEDGE & PERCEPTION OF EBP IN PEDIATRIC NURSING

Utilizing and participating in research-related activities in nursing develops fundamental care skills (Lee et al., 2017). To access, retrieve, and assess evidence in nursing practice, competencies are essential. Evidence-based nursing competency (EBNC) is the ability of a nurse to perform all aspects of their professional role in a way that is consistent with evidence-based nursing practice. (Fu et al., 2020). A clinician's perceived knowledge of nursing practice based on evidence and their views about delivering this care together comprise of their competence. (Oyesanya & Snedden, 2018). Fu and colleagues, (2020) in their studies reported that evidence-based nursing was affected by the nurses age (nurse who were younger in age presented better EBP competency), hospital level, EBN educational training and knowledge (Fu et al., 2020). Although it was noted in a Jordanian study that the nurses' age and work history were unrelated

to their understanding, attitude, and use of EBN. Nurses with higher education levels have more understanding and expertise regarding EBP (Aburuz et al., 2017). Knowledge deficiency is one of the most significant obstacles to the implementation of evidence-based practice. Despite the emphasis on EBP and the substantial body of research demonstrating its benefits, many nurses do not use evidence to direct their practice (Aburuz et al., 2017).

According to a quantitative study conducted in Ghana, the majority of nurses have a positive attitude about EBP since they are aware that it will enable them to give their patients safe treatment and increase their sense of job satisfaction. Despite the favourable opinions toward EBP, it was observed that training constraints made it difficult to learn about and apply EBP. (Atakro et al., 2020). Similarly, Jordanian nurses had positive attitude towards EBP, but knowledge and practice of EBN were not reflecting in the daily practice (Aburuz et al., 2017). The majority of the nurses and nursing students who participated in a different study from Nepal done by Karki et al. (2015) reported that they had not undergone EBP training. Additionally, it was said that although they had little knowledge and abilities, they had positive attitudes toward EBP.

According to a study conducted in Egypt, pediatric nurses had limited awareness of evidence-based nursing. Only a small number of pediatric nurses were proficient in using pertinent scientific resources and recognizing words that are frequently used in research. (Amin & Fakhry, 2015). For example, 330 nurses with a decade of experience participated in a study that assessed pediatric nurses' perceptions of their knowledge and attitudes regarding caring for children and adolescents with moderate-to-severe traumatic brain injury (TBI) based on the evidence. In this study, 177 nurses had a high level of evidence-based (EB) knowledge, compared to 124 nurses who had a poor level of EB knowledge; all groups had the same degree of education and primary role. Pediatric nurses' perceptions regarding treatment, sex-based patient differences after TBI, and their role in caring for patients with TBI varied considerably between the two evidence-based perceived knowledge groups. Nurses in the high evidence-based perceived knowledge group had more years since graduation, years in total of active nursing practice, and years in their current nursing position than those in the low evidence-based perceived knowledge group. Compared to nurses in the low evidence-based perceived knowledge group, the high evidence-based perceived knowledge group had more years since graduation, total years in active nursing practice, and total years in their current nursing position (Oyesanya & Snedden, 2018). In some cases, there are factors that can contribute to implementing Evidence based practice. In research to assess whether pediatric critical care nurses

were adequately knowledgeable about evidence-based guidelines for preventing ventilator-associated pneumonia (VAP). The findings indicate a significant relationship between the number of years of experience, prior instruction in VAP prevention recommendations, and nurses' awareness of these standards. However, there is no relationship between nurses' awareness of evidence-based guidelines for reducing ventilator-associated pneumonia and their age (Ahmed & Abosamra et al., 2015). In regards to nurses from Malawi working in the pediatric and obstetric departments on their knowledge, attitudes, and practices about evidence-based practice in the PMTCT program. The findings indicated that the nurses had positive attitudes regarding EBP despite having moderate knowledge of EBP and inadequate implementation skills. The qualifications and category of nurses were favourably correlated with knowledge of EBP and EBP training was linked to attitudes regarding EBP. Additionally, it was discovered that practice and experience were favourably correlated. (Mulenga & Naidoo, 2017).

FACILITATION AND BARRIERS RELATED TO EBP IN NURSING/PEDIATRIC NURSING

In a systematic study, Schaefer and Welton (2017) analyzed the concept of readiness of EBP in nurses. It was further stated that nursing readiness of EBP is the combination of organizational and personal readiness. The pillars that facilitate EBP in patient care are nursing training and equipping, and leadership support/development. Integrating evidence-based practice is not dependent on several qualified nurses collectively, not just one qualified nurse. Time allocation for finding and critiquing scientific materials and professional autonomy are necessary in evidence-based nursing practice. Educational level may have little significance in utilizing evidence-based practice in general nursing practice, it is important for nurses to receive training applicable to evidence-based practice training. In the aspect of training, ensuring accessibility to computer or other information databases, EBP mentors, current peer-reviewed nursing journals at the point of care. One of the greatest barriers to EBP had been reported to be lack of resources. Leadership development fosters EBP including providing practice setting towards EBP, time and resource allocation for literature findings and EBP implementation, encouraging positive attitudes toward increasing utilizing EBP into practice (Schaefer & Welton, 2017). Additionally, there are elements that support EBP, such as: EBP beliefs and implementation skills, creating EBP strategies, administrative support, and assistance from librarians from multidisciplinary education programs are all factors that help direct nurses in implementing best evidence in their care. (Melnik et al., 2014).

Efficacy in executing and implementing EBP both in nursing education and nursing practice had been hindered by underlying impediments up until now. EBP integration into clinical practice is difficult and low, according to studies carried out in various nations. The majority of patients do not receive treatment based on available scientific data (Linton & Prasun, 2013). For instance, in a study, the biggest barrier to implementing EBP was the inability to assess the quality and credibility of research papers and reports. (Farokhzadian et al., 2015). Lack of libraries in various units, the inability to conduct evidence searches on the internet, inadequate EBP practice guidelines, a lack of time, and insufficient workload release were some of the obstacles to EBP in nursing (Atakro et al., 2020; Karki et al., 2015). Limited access to information was one of the key challenges faced by nurses in a recent systematic assessment of EBP obstacles among nurses in low- and middle-income countries (Shayan et al., 2019). In a cross-sectional study, 253 Ethiopian nurses reported the following barriers to implementing EBPs: a culture that is not supportive of the implementation of EBP, a lack of autonomy to change practice, a lack of understanding of research terms and statistical terms used in research, difficulty evaluating the quality of research, an inability to accurately interpret the results of research, a lack of confidence in evaluating the quality of research, a lack of proficiency in the English language, and a lack of understanding of research terms and statistical terms used in research (Dereje et al., 2019). The primary obstacles noted by pediatric nurses included a lack of funding, difficulty reading research reports, a lack of time, and difficulty determining how research findings applied to clinical practice (Mulenga & Naidoo, 2017).

Despite their limited knowledge and abilities and implementation challenges, many nurses had positive attitudes toward EBP. It's imperative that nurses develop their EBP abilities. Implementing the most well-known methods into the clinical context while employing a scientific method is known as evidence-based practice. As a result, there will be a higher likelihood that consistent, safe, high-quality care will be delivered. Errors can be minimized by using evidence-based practice obtained from nursing research.

REFERENCES

- Aburuz, M. E., Hayeah, H., Al-Dweik, G., & Al-Akash, H. (2017). Knowledge, Attitudes and Practice about Evidence-Based Practice: A Jordanian Study. *Health Science Journal*, 11(2), 489-497.
- Ahmed, G., & Abosamra, O. (2015). Knowledge of Pediatric Critical Care Nurses Regarding Evidence Based Guidelines for Prevention of Ventilator-Associated Pneumonia (VAP). *Journal of Education and Practice*, 6(9), 94-103.
- Amin, F., & Fakhry, S. (2015). Pediatric Nurses' Knowledge, Perceived Barriers and Motivators Related to Evidence Based Nursing at University Children Hospitals, Egypt. *International Journal of Health Sciences and Research*, 5(6), 409-418.
- Atakro, C., A., Atakro, A., Akuoro, C. P., Aboagye, J. S., Blay, A. A., Addo, S. B., Adatar, P., and Agyare, D. F. (2020). Knowledge, attitudes, practices and perceived barriers of evidence-based practice among registered nurses in a Ghanaian Teaching Hospital. *International Journal of Africa Nursing Sciences*, 12(20), 1-7.
- Balakas, K., Smith, J. (2016). Evidence-Based Practice and Quality Improvement in Nursing Education. *Journal of Perinatal & Neonatal Nursing*, 30(3) pp 191-194.
- Beyea, S. C. & Slattery, M. J. (2013). Historical perspectives on evidence-based nursing. *Nursing Science Quarterly*, 26, pp 152–155
- Buckwalter, K. C., Cullen, L., Hanrahan, K., Kleiber, C., & McCarthy, A. (2017). Iowa model of evidence-Based Practice: Revisions and validation, *World views on Evidence-Based Nursing*, 14(3), pp 175-182.
- Camargo, F., Iwamoto, H., Galvao, C., Trindade, D., Goulart, M., & Garcia, L. (2017). Models for the implementation of Evidence-based practice in Hospital Based nursing: A narrative review. *Texto Contexto Enferm*, 26(4), e2070017-e2070029.
- Chiwaula, C., Chinkhta, M., Kamera, H., & Haruzivish, C. (2018). Evidence Bases Practice: A concept analysis. *Health Systems and Policy Research*, 5(3), 75-82.
- Dereje, B., Hailu, E., & Beharu, M. (2019). Evidence-based practice utilization and associate factors among nurses working in public hospitals of Jimma Zone Southwest Ethiopia: A cross sectional study. *General Medicine*, 7(1), 321-331.
- Disler, R. T., White, H., Franklin, N., Armari, E., & Jackson, D. (2019). Reframing evidence-based practice curricula to facilitate engagement in nursing students. *Nurse Education Practice*, 41, 1 –7.

- Farhhzadian, J., Khyourei, R., & Ahmadian, L. (2015). Evaluating factors associated with implementing evidence-based practice in nursing. *Journal of Evaluation in Clinical Practice*, 21(15), pp.1107-1113.
- Farokhzadian, J., Khajourei, R., & Ahmadian, L. (2015). Evaluating factors associated with implementing evidence-based practice in nursing. *Journal of Evaluation in Clinical practice*, 21(15) pp 1107-1113.
- Fiset, V., Graham, D., & Davies, B. (2017). Evidence-based practice in clinical nursing education: A scoping Review. *Journal of Nursing Education*, 56(9), pp 534-541.
- Fu, L., Su, Wei., Ye, X., Li, M., Shen, J., Chen, C., Guo, Q., Ye, L., He, Y. (2020). Evidence-Based Practice Competency and Related Factors Among Nurses Working in Public Hospitals. *The Journal of Health Care Organization, Provision and Financing*, 57: 1-9.
- Ingham-Broomfield, R. (2016). A nurses' guide to the hierarchy of research designs and evidence. *Australian Journal of Advanced Nursing*, 33(3), pp 38-43.
- Karki, S., Acharya, R., Budhwani, H., Shrestha, P., Chalise, P., Shrestha, U., Gautam, K., & Wilson, L. (2015). Perceptions and Attitudes towards Evidence Based Practice among Nurses and Nursing Students in Nepal. *Kathmandu University Medical Journal*, 52(4):308-15.
- Kim, S. C., Ecoff, L., Brown, C. E., Gallo, A. M., Stichler, J. F., & Davidson, J. E. (2017). Benefits of a regional evidence-based practice fellowship program: A test of the ARCC Model. *Worldviews on Evidence-Based Nursing*, 14(2), 90 –98.
- Linton, M.J., & Prasun, M. (2013). Evidence-based practice: collaboration between education and nursing management, 21: 15-16.
- Mackey, A., & Bassendowski, S. (2017). The History of Evidence-Based Practice in Nursing Education and Practice. *Journal of Professional Nursing*, 33(1), pp 51-55.
- Melnyk, B., Gallagher-Ford, L., & Fineout-Overholt, E. (2014). The establishment of evidence-based practice competencies for practicing registered nurses and advanced practice nurses in real-world clinical settings: proficiencies to improve healthcare quality, reliability, patient outcomes and costs. *Worldviews on Evidence-Based Nursing*, 11(1), pp 5-15.
- Mulenga, C. & Naidoo, J.R. (2017). 'Nurses' knowledge, attitudes and practices regarding evidence-based practice in the prevention of mother-to-child transmission of HIV Program in Malawi'. *Curationis* 40(1), a1656.
- Oyesanya, T., & Snedden, T. (2018). Pediatric nurses' perceived knowledge and beliefs of evidence-based practice in the care of children and adolescents with moderate-to-severe traumatic brain injury. *Journal for Specialists in Pediatric Nursing*, 23(2), e12209-e12220.

- Schaefer, J., & Welton, J. (2017). Evidence based practice readiness: A concept analysis. *Journal of Nursing Management*, 26(6): pp 621-619.
- Shayan, S. J., Kiwanuka, F., & Nakaye, Z. (2019). Barriers associated with evidence- based practice among nurses in low- and middle-income countries: A systematic review. *Worldviews on Evidence-Based Nursing*, 16(1), 12 –20.
- Speroni, K., Mclaughwin, M., & Friessen, M. (2020). Use of Evidence-based practice models and research finding in magnet-designated hospitals across the United States: national survey results. *Worldviews on Evidence-Based Nursing*, 17(2), pp 98-107.

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Chapter 5

VACCINE CONFIDENCE AND HESITANCY

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INTRODUCTION

The first vaccinations appeared in the eighteenth century as a successful preventative measure against the spread of dangerous illnesses. (Puri et al, 2020). Vaccine injection is regarded as a scientifically proven method of preventing the spread of infectious diseases. It includes administering a biological injection designed to elicit a protective reaction similar to that experienced during a typical contagion. It causes the body to develop the same kind of defense as it develops when it first comes into contact with an infectious mediator. This protects the body from disease, as well as its harmful pathophysiological effects and possible complications. (Kofłataj et al, 2020). Any number of vaccination attitudes, from cautious acceptance to open denial, might continue to be the driving force behind vaccine reluctance, which is described as a patient's unwillingness to get injections. Therefore, one of the obstacles to universal vaccination is false information regarding the benefits, medicinal makeup, and negative consequences of vaccination. It prevents complete buy-in and patient education. (Olson et al, 2020). Vaccine self-confidence is well-defined as the belief of efficacy in addition to protection of the injections as well as believe in the healthcare method that administers them, whereas contentment and suitability are related to the perceived risk of sickness and the accessibility of immunization treatments. (Carrieri et al, 2019). High vaccination rates depend on both political and provider trust in addition to public trust in vaccination. Embracing the drivers of vaccination confidence when supply, access, and facts are accessible necessitates accepting the belief-based contributing component, which can have profound local and contextual roots and alter over time and by vaccine. (Larson et al, 2018). In addition, perceived immunization benefits and protection as well as considered significance and spiritual compatibility are utilized to measure confidence. Vaccine trust is the assurance of success and protection of the injections as well as the healthcare method through oversees. The trust that injection is in the greatest concern of the population and so, inhabitants is referred to as vaccine self-confidence. (Paul et al, 2021). A postponement in accepting or refusing injections regardless of the readiness of preparation facilities is known as vaccine reluctance. (WHO, 2021). Injection may be viewed as a fruitless protective action when the alleged risk of contracting the illness is low-slung. Factors that affect convenience include physical accessibility, cost, geographical approachability, the ability to interpret information, and the use of immunization facilities. (Cadeddu et al, 2021). Confidence can be characterized as having faith in the efficacy and safety of immunizations, the program that provides them, as well as the consistency and competency of well-being care facilities and specialists, and so the justifications for vaccines that are recommended by policymakers. (Schellenberg & Crizzle,

2020). Due to the fact that they must also decide whether to vaccinate their children, parents play a crucial role. The general public's decisions on vaccination are significantly influenced by healthcare professionals. (Cadeddu et al, 2021). Through the assistance of societal and traditional media, anti-vaccine movements are gaining ground and have begun to affect politics and elections in a number of European nations. The demand for focused measures to restore confidence in vaccinations emphasizes the necessity of ongoing monitoring, preparation, and response strategies. (Larson et al, 2018). To enhance the exchange of best practices, coordinated initiatives across industries and nations should be encouraged. To track changes in confidence levels and enable quick reactions, a continuous monitoring system should be put in place. (Tsang & Wong, 2021).

VACCINES BENEFITS and SAFETY

Earlier revisions have exposed that injection resistance is a communal occurrence international, through a wide range of justifications offered for preparation denial. Thus, receiving hazards vs. welfares, spiritual beliefs, and a lack of information were the three most important public reasons. (Paul et al, 2021). Injections must have an influence on lengthening lifetime expectation, decreasing infectious issues, containing incapacity, improving residents' quality of life, reducing illness absence, saving, and modifying the epidemiological hazard and also, reducing public health risks by immunizing a large proportion of the population. (Chou et al, 2020). The aforementioned reasons may contribute to disease injection resistance, as displayed through previous studies that demonstrated a positive correlation concerning the desire to obtain coronavirus preparations and alleged protection. (Karafillakis et al, 2017). Religiosity is connected to a decreased intention to receive COVID-19 injections, and negative attitudes against vaccine injection are linked to a lack of enthusiasm for receiving the immunizations (Karlsson et al, 2021). Reliance on vaccines as a whole, race/ethnicity, and concern about COVID-19 contamination all affect vaccine hesitancy, with Black/African Americans having significantly more hesitancy. (Willis et al, 2021). Through immunization against bacterial illnesses, antibiotic resistance in microorganisms is also avoided. The amount of antigen, handling protocol, and effectiveness of the vaccinated person's protected method are factors in vaccine effectiveness, as are the choice and method of manufacture of preparation resources. (Kołtątaj et al, 2020). The broad vaccination against highly dangerous diseases remains hampered by vaccine fear. Worries around the danger of COVID-19 injections could contribute to preparation resistance, which would be in conflict with the global expansion of COVID-19 injections. (Dror et al, 2020). Another strategy is to arouse positive feelings about promoting health and wellbeing in one's society and, as a result, persuade

people to choose to get vaccinated against the most dangerous illness of our day. (Chou et al, 2020). There are many ways to think about and control both negative and good emotions. As part of vaccine education efforts, connecting to adverse feelings similar to distress and angst, rising alertness of the expressive influences about injection misinformation, and generating progressive feelings like compassion and optimism are just a few examples. (Wise, 2020).

REASONS for POOR VACCINE TRUST in the CURRENT ENVIRONMENT

The authors claim that the delay in the COVID-19 vaccine distribution offers a window of opportunity for addressing concerns about reluctance and vaccination adoption among LMICs. Continued research ought to be a top priority because everyone in the world must work together to combat this pandemic. Such study can guide contextualized advertising that will ultimately boost people's trust in and use of the vaccines that are already accessible. (Daley et al, 2018). When developing policies for corona virus immunization and communal wellbeing messages, health managers need to be aware of these factors. A history that not obtaining an influenza injection and a decreased self-perceived hazard of constricting the illness were two additional characteristics linked to vaccine hesitation that were frequently researched. doubts about the vaccinations' efficiency and safety as well as worries about their rapid development. (Badur et al, 2020). Low vaccination trust is mostly caused by misinformation and a lack of access to unbiased, reliable information. The development of anti-vaccination groups and the formation of vaccination policy have been significantly influenced by the internet and social media. According to a study of online vaccine skepticism, websites that oppose vaccination use emotional appeals, assert that mainstream medicine is false, and suggest that conspiracies are to blame for the illnesses that vaccinations purport to prevent. (Schellenberg & Crizzle, 2020). In all contexts, there is a lot of false information concerning vaccinations. Though the means of dissemination may vary, false information (hoaxes) concerning vaccinations may catch on if it is disseminated by influential people. In 2003, the use of the oral polio vaccine (OPV) was stopped in Nigeria because to suspicions that it was a plot by the Americans to sterilize Muslim females and spread the HI virus. (Fine et al, 2018). Religious extremism and the public's declining confidence in vaccination programs have continually hampered efforts to eradicate polio in developing nations like Pakistan. When vaccination safety concerns arise, they may be exaggerated and misunderstood, which encourages scare tactics and false information on social media. Poorly managed challenging circumstances may erode vaccine trust and

have a negative impact on immunization campaigns. (Chang et al, 2018). To rebuild public confidence in the healthcare system, it is essential to increase the amount of information accessible to the public and promote transparency concerning the risks and assistances of vaccines. For the general public, injection suppliers, and health authority officials, contact to reliable data supported by methodical accountability and reliability ought to be eased and guaranteed. (Aw et al, 2022). Following the 2009 H1N1 pandemic, popular confidence in the government was questioned throughout Europe, and poor vaccination program adherence was seen. In Japan, the percentage of girls who were eligible for the HPV vaccine who received it fell from 70% in 2013 to 1% in 2014. Untrue information was disseminated via internet media, reaching and influencing a larger, global audience. (Hiscott et al, 2020). Studying the global effects of this issue may be more challenging due to the diversity of vaccination hesitancy. This suggests that intellectual, psychological, demographical, and social factors all contribute to vaccine anxiety. (Karlsson et al, 2021). Because of complacency or a misperception of the illness's hazard, injection was considered not important. Confidence must do with having faith in the reliability of medical systems as well as the security and efficacy of immunizations. To be deemed handy, vaccines must be made available, reasonably priced, and administered in a welcoming setting. (Sallam, 2021). The multifaceted natural surroundings of injection hesitancy can be investigated by means of an epidemiologic triangle of conservational, mediator, and also host influences. Environmental issues contain things like laws governing public health, cultural norms, and media propaganda. (Daley et al, 2018). The agent considerations also take into account the knowledge of vaccine effectiveness and protection, in addition to the perceived illness vulnerability. Host characteristics are influenced by knowledge, prior experience, educational level, and socioeconomic status. (Olson et al, 2020). Producing enough vaccines, distributing them fairly, and having doubts about their efficacy are the main barriers to the proper implementation of disease immunization campaigns to combat the exceptional outbreak. Additionally, in some republics, resistance to injection may be a significant barrier to control efforts intended to minimize the negative effects of the illness pandemic. (Sallam, 2021).

ROLES of HEALTHCARE PROFESSIONALS in MAINTAINING VACCINE CONFIDENCE

The connection among patients or their paternities and health care specialist is crucial to their credibility since they are the greatest normal sources of evidence about injection, also in their interactions with parents, high-performing healthcare professionals (HCPs) do not

vehemently support the necessity for immunization. (Bhopal & Nielsen, 2021). HCPs who have received vaccinations are more likely than their counterparts who have not to advise patients to become immunized. Lack of information regarding benefits, worry about side effects, and skepticism about effectiveness and safety were all given as justifications for not promoting pneumococcal immunization. (Bernados & Ocampo, 2022). Studies have shown that HCPs' awareness of vaccination-related problems varies, and that training in vaccineology is either inadequate or nonexistent in many nations' curricula. (Klein et al, 2021). It is unrealistic to anticipate 100% effectiveness, as a vaccination might fail to elicit the proper immune reaction owing to handling mistakes or hereditary factors in the pathogen. During an epidemic, a tiny portion of unvaccinated people avoid becoming sick, while a smaller segment of those who have received the disease vaccine nevertheless become sick. (Alabdulla et al, 2021). Although vaccinations don't always result in a complete immune response, they may nonetheless minimize illness symptoms, as was the case with the rotavirus, pertussis, and influenza vaccines. Although the methods through which pathogen gene may affect immune reactions to vaccinations are well known, it may be challenging to convey their complexity. Another key effect of regular immunization is the reduction in illness severity and duration. (Beesley et al, 2021). HCP must describe the nature and function of vaccinations, as well as the risks and advantages for both the community and the child that are supported by scientific research. Transparency about vaccinations, VPDs, testing, components, possible adverse effects, and financing helps to build confidence. (Fobiwe et al, 2022). The data must be accurate, trustworthy, and up-to-date on VPDs, vaccination safety, and effectiveness from reputable sources. Researchers discovered that a presumed strategy, as opposed to a participative one, was more effective in persuading parents to get their children immunized. (Bell et al, 2020). Health care providers (HCPs) must be able to hear the worries of parents without bombarding them with information. One of the fundamentals of motivational interviewing is the use of this strategy to establish trustworthy communication between parents and HCPs. In order to assist them overcome their hesitation over vaccine acceptance, parents will get information that is specifically suited to their requirements. (Badur et al, 2020). HCPs need assistance to complete the requirements of this crucial information procedure. HCPs who are familiar with the advised vaccinations and their associated VPDs are more likely to advise immunization. Techniques for handling challenging interactions with reluctant people should be included in the training. To provide the necessary time for the information transmission, it is important to deploy F feasible workload solutions. (Fine et al, 2018).

LITERATURE REVIEW

Individuals and groups may behave in a variety of ways as an outcome of vaccine self-reliance, since pushing for injections to rejecting vaccinations. However, despite denying a specific injection like COVID-19 because of its innovation, formulation, or delivery method, consumers may still have a high level of overall vaccination certainty. (Williams et al, 2021). Injection of the vaccine is regarded as the distribution of the exact but safe components of the mediator by establishing a person's defensive immunity against the infectious agent. (WHO, 2021). Despite significant improvements in vaccination were done the previous period, injection resistance is still viewed as a main danger to universal health because injection preventable illnesses are resurfacing. (WHO, 2020). Health information gathered from various sources, including original media on the Internet and social media podia, may encourage vaccine reluctance. Social media has grown in popularity globally as technology has advanced. Social media, as opposed to traditional media, enables individuals to produce and distribute content fast and without editorial control. Ideological isolation is facilitated by the ability of users to select the content streams they want to view. (Puri et al, 2020). The way a warning is assessed or taken into consideration takes into account the likelihood that the conduct will continue to be harmful as well as its likelihood of happening. (Tsang & Wong, 2021). From the perspective of public health, this trend is concerning because stopping the spread of the disease requires protecting people. On the other hand, caution when immunizing against disease is understandable given the disease's novelty, the extraordinarily rapid rate of vaccine improvement, and certain populations' cynicism of the field and medical professionals. (Williams et al, 2021). Among the many initiatives to reduce vaccine skepticism and raise vaccine trust, evidence-based communication strategies are essential. Considerable thought can be given to how emotion affects communication efforts. (Olson et al, 2020). In Europe, where several countries have faced serious confidence problems in the previous 20 years, which have contributed to the catastrophic measles outbreaks of today, the public's lack of trust in vaccination has become more generally acknowledged. (Machingaidze et al, 2021). The approval rates for corona virus injections experimented with differ significantly between nations and regions worldwide. It is a major challenge for determinations the control of existing COVID-19 outbreak as COVID-19 approval rates as low as 60% have been observed in a number of trials. (Aw et al, 2021). WHO has highlighted vaccine resistance as the main danger to international wellness. In the ordinal age, patients can contact information about their wellbeing through a diversity of venues, containing the Internet and local media display place. (Puri et al, 2020). Numerous strategies, such as health education campaigns, school founded vaccinations, commercial incentives,

and compulsory injection, can be used to enhance teenage vaccination rates. Targets include teenagers, parents, and medical professionals. (Cadeddu et al, 2021). The manufacturing of enough vaccines, its equitable distribution, and skepticism about its efficacy are the main barriers to the deployment of disease immunization campaigns to combat the exceptional pandemic. Additionally, in some republics, resistance to injection may be a significant barrier to control efforts intended to minimize the negative effects of the illness pandemic. (Willis et al, 2021). Concerns about side effects are the most frequent causes of hesitation, but vaccine acceptance is mainly clarified by a desire for special defense against corona virus. It is crucial to remember that expressed intentions may not necessarily result in vaccination usage. (Wise, 2020). Perhaps there is a greater perceived need for or benefit of vaccines where numerous communicable illnesses that are still treatable with vaccines nonetheless claim thousands of lives each year as a result of lived experience. (Olson et al, 2020). According to a study published in the journal *Frontiers in Public Health*, vaccine doubters are less likely to view people as equals and more likely to hold conspiracy beliefs. The research looked at a growing percentage of paternities in the industrialized creation think that adopting a “natural lifestyle” and practicing greater sanitation and also cleanliness willpower eradicate infections. They say that children’s bodies are inherently flawless and that vaccines enter the body in unnatural ways. Many of these parents might not be aware of the seriousness of diseases that can be prevented by vaccination and the potential repercussions. (Karafillakis et al, 2017). Attitudes of vaccination skeptics and non-skeptics toward other members of society. When developing communication methods for vaccines, the authors’ findings should be taken into consideration. (Carrieri et al, 2019).

CONCLUSIONS

In high-income nations and regions, there is still significant anxiety about the COVID-19 immunization. Concern about vaccinations was more prevalent in older, female, and less educated or wealthy individuals. Additionally, it appears that trust at different system levels influences vaccine apprehension. Healthcare administrators must take these factors into account when creating COVID-19 vaccination policies and public health messages. (Aw et al, 2021). Many anti-vaccination make religious arguments that are primarily directed at people with fundamentalist beliefs. These statements have a tremendous impact on particular groups in society, despite the fact that they are based on unproven data or are made with malice. (Dror et al, 2020). Recent years have seen a sharp increase in anti-vaccination movements, and their misinformation threatens to exacerbate the epidemiological state by distorting social perceptions.

While other points of view express trust in a government, politician, or vaccination company conspiracy or in the incompetence of scientists and practitioners, anti-injection program slogans frequently rest on easily disproved erroneous notions and fabrications. (Kołtataj et al, 2020). COVID-19 outbreak has vaccine uptake rates that are below 60%, which would seriously hamper attempts to contain it. Russia, Eastern and The Middle East Europe, all had lower approval degrees than other regions. High approval degrees in South East Asia might contribute to effective pandemic containment. In addition to Central and South America, further research is advised to evaluate the attitudes of the overall public and healthcare professionals in Africa, Middle East and Central Asia. (Aw et al, 2022). The mass production of vaccines, their equitable distribution around the globe, and the uncertainty surrounding their long-term effectiveness are the main obstacles that might prevent the successful deployment of corona immunization campaigns to combat the extraordinary epidemic. At least in certain nations/regions, vaccine reluctance may be the main obstacle to the control struggles to decrease the harmful special effects of this epidemic. (Fobiwe et al, 2022). Managements, health guiding principle creators, and mass media outlets as well as social media businesses must work together to address infection instillation reluctance. It is advised to increase public confidence in vaccination by disseminating timely and concise communications via reliable means that support the security and effectiveness of the vaccines that are already on the market. (Bernados & Ocampo, 2022). In high income nations or areas, vaccine reluctance is still a major issue. Younger people, women, non-White people, and those with lower learning or income intensities were other likely to be vaccination reluctant. Additionally, it seems that trust at various system levels influences vaccination reluctance. (Hiscott et al, 2020). People are questioning vaccinations more often and occasionally postponing or rejecting vaccination due to a decline in faith in medical authorities and science as well as the fast worldwide dissemination of false information. Individual vaccination acceptability is predisposed by a multiplicity of variables, containing awareness of the dangers and advantages of vaccinations as well as more subtle ones including cultural, religious, emotional, and social considerations. (Bhopal & Nielsen, 2021). HCPs are pioneers in the vaccination process and should be well-equipped with the necessary expertise to manage waning vaccine confidence. Understanding the justification and advantages of vaccination for both individuals and communities requires respecting people's beliefs and lifestyles while presenting all facts that is supported by science. The public's faith in the immunization system and in health officials determines the effectiveness of any vaccination approach. (Klein et al, 2021).

RECOMMENDATIONS

Governments need to be obvious about their disease reaction plans, vaccine availability, and decision-making procedures. While it's vital to record and report these incidences, too much media attention may discourage people from being vaccinated. Recognizing of adverse actions afterward vaccination is a crucial factor of evaluating vaccination program interventions . (Machingaidze et al, 2021). To combat the widespread occurrence of COVID-19 vaccination resistance, governments, health policymakers, and media sources—especially social media corporations—must collaborate. It is proposed that the general public develops faith in COVID-19 injections by receiving timely and clear information regarding the effectiveness of currently available immunizations from reliable sources. (Sallam, 2021). Both the general public and the scientific community seem to have lost faith in health professionals and research, and rapid global disinformation propagation is linked to a rise in the total of individuals who are inquiring vaccines and postponing or rejecting immunization. Understanding vaccine risks and benefits as well as other complex contributing factors like traditional, spiritual, expressive, and cultural influences affect each person's willingness to receive vaccinations. (Willis et al, 2021). In order to successfully implement vaccine research findings and outcomes into vaccination campaigns and to replace misinformation with evidence-based communication, it is necessary to work in a collaborative, integrated, directed, and controlled manner. (WHO, 2020). Vaccine resistance is so strong that it threatens population immunity in a particularly vulnerable and rural state in the United States. It is also higher in socioeconomic groups that have had disproportionate COVID-19 morbidity and mortality. Racial and ethnic differences highlight the medical establishment's past and present skepticism as well as communities of color's ongoing struggles with racism and prejudice. (Dror et al, 2020). Finally, the public health message for the COVID-19 vaccine must consider people's worries of contracting an infection, their belief in vaccines, and the history and current abuse of many racial and ethnic minorities. To learn how fear and trust may or may not explain vaccine apprehension among various racial groups, more research is required. Different processes are thought to contribute to vaccine resistance in various racial groupings. (Tsang & Wong, 2021). Smartphones have emerged as a crucial tool for self-education, but they may also pose difficulties due to inadequate and incorrect information that may be challenging to comprehend. (Bernados & Ocampo, 2022). Maintaining a fine balance between sharing what is known and admitting the unanswered questions will be crucial when new vaccines enter the market. Investigators and medical companies ought to be as open as they can, making inquiry information on disease

vaccinations easily accessible. And also Universal therapeutic papers need to make sure that the usage of expedited reviews doesn't weaken the integrity of the peer of the realm reviewing method. (Beesley et al, 2021). Adverse reactions to vaccinations are crucial for tracking how vaccination programs are being implemented, but extensive media coverage may potentially put off potential vaccine recipients. The media should provide accurate and balanced information to its viewers while reporting in a responsible and transparent way. People should use social media and the internet properly to avoid disseminating misinformation or using language that can increase vaccination reluctance. (Alabdulla et al, 2021). In particular among nations with very varying social, economic, and geopolitical histories, there is no one strategy that can be used to boost public trust in vaccination. Different tactics have been developed to persuade people who are averse to vaccination and parents who are worried that vaccinations may damage their kids to be immunized. (Bell et al, 2020). The improvement or restoration of vaccination faith and trust is the responsibility of medical organizations, the medical manufacturing, and wellbeing consultants on resident, nationwide, and worldwide levels, and also through evidence tailored to diverse viewers, like as audiovisual reviews or simple English descriptions of clinical trials, the business might do more to allay people's anxieties. (Fobiwe et al, 2022).

REFERENCES

- Alabdulla, M., Reagu, S. M., Al-Khal, A., Elzain, M., & Jones, R. M. (2021). COVID-19 vaccine hesitancy and attitudes in Qatar: A national cross-sectional survey of a migrant-majority population. *Influenza and other respiratory viruses*, 15(3), 361-370. (Alabdulla et al, 2021)
- Aw, J., Seah, S. S. Y., Seng, B. J. J., & Low, L. L. (2022). COVID-19-Related Vaccine Hesitancy among Community Hospitals' Healthcare Workers in Singapore. *Vaccines*, 10(4), 537. (Aw et al, 2022)
- Aw, J., Seng, J. J. B., Seah, S. S. Y., & Low, L. L. (2021). COVID-19 vaccine hesitancy—A scoping review of literature in high-income countries. *Vaccines*, 9(8), 900. (Aw et al, 2021)
- Badur, S., Ota, M., Öztürk, S., Adegbola, R., & Dutta, A. (2020). Vaccine confidence: the keys to restoring trust. *Human vaccines & immunotherapeutics*, 16(5), 1007-1017. (Badur et al, 2020)
- Beesley, R. P., Costello, W., Angevare, S. P., Wouters, C., Wulffraat, N., & Uziel, Y. (2021). Survey of adult and paediatric rheumatology patients suggests information about COVID-19 vaccination will aid uptake. *Rheumatology*, 60(7), 3474-3475. (Beesley et al, 2021)
- Bell, S., Clarke, R., Mounier-Jack, S., & Paterson, P. (2020). Parents' and guardians' views on the acceptability of a future COVID-19 vaccine for themselves and their children: cross-sectional survey and qualitative interview data. (Bell et al, 2020)
- Bernados Jr, S., & Ocampo, L. (2022). How Do People Decide on Getting Vaccinated? Evaluating the COVID-19 Vaccination Program through the Lens of Social Capital Theory. *Social Sciences*, 11(4), 145. (Bernados & Ocampo, 2022).
- Bhopal, S., & Nielsen, M. (2021). Vaccine hesitancy in low-and middle-income countries: potential implications for the COVID-19 response. *Archives of Disease in Childhood*, 106(2), 113-114. (Bhopal & Nielsen, 2021).
- Cadeddu, C., Castagna, C., Sapienza, M., Lanza, T. E., Messina, R., Chiavarini, M. & de Waure, C. (2021). Understanding the determinants of vaccine hesitancy and vaccine confidence among adolescents: a systematic review. *Human Vaccines & Immunotherapeutics*, 1-17. (Cadeddu et al, 2021)
- Carrieri V, Madio L, Principe F. Vaccine hesitancy and (fake) news: quasi-experimental evidence from Italy. *Health Econ*. 2019; 28 (11):1377–82. doi:10.1002/hec.3937.
- Chang AY, Riumallo-Herl C, Perales NA, Clark S, Clark A, Constenla D, Garske T, Jackson M, Jean K, Jit M, et al. The equity impact vaccines may have on averting deaths and medical impoverishment in developing countries. *Health Aff (Millwood)*. 2018;37: 316–24. (Chang et al, 2018)
- Chou, W. Y. S., & Budenz, A. (2020). Considering emotion in COVID-19 vaccine communication: addressing vaccine hesitancy and fostering vaccine confidence. *Health communication*, 35(14), 1718-1722. (Chou et al, 2020)

- Daley, M.F.; Narwaney, K.J.; Shoup, J.A.; Wagner, N.M.; Glanz, J.M. Addressing Parents' Vaccine Concerns: A Randomized Trial of a Social Media Intervention. *Am. J. Prev. Med.* 2018, 55, 44–54.
- Dror, A. A., Eisenbach, N., Taiber, S., Morozov, N. G., Mizrachi, M., Zigron, A. & Sela, E. (2020). Vaccine hesitancy: the next challenge in the fight against COVID-19. *European journal of epidemiology*, 35(8), 775-779
- Fine P, Mulholland K, Scott J, Edmunds W. Community protection. In: Plotkin S, Orenstein W, Offit P, Edwards K editors. Plotkin's vaccines. Philadelphia (PA): Elsevier. 2018:1512–31. (Fine et al, 2018)
- Fobiwe, J. P., Martus, P., Poole, B. D., Jensen, J. L., & Joos, S. (2022). Influences on Attitudes Regarding COVID-19 Vaccination in Germany. *Vaccines*, 10(5), 658 (Fobiwe et al, 2022)
- Hiscott, J., Alexandridi, M., Muscolini, M., Tassone, E., Palermo, E., Soultsioti, M., & Zevini, A. (2020). The global impact of the coronavirus pandemic. *Cytokine & growth factor reviews*, 53, 1-9 (Hiscott et al, 2020)
- Karafillakis, E.; Larson, H.J.; Consortium, A. The benefit of the doubt or doubts over benefits? A systematic literature review of perceived risks of vaccines in European populations. *Vaccine* 2017, 35, 4840–4850.
- Karlsson, L.C.; Soveri, A.; Lewandowsky, S.; Karlsson, L.; Karlsson, H.; Nolvi, S.; Karukivi, M.; Lindfelt, M.; Antfolk, J. Fearing the disease or the vaccine: The case of COVID-19. *Personal. Individ. Differ.* 2021, 172, 110590.
- Klein, J. K., Middleman, A. B., & Quinn, J. R. (2021). 10. COVID-19 Impact on Parent/Young Adult Attitudes and Beliefs Toward Vaccines for Adolescents and Young Adults. *Journal of Adolescent Health*, 68(2), S6 (Klein et al, 2021)
- Kołłątaj, W. P., Kołłątaj, B., Panasiuk, L., Sobieszcański, J., & Karwat, I. D. (2020). Anti-vaccine movements—a form of social activity for health care, ignorance or diversion aimed at destabilizing the health situation? Part 1. Epidemiological safety. Vaccinations—pros and cons. *Annals of Agricultural and Environmental Medicine*, 27(4), 544
- Larson, H., de Figueiredo, A., Karafillakis, E., & Rawal, M. (2018). State of vaccine confidence in the EU 2018. *Luxembourg: Publications Office of the European Union*, 10, 241099
- Machingaidze, S., & Wiysonge, C. S. (2021). Understanding COVID-19 vaccine hesitancy. *Nature Medicine*, 27(8), 1338-1339
- Olson, O.; Berry, C.; Kumar, N. Addressing Parental Vaccine Hesitancy towards Childhood Vaccines in the United States: A Systematic Literature Review of Communication Interventions and Strategies. *Vaccines* 2020, 8, 590.
- Paul, E.; Steptoe, A.; Fancourt, D. Attitudes towards vaccines and intention to vaccinate against COVID-19: Implications for public health communications. *Lancet Reg. Health Eur.* 2021, 1.

- Puri, N., Coomes, E. A., Haghbayan, H., & Gunaratne, K. (2020). Social media and vaccine hesitancy: new updates for the era of COVID-19 and globalized infectious diseases. *Human vaccines & immunotherapeutics*, 16(11), 2586-2593.
- Sallam, M. (2021). COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. *Vaccines*, 9(2), 160.
- Schellenberg N, Crizzle AM. Vaccine hesitancy among parents of preschoolers in Canada: a systematic literature review. *Can J Public Health*. 2020 Aug; 11:1–23.
- Tsang, N. K., & Wong, O. (2021). Traveler's adoption of travel advisory system: A case of Hong Kong's outbound travel alert system. *Journal of Travel & Tourism Marketing*, 38(2), 213–231. <https://doi.org/10.1080/10548408.2021.1884637>.
- Williams, N. L., Nguyen, T. H. H., Del Chiappa, G., Fedeli, G., & Wassler, P. (2021). COVID-19 vaccine confidence and tourism at the early stage of a voluntary mass vaccination campaign: a PMT segmentation analysis. *Current Issues in Tourism*, 1-15.
- Willis, D. E., Andersen, J. A., Bryant-Moore, K., Selig, J. P., Long, C. R., Felix, H. C. & McElfish, P. A. (2021). COVID-19 vaccine hesitancy: Race/ethnicity, trust, and fear. *Clinical and translational science*, 14(6), 2200-2207.
- Wise, J. Covid-19: New Coronavirus Variant Is Identified in UK; British Medical Journal Publishing Group: London, UK, 2020.
- World Health Organization (WHO) 2020. Draft Landscape of COVID-19 Candidate Vaccines. Available online: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>.
- World Health Organization (2021). Rolling updates on Coronavirus Disease. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>.