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RESEARCH ARTICLE

Septo-columellar reconstruction with radial forearm free flap

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Abstract

Introduction: Columellar subunit reconstruction is described as one the most challenging area in the literature. Radial forearm free flap (RFFF) can easily provide the reconstruction of columella and neighbouring regions with different styles of designs and different types of tissues included if needed.

Methods: Patients who have large composite defects in the septo-columellar region and have been reconstructed with RFFF between 2018-2021 were included in the study. Patients' age, gender, etiology of septocolumellar defect, anatomical deficiencies on nose, flap sizes and designs, cartilage donor site, recipient vessels, flap donor site repair methods, time of hospital stay, and complications were investigated.

Results: Six patients, comprising five males and one female with an average age of 50.8 years, were evaluated. The etiologies were congenital agenesis in one patient, trauma in two patients, and tumors in three patients. Adipofascial radial forearm free flaps (RFFF) were utilized in two patients, with primary closure of the donor sites. To prevent excessive skin thickness in septal mucosal reconstruction, only adipofascial flaps were employed. The facial artery and vein served as the recipient vessels in all cases, with the pedicle tunneled from the nasal region to the submandibular region. The average flap size was 5.08 x 4.66 cm. Septal cartilage was used to create the cartilage framework in two cases, while costal cartilage was used in the remaining cases. The mean operation time was 6.6 hours, the average ICU stay was 16.3 hours, and the mean hospitalization duration was 6.5 days. Complications included scar spread and synechia at the flap donor site in two different patients.

Conclusion: Using the facial artery and vein for recipient vessels makes the new skin scarring away from midface area. RFFF provides an excellent option for optimal septocolumellar reconstruction deriving from a variety of etiologies with the disadvantage of sacrificing a main artery in upper extremity.

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Introduction

It is known that the nose contributes greatly to the cosmetic perception of the face. Reconstruction of any of the subunits of the nose therefore improve the facial cosmetic results. Columellar defects often occur after tumor surgery and traumatic losses, and rarely congenital defects may be present.[1] Different combinations of septal and medial crural cartilage, mucous and columellar skin deficiencies accompanying cartilages can be seen in all etiologies. Skin grafts, composite grafts, washio flap, nasolabial flap, and especially forehead flap and free flaps are the methods that are usually preferred in columellar reconstruction, with or without prefabrication.[2,3]

Columellar subunit reconstruction is described as one the most challenging due to the scarcity of regional flap options and technical difficulties of microsurgical methods.[4] In the free flap option, a long pedicle and a thin, pliable structure are important requirements for reconstruction of the columella. The study aims to assess the efficacy of a novel treatment approach, evaluating different designs of the radial forearm free flap (RFFF) which provide favorable outcomes due to its thinness and flexibility. RFFF can be harvested as an adipofascial flap or fasciocutaneous flap. Primary repair of the RFFF donor site will be easier when the dermal component content taken is as small as possible, but this is dependent on the selection of cases with appropriate defects.

In this study, six cases with columellar defects, due to different etiologies, were treated with a single-session operation, cartilage grafts and adipofascial or dermoadipofascial RFFF.

Methods and Cases

Patients who have large composite defects in the septocolumellar region and have been reconstructed with RFFF between 2017-2020 were included in the study. All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval of the study was obtained from the ethics committee of Kocaeli University The Non-Interventional Clinical Research Ethics Committee, dated 14.12.2023 and numbered 2023/413. Patients' age, gender, etiology of septocolumellar defect, surgical history of the region, anatomical deficiencies on nose, flap sizes and designs, cartilage donor site preference, recipient vessels for flaps, flap donor site repair methods, time of hospital stay, and complications were investigated. Surgical techniques of some case examples with different etiologies are described below.

Case 1

A 24-year-old female patient was evaluated for congenital columellar agenesis. On physical examination, columellar skin, medial crural cartilages, agenesis of septal caudal cartilage and mucosa were evaluated. On detailed examination, it was seen that the caudal cartilaginous septum was agenetic, the anterior nasal spine (ANS) was present, bilaterally the lower lateral cartilages terminated on soft triangular fossa, the bilateral medial crural cartilages were agenetic, and the skin covering of this area was rudimentary towards the mucosa. The patient's medical history revealed that she was born at the age of seven gestational months and there was a disorganized, band-like structure in the columellar region at birth. This structure disappeared spontaneously, while being followed in the neonatal Intensive Care Unit (ICU). A history of necrosis due to Continuous Positive Airway Pressure compression was suspected.

Examination showed that there was no narrowing or any alar fluctuation in the vestibular opening due to adequate support of the existing part of the septum and the upper lateral cartilages. The nasal dorsum remained stable from radix to nasal tip. There was a complex defect of approximately 2.5 x 5 cm on the sagittal plane, because of agenesis of the caudal septal and columellar areas. For the characteristics of all patients see Supplemental Table-1.

Table 1:
Information concerning appearance and anatomical assessment at presentation, flap features, and follow-up data for patients. (AF: Adipofascial, DAF: Dermoadipofascial)

case	1	2	3	4	5	6
age	24	54	36	62	60	69
sex	F	M	M	M	M	M
aetiology	Congenital	Trauma	Trauma	Tumor	Tumor	Tumor
Medial Crural Cartilage	-	-	-	-	-	-
Caudal Septal Cartilage	-	-	-	-	-	-
Anterior Nasal Spine	-	-	-	+	+	+
Surgical History	-	+	+	-	+	-
Flap Design	AF	AF+DAF	AF	AF+DAF	AF+DAF	AF+DAF
Flap Size (cm)	5 X 3	5 X 6	5 X 5	4 X 5	5 X 4	6.5 X 5
Cartilage Donor Site	Septum	Septum	Costal	Costal	Costal	Costal
Recipient Vessels (Artery/ Vein)	Facial	Facial	Facial	Facial	Facial	Facial
Donor Site Complication	Linear Skar spread on donor site	STSG -	Linear Synechia L- Strut failure	STSG -	STSG -	STSG -
Hospitalisation (day)	6	6	6	8	6	7

Ulnar artery dominance was observed in the left upper extremity after doing The Allen test. Flow directions, flow velocities and flow forms were evaluated bilaterally with Color Doppler Ultrasonography. The RFFF was harvested as an adipofascial flap. Preparation of the nasal area began when rudimentary skin tissues were dissected from the mucosa border and the nasal tip region. These were saved as two viable skin flaps to be used for columellar skin reconstruction at the end of the adipofascial flap adaptation. Septal cartilage grafts were used for constructing the L-strut, and using polydioxanone sutures, the cefalic septal cartilage and maxillary periosteum were used as anchor points. The base of the apertura piriformis was accessed through the mucosa at the base of the right alar base and subcutaneous dissection was performed towards the right mandible corpus. After exposing the facial artery and vein with a right submandibular horizontal skin incision, a tunnel was created for the pedicle by subcutaneous dissection. The RFFF was planned and harvested with a minimum pedicle length of 15 cm and without any skin component. Pedicle tunneling was carefully performed, avoiding any rotation or buckling. Subsequently, 3-0 polyglactin suspension sutures were passed separately to the most cephalic mucosal part where the flap would be reconstructed. Flap adaptation was started using these sutures and the other parts were repaired with 4-0 polyglactin. Adipofascial tissue was also fixed to the septal cartilage in the midline supratip region, and new-transseptal, 5-0, rapid polyglactin sutures were placed to close the dead space between two half parts of the flap following folding. Right facial artery and vein end-to-end micro-anastomoses to the RFFF were performed with 9-0 nylon. For the columellar skin reconstruction of the adipofascial flap, rudimentary skin flaps were mutually repaired. The operation was terminated by placing intranasal packs, under-flap penrose drains, and hemovac drains in the flap donor site and splint on the forearm.

In the peroperative period, even the presence of a pulse in the columellar region was clearly observed. However, in order for mucolysis and skin epithelization to occur spontaneously from rudimentary flaps, no split thickness skin graft (STSG) was used, and nasal pads soaked in pomade were changed daily for the first postoperative week. During this 7-day hospitalization period, the patient was followed closely. No healing problem or any other complications occurred. (Case1 is shown in Figure-1)

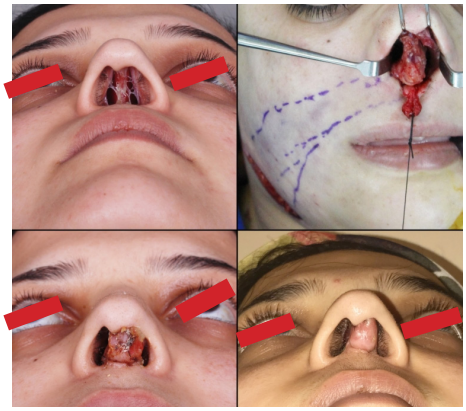

Figure 1 : A 24-year-old female patient with congenital columellar agenesis, with absence of columellar skin, medial crural cartilages, septal caudal cartilage and mucosa (Above left). Suspension of the rudimentary skin flaps with the silk suture and the tunnel in which the RFFF flap was passed from the nasolabial area to the right submandibular area is shown (Above right). Post-operative appearance of the area on the seventh day (below left) and at six months (below right).

Case 3

A 36-year-old male patient had a nasal deformity due to explosion injury, for which he had previously undergone nasal reconstruction with a pre-expanded forehead flap in another center. There was a depressed scar line from the nasal dorsum to the right lower lateral cartilage, 60% of the lower septal area was absent, there was a septal fistula of approximately 3 x 4 cm, the medial crural cartilages were absent, the skin in the columellar area was irregular, inadequate and also folded towards the nasal cavity because of the absence of cartilage support.

After similar preparations, an L-strut was created with costochondral cartilage grafts and the pedicle of the RFFF was tunneled and anastomosed to the left facial artery and vein. Suspension sutures were placed caudally beginning from the cephalic region. The mucosa on the cephalic part of the presented columellar skin flap was shaved and a rough surface was created for healthy contact with the RFFF. At the end of the operation, fixation was completed with caudal trans-septal sutures before dressing closures, drains and nasal pads were applied. (Case 3 is shown in Figure-2)

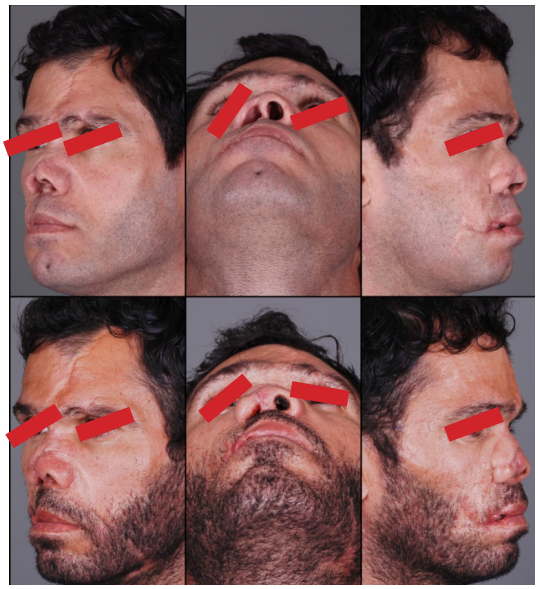

Figure 2:
A 36-year-old male patient with a nasal deformity due to an explosion injury. There was an absence of cartilaginous septal area and there was a septal fistula of approximately 3x4 cm size, the medial crural cartilages were absent, the skin in the columellar area was irregular, inadequate and also folded towards the nasal cavity because of absence of cartilage support (Above). Basal and oblique views are seen at the third post-operative month (Below).

Case 6

A 69-year-old male patient was evaluated due to a nasal mucosal mass exhibiting bilateral growth for a period of four years. A mucosal mass in septo-columellar area, which was larger on the left than the right, and that caused erythema of the left nostril base was observed. The patient's investigational biopsy was reported as a well-differentiated squamous cell carcinoma (SCC). No pathological lymph node was detected in the neck, either with palpation or with superficial ultrasonography. As the tumor was considered a high-risk SCC, left modified radical supraomohyoid lymph node dissection was performed after wide resection under general anesthesia. The cartilaginous roof was reconstructed with costochondral cartilage grafts as the L-strut, and the cephalic septal cartilage was fixed inferiorly to the ANS and superiorly to cephalic septal cartilage. Left facial artery and vein were used as recipient veins. The defect was reconstructed with partial skin islands and partial adipofascial RFFF taken from the left upper extremity. The upper-cephalic margin of the flap was defined with a transdermal bolster suture extending to the nasal dorsum. Figure 3 and 4 shows the steps of patient surgical procedure and Figure 5 shows the scheme of surgery stages. STSG was used for repair of the flap donor site.

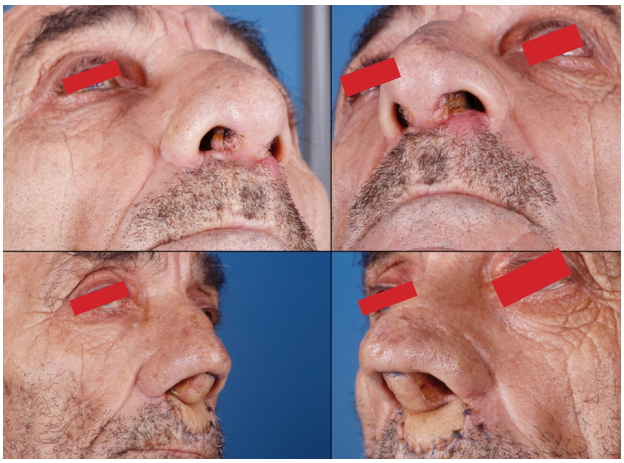

Figure 3:
A 69-year-old male patient presented with a well-differentiated, squamous cell carcinoma of the septocolumellar area with no evidence of lymphadenopathy by palpation or radiologically (Above). After wide resection of the mass and supraomohyoid, modified radical neck lymphadenectomy, the septocolumellar area was reconstructed with costochondral grafts and dermoadipofascial RFFF. The right and left sided oblique views are seen on the seventh postoperative day (Below).

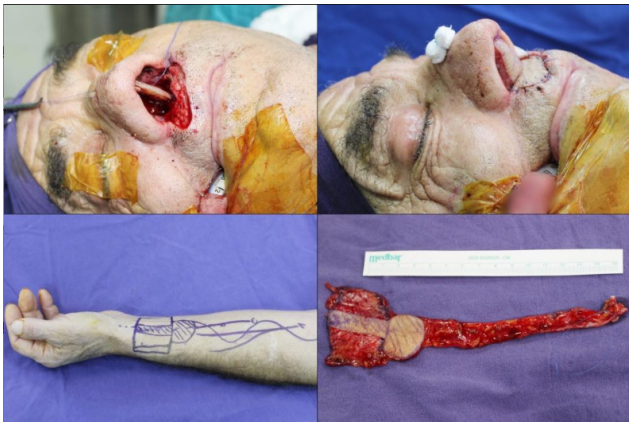

Figure 4 :
After reconstruction of the cartilage framework using costal cartilage grafts, the framework was fixed to both the ANS and the cephalic part of the septal cartilage. The polyglactin suspension and bolster sutures were prepared for suspending both the framework and the surrounding adipofascial parts of the RFFF (Above). The dermo-adipofascial RFFF planning on the donor extremity (Below right) and its appearance after harvesting (Below left).

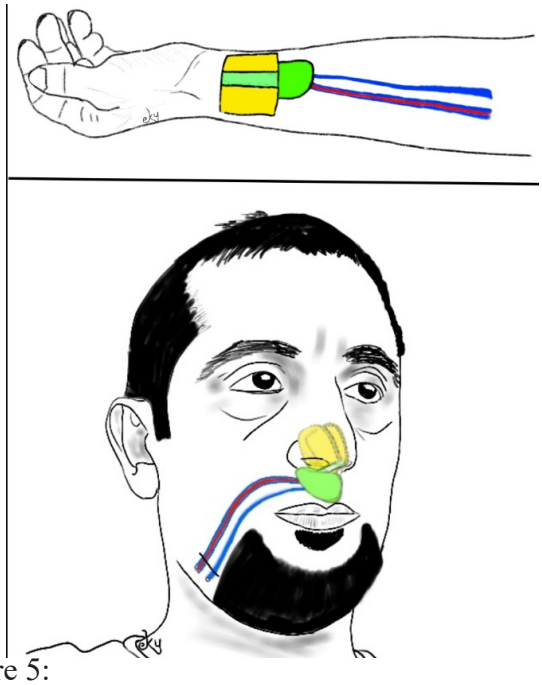

Figure 5:
The flap design made on the forearm is seen before the RFFF was harvested.
Yellow quadrangular areas are deepitelized to form the septal mucosa bilaterally. (Above) After adapting the flap and tunneling the pedicle to the submandibular region subcutaneously is seen. The fact that the recipient vessels are in an area far from the face provides an advantage in terms of scarring.(Below)

Results

All patients were male except one case. The average age of the patients was 50,8 years old. In two patients, RFFF design was planned using adipofascial flaps and donor sites were repaired primarily, while in the other patients, a STSG was used for donor site repair, since partial skin tissue was included in the flap for any skin reconstruction. In all cases facial arteries and veins were used as recipient vessels and the RFFF pedicle was tunneled subcutaneously. Thus new scar formation was prevented in the middle of the face. Concomitant veins of the radial artery were used as the donor vein in all patients. Average flap size was 5.08 x 4.66 cm. Sufficient septal cartilage was present in two cases to create the L-strut with cartilage grafts, while in the other cases this was not possible, and the sixth costochondral areas were used. While the maxillary anterior region was used in three cases to support the L-strut graft caudally, in the remaining cases the ANS could be used.

In two patients, the operation was performed while preserving the columellar rudimentary skin tissue, while reconstruction was completed with a columellar skin island from the RFFF in four patients. Left-sided, type 3, modified radical supraomohyoid neck dissection was performed for case-6 with septocolumellar SCC. The average operation time was 6.6 hours. After the operation, all patients were followed in the ICU, due to the length of operation time. The average duration of stay in the ICU was 16.3 hours.

In all cases STSGs were not placed on the adipofascial flaps used for septal mucosal reconstruction. Healing was expected as a result of secondary follow-up, through mucolysis. For this, daily pomade tampon changes and other moisturising creams were applied to prevent synechia and fascial drying. Average hospitalization time was 6.5 days. On follow-up after discharge, no problem was encountered in the formation of mucolysis. However, in Case 3 subtotal obstruction and synechia occurred in the right nasal passage and the patient was re-operated due to difficulty in breathing.

There were no problems about healing or any other complication in the late follow-up for any patient except the scar spread on RFFF donor site in Case-1. In Case 6, histopathological examination of the neck dissection tissues showed that all lymph nodes were reactive. Thus this patient required medical multidisciplinary oncological follow-up and no recurrence was encountered in the 15th month post-operatively.

Discussion

One of the most challenging areas in nasal reconstruction is the columellar area.[5] It has a wide range of repair options, from with skin grafts to free flap repair.[6] Both the STSG and full thickness skin grafts techniques, which have been reported to have success rates approaching 90%, are good options for superficial defects because of the lack of volume and consisting of the contraction and depression on the late period.[7,8] Skin with adipose tissue composite grafts can be useful in terms of volume if there is no need for any new cartilage support in the defective area.[6] In case of combined skin and cartilage defects, auricular chondrocutaneous composite grafts are usable. Chang et al, performed columella reconstruction with auricular chondrocutaneous composite grafts in fourteen children aged 5-13 years, and achieved 100% success in grafts with a maximum size of 1.5 x 0.8 cm.[9] In a study by Son et al, the nasal defects of seventeen adult patients were reconstructed with composite grafts, with a maximum size of 1.0 x 1.9 cm. One of the grafts necrosed and this was attributed to smoking.[10]

As the defect deepens and increases in size radially, solely composite graft options become inadequate and local flap options with or without cartilage graft are required. Single or two-stage operations can be performed with alar rim flap, nasal sill flap and vestibule flap.[11,12] There is also a mucosal flip-over method that can be carried out gradually, with or without prefabrication, from the upper lip mucosa.[13,14] Nasolabial,[15] nasofascial[16] and melolabial[17] island flaps are also useful flaps but all these flaps are generally only sufficient for columellar reconstruction; the cannot contribute to septal area reconstuctions due to their size and they may need the support of the caudal septal chondromucosal area after flap transfer.

The landmark flap in nasal reconstruction is the paramedian forehead flap. This flap is flexible enough to be used for subtotal reconstruction of the nose with two or three staged operations.[18] In cases where a wide flap is required, the donor site scar can be left linear with the pre-expanded forehead flap.[19] In addition, prelamination options, such as mucosal, osseos or cartilagineous reconstruction highlight the utility of the paramedian forehead flap.[20] However, when there is a low hairline, difficulties may arise in the reconstruction of the columellar region. Thus the use of a paramedian forehead flap alone is not usually sufficient for isolated septocolumellar reconstruction. Although oblique designed forehead flaps are available, hair-bearing forehead flap transfers often occur in classical forehead flap applications, because of the long distance of the columellar area to the flap rotation arc point.

Local flap options provide excellent texture and color match without the difficulties and morbidities of microsurgical techniques. There are instances in which free flap surgery becomes an imperative option. The reasons for free flap option for nasal reconstruction include total nasal defects, defects involving nasal linings and defects which involve the upper lip or cheek.[21] A free flap option needs to possess some key characteristics including being pliable and thin. It should also be covered by thin skin if the plan is to harvest a fasciocutaneous flap. These characteristics help to create the required contours around the nasal framework or to provide adequate lining without obstructing the nasal airway.

Since the recipient vascular structures are usually selected from the facial and angular arteries, it would be more appropriate to choose a long pedicle with a large diameter. Choosing the recipient area as close to the nose as is practicable means minimal free flap donor site morbidity but may cause other problems such as appropriateness of recipient vascular structures, the need for a super-microsurgical procedure and thus surgical experience.[22] In addition, there may be permanent scarring in the central area of the face, for example a scarring of the nasolabial sulcus. It has been shown that it is possible to access these recipient vessels using an intraoral approach which eleminates this scar risk.[23]

The free flap options commonly used in the literature are the dorsalis pedis flap,[24] the first dorsal metacarpal flap[25] and the radial forearm flap.[26] The first dorsal metacarpal flap has an artery with a diameter of 0.5-1.0 mm and can be planned as a double skin island flap. The dorsalis pedis flap has a relatively larger arterial diameter and a longer pedicle than the first metacarpal flap. The donor sites of both flaps are often repaired with skin grafts, but it is harder to hide the scar on the hand. The dorsalis pedis flap vessels may be badly affected if the patient suffers from atherosclerosis and so might be a risky choice in elderly patients. While these two flaps can reconstruct the columella, it is thought that they do not have sufficient dimension for large septal mucosal reconstruction. The pedicle of both flaps is not long enough to anastomose the facial artery and vein. For this reason, the angular artery should be used as the recipient artery or vein grafts should be used both for artery and vein anastomoses when employing these flaps.

The RFFF is frequently used in head and neck reconstruction.[27] There are many advantages of the RFFF including permitting the removal of more than one skin island, and being used as an innervated fasciocutaneous flap with the antebrachial cutaneous nerves.[28] It is possible to harvest the RFFF with the palmaris longus tendon, partial muscle tissues and a bone segment of the radius.[29] This flap also has the option of being harvested adipofascially, meaning that the donor site morbidity can be minimized.[30] One of the most important benefits of the RFFF is its long pedicle and large vascular diameter. This provides a technical advantage in microsurgical applications and increases the number of recipient vascular area options. This study has shown that transferring the recipient area to the submandibular area provided increased cosmetic benefit, as a submandibular scar is preferable to a mid-facial scar for the majority of patients. Care should be taken while performing tunneling and pedicle transfer, because there are risks, such as intimal trauma due to hard manipulation and pedicle rotation or strangulation. In order to reduce these risks, the author uses a temporary suture that holds the adventitia of the distal ends of all pedicle elements together and also marks the semi-surface of the pedicle from beginning to the end of the vascular structures.

In septal reconstruction, local mucosal flaps are the first preference and can be combined with cartilage grafts or acellular dermal matrices.[31] However, free flaps are needed in large defects due to existing mucosal tissue insufficiency. The temporo-parietal fascia (TPF) flap is an ideal flap option for septal reconstruction[32] because of location, minor donor site morbidity, and the desired pliable and thin nature of TPF. However, the anatomic relation to the proximal part of the superficial temporal artery and vein make harvesting the TPF more challenging and the pedicle of the TPF is generally believed to not be as long as the pedicle of an RFFF.

The RFFF has a wide variety of tissue transfer options, including adipofascial, fasciocutaneous and osteocutaneous flaps, with neurosensory innervation if needed. It has a long vascular pedicle from the proximal edge of the skin paddle to the take off point from the brachial artery, just distal to the antecubital fossa. The RFFF is a reconstructive workhorse due to its reliable anatomy, pliability, multiple design options and ease of harvest.[33] The venous drainage system of the RFFF has a pair of concomitant deep veins and the cephalic vein, which is superficial. Cha et al. pointed out that the success rates of the RFFF has derived from its venous system and the concomitant venous drainage system has proven a reliable system in practice.[34] We did not include the cephalic vein while harvesting the RFFF, as we prefer to anastomose only concomitant veins because of the flap design, and have not experienced any venous complication.

Although there scarce evidence in the literature concerning septal mucosal reconstruction, the general consensus appears to be that if the free flap has a thick dermal component, there may be a slight risk of the narrowing of the nasal passages. Fascial or adipofascial flaps may be preferred to prevent this risk. With the contribution of surgical area edema after placement of the adipofascial flaps for septal mucosal reconstruction, the risks of synechiae and stenosis in the late period cannot be ignored. One option to reduce this risk is skin grafting, but in our study we preferred to wait for spontaneous epithelization, promoted with the post-operative use of periodically changed nasal tampons. One patient`s cartilage framework had migrated postero-laterally and mucosal sagging occured in the postoperative period, therefore synechia and "force breathing" on the contralateral side was inevitable.

Donor site morbidity, colour mismatch, loss of the radial artery and cold intolerance in the late period can be considered as the most important disadvantages of the RFFF. In this study, in two patients there was no need for columellar skin reconstruction. Therefore, donor site morbidity risk and rates varied in our patients. In the late period, no patient complained of upper extremity cold intolerance associated with the RFFF donor site.

Conclusion

The RFFF is one of the workhorse flaps for head and neck reconstruction because of its versatility. Although several microsurgical options are usable for septocolumellar reconstruction, use of the RFFF allows for a longer and wider pedicle facilitating the microsurgical procedure. Anastomoses with the facial arteries and veins and careful tunneling of the pedicle meant scarring was restricted to the sub-mandibular area rather than mid-facially. The biggest disadvantage of RFFF is sacrificing a main vessel in upper extremity. In our experience the RFFF provides an excellent option for optimal septo-columellar reconstruction deriving from a variety of etiologies.

References

1. Mavili ME, Akyurek M. Congenital isolated absence of the nasal columella: Reconstruction with an internal nasal vestibular skin flap and bilateral mucosa flaps. Plast Reconstr Surg. 2000. doi:10.1097/00006534-200008000-00022
2. Benito-ruiz J, Raigosa M, Yoon TS. Columella Reconstruction Using a Free Flap From the First Web Space of the Foot. 2012;69(3):279-282. doi:10.1097/SAP.0b013e31822af8b9
3. Tzur R. Columellar reconstruction : a refinement of technique. 2018;19(2):148-151.
4. Jayarajan R. Total columella reconstruction using nasocheek flap and septal cartilage graft. Plast Reconstr Surg - Glob Open. 2015. doi:10.1097/GOX.0000000000000538
5. Bouguila J, Zairi I, Yacoub K, et al. Columella defects: Yet a challenge! Ann Chir Plast Esthet. 2008. doi:10.1016/j.anplas.2008.04.003
6. Faris C, Vuyk HD. Reconstruction of Nasal Tip and Columella. Facial Plast Surg Clin North Am. 2011. doi:10.1016/j.fsc.2010.10.012
7. ROBINSON JK, DILLIG G. The Advantages of Delayed Nasal Full-Thickness Skin Grafting After Mohs Micrographic Surgery. Dermatologic Surg. 2002. doi:10.1097/00042728-200209000-00013
8. Rustemeyer J, Günther L, Bremerich A. Complications after nasal skin repair with local flaps and full-thickness skin grafts and implications of patients' contentment. Oral Maxillofac Surg. 2009. doi:10.1007/s10006-008-0139-z
9. Chang CS, Swanson JW, Wilson A, Low DW, Bartlett SP. Columellar Reconstruction following Nasal Continuous Positive Airway Pressure Injury. Plast Reconstr Surg. 2018. doi:10.1097/PRS.0000000000003978
10. Son D, Kwak M, Yun S, Yeo H, Kim J, Han K. Large auricular chondrocutaneous composite graft for nasal alar and columellar reconstruction. Arch Plast Surg. 2012. doi:10.5999/aps.2012.39.4.323
11. Odobescu A, Servant JM, Danino IW, Danino MA. Nostril alar rim threshold flap for columellar reconstruction. J Plast Reconstr Aesthetic Surg. 2011. doi:10.1016/j.bjps.2011.01.004
12. Bilkay U, Tokat C, Ozek C, Erdem O, Cagdas A. Reconstruction of Congenital Absent Columella. J Craniofac Surg. 2004. doi:10.1097/00001665-200401000-00018
13. Scott AR, Boahene KD. A novel approach to columellar reconstruction in a child. Laryngoscope. 2018. doi:10.1002/lary.27229
14. Agrawal K, Shrotriya R, Pabari M. An innovative technique for columellar reconstruction using 'flip-over' Buccal mucosa flap. J Clin Diagnostic Res. 2016. doi:10.7860/JCDR/2016/19864.8111
15. Jang SY, Kim WS, Kim HK, Bae TH. Nasal columellar reconstruction with reverse lateral nasal artery pedicled nasolabial island flap. J Craniofac Surg. 2018. doi:10.1097/SCS.0000000000004268
16. Sherris DA, Fuerstenberg J, Danahey D, Hilger PA. Reconstruction of the nasal columella. Arch facial Plast Surg Off Publ Am Acad Facial Plast Reconstr Surgery, Inc Int Fed Facial Plast Surg Soc. 2002. doi:10.1001/archfaci.4.1.42
17. Younger RAL. The versatile melolabial flap. Otolaryngol - Head Neck Surg. 1992. doi:10.1177/019459988910700602.1
18. Smart RJ, Yeoh MS, Kim DD. Paramedian Forehead Flap. Oral Maxillofac Surg Clin North Am. 2014. doi:10.1016/j.coms.2014.05.008
19. Zhu S, Liu Y, Zang M, et al. Facial Defect Reconstruction Using the True Scarless Pre-Expanded Forehead Flap. J Craniofac Surg. 2018. doi:10.1097/SCS.0000000000004450
20. Prasanna NS. Nasal reconstruction with pre-laminated forehead flap. Indian J Plast Surg. 2017. doi:10.4103/ijps.IJPS_165_17
21. Antunes MB, Chalian AA. Microvascular Reconstruction of Nasal Defects. Facial Plast Surg Clin North Am. 2011. doi:10.1016/j.fsc.2010.10.014
22. Wei J, Chen Q, Herrler T, et al. Supermicrosurgical reconstruction of nasal tip defects using the preauricular reversed superficial temporal artery flap. J Plast Reconstr Aesthetic Surg. 2020. doi:10.1016/j.bjps.2019.06.028
23. Stalder MW, Sosin M, Urbinelli LJ, et al. Avoiding Facial Incisions with Midface Free Tissue Transfer. Plast Reconstr Surg - Glob Open. 2017. doi:10.1097/GOX.0000000000001218
24. Bayramiçli M. The distal dorsalis pedis flap for nasal tip reconstruction. Br J Plast Surg. 1996;49(5):325-327. doi:10.1016/S0007-1226(96)90165-4
25. Beahm EK, Walton RL, Burget GC. Free first dorsal metacarpal artery flap for nasal lining. Microsurgery. 2005. doi:10.1002/micr.20163

26. Walton RL, Burget GC, Beahm EK. Microsurgical reconstruction of the nasal lining. Plast Reconstr Surg. 2005. doi:10.1097/01.PRS.0000164683.34767.2F
27. Santamaria E, Granados M, Barrera-Franco JL. Radial forearm free tissue transfer for head and neck reconstruction: Versatility and reliability of a single donor site. Microsurgery. 2000. doi:10.1002/1098-2752(2000)20:4<195::AID-MICR10>3.0.CO;2-W
28. Santamaria E. Sensation recovery on innervated radial forearm flap for hemiglossectomy reconstruction by using different recipient nerves. Plast Reconstr Surg. 1999. doi:10.1097/00006534-199902000-00013
29. Cordeiro PG, Bacilious N, Schantz S, Spiro R. The radial forearm osteocutaneous "sandwich" free flap for reconstruction of the bilateral subtotal maxillectomy defect. Ann Plast Surg. 1998. doi:10.1097/00000637-199804000-00013
30. Pangrazi PP, De Francesco F, Di Rienzo A, Riccio M. Adipofascial Radial Forearm Free Flap for Anterior Skull Base Reconstruction in Complicated Forebrain Oncological Surgery. J Craniofac Surg. 2019. doi:10.1097/SCS.0000000000005559
31. Chhabra N, Houser SM. Endonasal repair of septal perforations using a rotational mucosal flap and acellular dermal interposition graft. Int Forum Allergy Rhinol. 2012. doi:10.1002/alr.21030
32. Helman S, Kadakia S, Guthrie A, Mourad M, Mashkevich G. Temporoparietal Fascia Free Flap for Nasoseptal Perforation Repair. Craniomaxillofac Trauma Reconstr. 2018. doi:10.1055/s-0037-1604425
33. Moscoso JF, Urken ML. Radial forearm flaps. Otolaryngol Clin North Am. 1994. doi:10.1201/b13386-26
34. Cha YH, Nam W, Cha I-H, Kim HJ. Revisiting radial forearm free flap for successful venous drainage. Maxillofac Plast Reconstr Surg. 2017. doi:10.1186/s40902-017-0110-8

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RESEARCH ARTICLE

The effect of maternal asthma on serum PAPP-A levels and first trimester aneuploidy screening test running

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Abstract

Introduction: PAPP-A (Pregnancy-associated plasma protein-A) is considered a pro-inflammatory marker and its serum levels are elevated in non-pregnant patients with asthma. In the current research, we aimed to investigate whether maternal serum PAPP-A levels, a biomarker for first-trimester aneuploidy screening, differ in pregnant women with asthma compared to healthy pregnant women.

Methods: In the first step, maternal serum PAPP-A MoM values, used as the first-trimester fetal aneuploidy screening marker, were compared between pregnant women with asthma and a healthy pregnant group. In the second step, the groups compared whether PAPP-A and fβ-HCG (free β human chorionic gonadotropin) levels were below or above the cut-off values for Trisomy 21 and compared them according to maternal age (<35; ≥35).

Results: The median PAPP-A level was found to be 2.15 IU/L (0.41-9.91) in the asthma group and 2.54 IU/L (0.56-11.40) in the control group, and there was no difference between the groups (P=0.363). The median PAPP-A MoM value was 0.99 (0.15-3.28) in the asthma group and 1.07 (0.33-3.37) in the control group. This result did not show a statistically significant difference (P = 0.694). No statistically significant difference was shown between the groups below and above 35 age (P=0.456).

Conclusion: Maternal serum PAPP-A levels in pregnant women with asthma do not vary compared to the healthy pregnant group without asthma. Based on the results of our study, the first-trimester fetal aneuploidy screening test is a reliable screening method for pregnant women with asthma.

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Introduction

Asthma is a disease accompanied by chronic airway inflammation characterized by hyperreactivity to stimuli and reversible obstruction. It is associated with significant maternal morbidity. In a large prospective study, the exacerbation rate of the disease in pregnant women followed up with mild asthma, moderate asthma, and severe asthma were 12.6%, 25.7%, and 51.9%, respectively.[1] In the same study, it was observed that 23% of asthma in pregnant women improved and 30% became worse. While the effects of pregnancy on asthma vary, pregnant women with asthma are at high risk for pregnancy complications. The first trimester is generally well-tolerated in patients with asthma since acute episodes are not very frequent. The National Asthma Education and Prevention Program (NAEPP) classified asthma as mild intermittent, mild persistent, moderate persistent, and severe persistent. Asthma is observed at approximately 8% during pregnancy.[2]

Prenatal screening for fetal aneuploidy such as Trisomy 21,13 and 18 is recommended in the first trimester of pregnancy. In this aneuploidy screening test performed when the crown-rump length (CRL) is 45-84 mm between 11+0 and 13+6 weeks of gestation, two maternal serum markers are used.[3] It is known that pregnancy-associated plasma protein-A (PAPP-A) has a median value (MoM) of 0.4 times in pregnancies with trisomy 21 fetuses, and the free β subunit (fβ-hCG) of human chorionic gonadotropin is known to increase to a median MoM value of 1.8 in pregnancies with Down's syndrome. PAPP-A and fβ-hCG together can identify 60-65% of Down's syndrome in the first trimester with a 5% false-positive rate. When these maternal serum markers are combined with the measurement of nuchal translucency (NT) in ultrasonography and the positive threshold value is traditionally accepted as 1/270, the trisomy 21 detection rate of the test reaches 87.5-88.9%.[4]

Pregnancy-associated plasma protein-A (PAPP-A) is a glycoprotein and its concentration in the maternal circulation increases throughout pregnancy. Due to its proteolytic activity in the insulin-like growth factor system, it functions as a regulatory protein. Low PAPP-A levels were associated with adverse pregnancy outcomes such as preeclampsia and intrauterine growth retardation (IUGR).[5] PAPP-A is a pro-atherosclerotic metalloproteinase and an inflammatory marker. It has been shown that its serum level is elevated in non-pregnant asthma patients. Furthermore, a significant correlation has been revealed between PAPP-A concentration and the severity of asthma.[6]

In light of this information, we aimed to investigate whether first-trimester maternal serum PAPP-A levels varied in pregnant women with asthma compared to the healthy pregnant population and the findings' impacts on first-trimester aneuploidy screening results.

Material and Methods

This research is a case-control study. . The ethics committee approval was obtained with the decision number E2-22-1569 on 30/03/2022. Eighty-seven pregnant women with asthma aged between 18-45 years, who attended their routine check-ups regularly in the Perinatology Outpatient Clinic of Ankara City Hospital in the two years between January 2020 and January 2022, and had the first-trimester fetal aneuploidy screening between 11th and 14th gestational weeks in our hospital, were determined as the case group. Randomly selected 97 healthy pregnant women, who continued their follow-ups regularly in the antenatal outpatient clinic in the same age and gestational week range and did not have any chronic or pregnancy-related disease, were determined as the control group. In the case group, pregnant women with additional chronic and pregnancy-related conditions other than asthma were excluded from the study. The study did not include pregnant women with suspected or diagnosed with fetal chromosomal or structural abnormality in the first trimester. Informed consent was obtained from all the participants.

First-trimester serum PAPP-A level and MoM range, fβ-hCG level and MoM range for each patient in the case and control groups, and biochemical Trisomy 21 risk ratio determined due to aneuploidy screening were recorded. PAPP-A and fβ-hCG levels were studied by the chemiluminescent immunoassay method. The patient's age, parity, smoking consumption status, body mass index (BMI), sociodemographic characteristics, and medical history were examined. Routine obstetric and ultrasonographic examinations of the patients were performed. The groups of medicines they used were classified according to the lines of treatment. Patients who were followed up and treated in the chest diseases outpatient clinic were divided into groups according to the treatments they received. The patients who did not

need drugs due to asthma during pregnancy were taken as Group 1. The patients who have mild intermittent and mild persistent asthma which received 1.-2. step treatment using low-dose inhaled corticosteroids (ICS) or short-acting beta-agonist alone were taken as Group 2. The moderate and severe persistent asthma patients who received 3rd step and above asthma treatment using leukotriene receptor agonist (LTRA) together with medium-high dose ICS and long-acting beta-agonist (LABA) were taken as Group 3.

Statistical analysis

Statistical analyses were performed with the help of IBM SPSS version 25 software. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were presented using the median and interquartile range for non-normally distributed variables. Independent groups were compared using the Mann-Whitney U test since they did not show a normal distribution. Since the variables were non-normally distributed, Spearman's test was used for correlation coefficients. The Chi-square test was used to compare the ratios between the groups. Cases with a p-value below 0.05 were accepted as statistically significant results.

Results

The sociodemographic characteristics of the pregnant women with asthma and healthy control groups were compared. There was no significant difference between the groups in terms of mean age (P=0.951), mean BMI (P=0.615), parity (P=0.298), and smoking status (P=0.635) (Table 1).

Table 1. Comparison of the sociodemographic characteristics of asthma and control groups

		ASTHMA GROUP (n=87)	CONTROL GROUP (n=97)	P-VALUE
Age Median (min-max)		27.0 (20-45)	27 (19-40)	0.951[a]
BMI Median (min-max)		24.9 (18.9-32.3)	25.2 (18.2-31.1)	0.615[a]
Parity N (%)				
	primiparity	32 (36.8%)	43 (44.3%)	0.298[b]
	multiparity	55 (63.2%)	54 (55.7%)	
Smoking N (%)				
	yes	4 (4.6%)	6 (6.2%)	0.635[b]
	no	83 (95.4%)	91 (93.8%)	

Table 1.
BMI: body mass index. aMann Whitney U test was used to compare the measurement values of two independent groups. b Chi-square test was used to compare the ratios between the groups

The biochemical parameters of the first-trimester fetal aneuploidy screening test were compared between asthma and control groups. The median (min-max) values of the parameters examined are presented in Table 2. The median PAPP-A levels (P=0.363) and the median PAPP-A MoM values (P= 0.694) were compared between asthma and control groups. The results were similar between the groups. When fβ-HCG levels (P= 0.338) and fβ-HCG MoM values (P=0.278) were compared between the groups, the result was not found to be statistically significant (Table 2).

Table 2. Comparison of serum biochemical parameters in the first-trimester aneuploidy screening between the groups

	Asthma Group N: 87 Median (min-max)	Control Group N:97 Median (min-max)	P-value
PAPP-A (IU/L)	2.15 (0.41-9.91)	2.54 (0.56-11.40)	0.363[a]
PAPP-A MoM	0.99 (0.15-3.28)	1.07 (0.33-3.37)	0.694[a]
fβ-HCG (ng/ml)	31.10 (10.40-136.00)	35.70 (11.20-155.00)	0.338[a]
fβ-HCG MoM	0.81 (0.23-3.37)	0.97 (0.22-3.63)	0.278[a]

PAPP-A: Pregnancy-associated plasma protein-A; fβ-HCG: free β human chorionic gonadotropin; MoM: Multiples of median. aMann Whitney U test was used to compare the measurement values of two independent groups.

PAPP-A MoM values were compared between asthma and control groups at the cut-off value below and above 0.4 MoM. 3 (3.4%) pregnant women in the asthma group and 2 (2.1%) pregnant women in the control group were below 0.4 MoM. In comparison, there were 84 (96.6%) pregnant women in the asthma group and 95 (97.9%) pregnant women in the control group above 0.4 MoM, and the result was not statistically significant (P=0.564). fβ-HCG values were compared between asthma and control groups at the cut-off value below and above 2 MoM. The result was not statistically significant (P=0.244) (Table 3).

Table 3. Comparison of asthma and control groups according to PAPP-A MoM and fβ-HCG MoM Trisomy 21 cut-off values

		ASTHMA GROUP N (%)	CONTROL GROUP N (%)	P-VALUE
PAPP-A	< 0,4 MoM	3 (3.4%)	2 (2.1%)	0.564[b]
	> 0,4 MoM	84 (96.6%)	95 (97.9%)	
TOTAL		87 (100%)	97 (100%)	
fβ-HCG	> 2 MoM	7 (8%)	13 (13.4%)	0.244[b]
	< 2 MoM	80 (92%)	84 (86.6%)	
TOTAL		87 (100%)	97 (100%)	

PAPP-A: Pregnancy-associated plasma protein-A; fβ-HCG: free β human chorionic gonadotropin; MoM: Multiples of median. b Chi-square test was used to compare the ratios between the groups.

PAPP-A and PAPP-A MoM values were separately compared between the groups under and over 35 years of age. While the median PAPP-A value was found to be 2.10 IU/L (0.41-9.91) in the asthma group under 35 years of age, the median value was found to be 2.48 IU/L (0.56-11.40) in the control group, and the results were similar between the groups (P=0.225). While the median PAPP-A MoM value was 0.97 MoM (0.15-3.28) in the asthma group, the median value was 1.03 MoM (0.33-3.37) in the control group, and no significant difference was determined between the groups (P=0.431). Whereas the median PAPP-A value was found to be 3.24 IU/L (1.20-6.98) in the asthma group over 35 years of age, the median value was 4.19 IU/L (1.20-5.34) in the control group, and the results were similar between the groups (P=1.0). While the median PAPP-A MoM value was found to be 1.32 MoM (0.75-2.75) in the asthma group, the median value was found to be 1.28 MoM (0.53-2.75) in the control group, and no statistically significant difference was shown between the groups (P=0.456) (Table 4).

Table 4. Comparison of PAPP-A (IU/L) and PAPP-A MoM values between the groups under and over 35 years of age

GROUP	AGE	PAPP-A (IU/L) Median (min-max)	P-value	PAPP-A MoM Median (min-max)	P-value
ASTHMA N:87	< 35 years N:76	2.10 (0.41-9.91)	0.225[a]	0.97 (0.15-3.28)	0.431[a]
CONTROL N:97	< 35 years N:88	2.48 (0.56-11.40)		1.03 (0.33-3.37)	
ASTHMA N:87	≥ 35 years N:11	3.24 (1.20-6.98)	1.0[a]	1.32 (0.75-2.75)	0.456[a]
CONTROL N:97	≥ 35 years N:9	4.19 (1.20-5.34)		1.28 (0.53-2.75)	

PAPP-A: Pregnancy-associated plasma protein-A;-MoM: Multiples of median. aMann Whitney U test was used to compare the measurement values of two independent groups.

The asthma group was divided into treatment groups according to the type of asthma treatment provided to the patients during pregnancy. PAPP-A MoM and PAPP-A IU/L levels were compared between the groups. There was no statistically significant difference in PAPP-A MoM (P=0.738) and PAPP-A (IU/L) levels (P=0.588) among the first group that did not receive asthma treatment during pregnancy, the second group that used either a short-acting beta-agonist or low-dose inhaled corticosteroids alone, and the third group that received combined treatment with LABA + ICS (Table 5).

Table 5. Comparison of PAPP-A MoM and PAPP-A (IU/L) levels according to the steps of treatment provided in the asthma group

Medication	N (%)	PAPP-A MoM Median (min-max)	P-value	PAPP-A (IU/L) Median (min-max)	P-value
None	7 (8%)	0.84 (0.48-1.49)	0.738[a]	1.73 (0.76-4.07)	0.588[a]
1.-2. Step medication	37 (%42.5)	1.01 (0.15-2.75)		2.34 (0.41-7.02)	
≥3. Step Medication	43 (%49.4)	0.95 (0.39-3.28)		2.15 (0.53-9.91)	

1st - 2nd step treatment: treatment with a short-acting beta-agonist or low-dose ICS alone
≥3rd step treatment: combined treatment using LABA + ICS together. aMann Whitney U test was used to compare the measurement values of two independent groups.

Discussion

Based on the literature data showing that serum PAPP-A levels are elevated in asthma patients, we compared first-trimester PAPP-A levels between pregnant women with asthma and the healthy control group without asthma. Both groups' mean age, BMI, and smoking status were similar in our study. We did not reveal a significant difference in PAPP-A level, PAPP-A MoM values independent of the gestational week, fβ-HCG level, and fβ-HCG MoM value between pregnant women in asthma and healthy control group. Upon comparing the cut-off values taken as a basis for Down's syndrome (PAPP-A 0.4 MoM, fβ-HCG 2.0 MoM), there was no statistical difference between the groups below and above the cut-off values. When maternal age under and over 35 years was evaluated separately between the groups, the biochemical parameters were similar. When we divided asthma patients into groups according to the medical treatments and compared them, we revealed that the treatment type or severity did not affect PAPP-A levels and PAPP-A MoM values.

PAPP-A was defined in 1974 for the first time.[7] Circulating PAPP-A was primarily derived from syncytiotrophoblasts. Nowadays, it is included in the screening program for Trisomy 21 since low maternal serum levels are associated with Trisomy 21,18,13. The multiple of the median (MoM) unit, which shows the expression of PAPP-A concentration independent of the gestational week. This screening program determines which pregnant group should be recommended for diagnostic chorionic villus sampling (CVS) or amniocentesis. In the screening test for trisomy 21, the PAPP-A cut-off value was accepted as 0.405 MoM (95% confidence interval 0.28 to 0.67),[8] while it was 0.25 MoM for trisomy 13, Patau syndrome[9] and 0.15–0.22 MoM for trisomy 18, Edward's syndrome.[10] PAPP-A levels have been used as a parameter for screening tests in obstetrics and have also become a marker used to evaluate the prognosis of pregnancy. Based on the results of the FASTER study, PAPP-A MoM levels β 5th percentile were associated with spontaneous pregnancy loss, low birth weight, preeclampsia, gestational HT, preterm birth, PPROM, and ablatio placenta. It was concluded that low maternal serum PAPP-A levels in the first trimester were strongly associated with poor pregnancy outcomes.[11] Other studies in the literature support this result.[12,13]

Insulin-like growth factor (IGF) binding protein (IGFBP)-4 is an essential regulator of the IGF system and a substrate for the pregnancy-associated plasma protein-A (PAPP-A) enzyme, which is a dimeric protein detected in high concentrations in the plasma of pregnant women. PAPP-A is a local regulatory protein for IGF bioavailability. PAPP-A is secreted as a disulfide-linked homodimer and is classified as a metzincin metalloproteinase linked to the matrix metalloproteinase family.[14] The bioactivity of IGFBP-4 and PAPP-A has biological significance because it is associated with several pathological conditions such as metabolic disorders, type 2 diabetes mellitus, atherosclerotic/cardiovascular diseases (CVD), and tumorigenesis. At the posttranslational stage, IGFBP-4 is regulated by the proteolytic degradation of the PAPP-A enzyme.[15] PAPP-A is expressed and presented in various tissues and fluids, including adipose tissue, human osteoblasts, fibroblasts, ascitic fluids, and pleura. It reaches detectable levels in maternal blood after embryo implantation following fertilization and increases throughout pregnancy, reaching its highest level at term.[16] Its level is significantly lower in healthy non-pregnant women, but it is found in higher serum concentrations in males and females. PAPP-A is not a pregnancy-specific protein and is synthesized in many different cell types in males and females, such as fibroblasts, osteoblasts, vascular smooth muscle cells, testis, ovary, endometrium, fallopian tubes, kidney, bone, and colon.[17] PAPP-A is associated with inflammatory conditions, and its expression level is upregulated by proinflammatory cytokines such as IL-1β and tumor necrosis factor (TNF)-α.[18]

A study carried out in 2007 investigated the importance of the PAPP-A level in asthma disease. Because PAPP-A is a potential pro-atherosclerotic metalloproteinase and a new inflammatory marker, PAPP-A levels were compared in 35 asthma patients and 20 healthy subjects. Patients using only B2 agonists were included in the study, while those using corticosteroids or other anti-inflammatory drugs were excluded. PAPP-A concentrations were found to be 8.1±5.0 mU/L in the asthmatic group and 4.9±2.1 mU/L in the control group, statistically significantly higher in the asthmatic group. When compared according to the severity of asthma, it was considerably higher in stage 3 asthma patients than in the control group and other first and second-stage

asthma patients.[6] In another study investigating the relationship between PAPP-A levels and the severity of the disease in patients with Chronic Obstructive pulmonary disease (COPD), which is defined by chronic airflow limitation and increased airway inflammation, the average PAPP-A level in the group of 75 people with COPD was 33.7±36.8 ng/ml, and in the control group with 35 people was 13.8±9.9 ng/mL. This difference was statistically significant between the groups. PAPP-A levels were higher in stage 1 and 2 COPD groups than in stage 3 and 4 COPD patients. This study stated that PAPP-A could be a new marker showing inflammation in diseases such as asthma, pulmonary embolism, and lung cancer.[19] A study on 36 severe allergic asthma patients and 36 healthy control subjects from Turkey determined that PAPP-A and IGFB-4 levels were higher in patients with allergic asthma. In contrast, IGF-1 levels were similar between the groups. Omalizumab treatment was applied to the allergic asthma case group for six months. A significant decrease was observed in PAPP-A, IGFBP-4, and IGF-1 levels after treatment.[20] Studies state that PAPP-A levels may be a sensitive and specific early diagnostic biomarker in acute coronary syndrome, coronary artery diseases,[21,22] and cardiovascular diseases.23 The limitations of our study are that our sample size is relatively small, and the study is a single-center study.

Conclusion

This is the first study that evaluates serum PAPP-A levels in pregnant women with asthma to the best of our knowledge. Maternal serum PAPP-A level in pregnant women with asthma was not observed to vary compared to the healthy pregnant group without asthma. We revealed that medical treatments used for asthma treatment did not influence PAPP-A levels. Based on the results of our study, although first-trimester fetal aneuploidy screening seems to be a reliable screening method in pregnant women with asthma, more extensive studies are needed.

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Statements & Declarations

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Conflict of interest disclosure

The authors declare that they have no conflicts of interest.

Ethics approval

The study protocol was approved by Ankara City Hospital No. 2 Clinical Research Ethics Department and was performed in line with the Declaration of Helsinki. The ethics committee approval was obtained with the decision number E2-22-1569 on 30/03/2022.

Informed consent

Informed consent was obtained from all participants.

Author Contribution

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by [Bergen Laleli Koc], [Ozgur Kara], [Atakan Tanacan], [Deniz Oluklu], [Betul Akgun Aktas], [Ecem Kaya], [Dilek Sahin]. The first draft of the manuscript was written by [Bergen Laleli Koc] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Schatz M, Dombrowski MP, Wise R, et al.: Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol. 2003, 112:283-288. 10.1067/mai.2003.1516
2. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. J Allergy Clin Immunol. 2005, 115:34-46. 10.1016/j.jaci.2004.10.023
3. Canick JA, Lambert-Messerlian GM, Palomaki GE, et al.: Comparison of serum markers in first-trimester down syndrome screening. Obstet Gynecol. 2006, 108:1192-1199. 10.1097/01.AOG.0000241095.19638.f2
4. Wapner R, Thom E, Simpson JL, et al.: First-trimester screening for trisomies 21 and 18. N Engl J Med. 2003, 349:1405-1413. 10.1056/NEJMoa025273

5. Kirkegaard I, Uldbjerg N, Oxvig C: Biology of pregnancy-associated plasma protein-A in relation to prenatal diagnostics: an overview. Acta Obstet Gynecol Scand. 2010, 89:1118-1125. 10.3109/00016349.2010.505639
6. Coskun A, Balbay O, Duran S, et al.: Pregnancy-associated plasma protein-A and asthma. Adv Ther. 2007, 24:362-367. 10.1007/bf02849905
7. Lin TM, Galbert SP, Kiefer D, Spellacy WN, Gall S: Characterization of four human pregnancy-associated plasma proteins. Am J Obstet Gynecol. 1974, 118:223-236. 10.1016/0002-9378(74)90553-5
8. Krantz DA, Larsen JW, Buchanan PD, Macri JN: First-trimester Down syndrome screening: free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Am J Obstet Gynecol. 1996, 174:612-616. 10.1016/s0002-9378(96)70436-2
9. Spencer K, Ong C, Skentou H, Liao AW, K HN: Screening for trisomy 13 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn. 2000, 20:411-416.
10. Tul N, Spencer K, Noble P, Chan C, Nicolaides K: Screening for trisomy 18 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn. 1999, 19:1035-1042. 10.1002/(sici)1097-0223(199911)19:11<1035::aid-pd694>3.0.co;2-2
11. Dugoff L, Hobbins JC, Malone FD, et al.: First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol. 2004, 191:1446-1451. 10.1016/j.ajog.2004.06.052
12. ATAMAN YILDIRIM Z, TUĞRUL ERSAK D, TİMUR B, KAHYAOĞLU S: The Predictive Value of First and Second Trimester Screening Test Biomarkers in Preeclampsia. Forbes Journal of Medicine. 2022, 3.
13. D'Antonio F, Rijo C, Thilaganathan B, et al.: Association between first-trimester maternal serum pregnancy-associated plasma protein-A and obstetric complications. Prenat Diagn. 2013, 33:839-847. 10.1002/pd.4141
14. Overgaard MT, Boldt HB, Laursen LS, Sottrup-Jensen L, Conover CA, Oxvig C: Pregnancy-associated plasma protein-A2 (PAPP-A2), a novel insulin-like growth factor-binding protein-5 proteinase. J Biol Chem. 2001, 276:21849-21853. 10.1074/jbc.M102191200
15. Hjortebjerg R: IGFBP-4 and PAPP-A in normal physiology and disease. Growth Horm IGF Res. 2018, 41:7-22. 10.1016/j.ghir.2018.05.002
16. Bischof P, DuBerg S, Herrmann W, Sizonenko PC: Pregnancy-associated plasma protein-A (PAPP-A) and hCG in early pregnancy. Br J Obstet Gynaecol. 1981, 88:973-975. 10.1111/j.1471-0528.1981.tb01683.x
17. Overgaard MT, Oxvig C, Christiansen M, et al.: Messenger ribonucleic acid levels of pregnancy-associated plasma protein-A and the proform of eosinophil major basic protein: expression in human reproductive and nonreproductive tissues. Biol Reprod. 1999, 61:1083-1089. 10.1095/biolreprod61.4.1083
18. Conover CA, Harrington SC, Bale LK: Differential regulation of pregnancy associated plasma protein-A in human coronary artery endothelial cells and smooth muscle cells. Growth Horm IGF Res. 2008, 18:213-220. 10.1016/j.ghir.2007.09.001
19. Talay F, Tosun M, Yaşar ZA, et al.: Evaluation of Pregnancy-Associated Plasma Protein-A Levels in Patients with Chronic Obstructive Pulmonary Disease and Associations with Disease Severity. Inflammation. 2016, 39:1130-1133. 10.1007/s10753-016-0345-z
20. Bulut I, Ozseker ZF, Coskun A, Serteser M, Unsal I: Pregnancy-associated plasma protein-A (PAPP-A) levels in patients with severe allergic asthma are reduced by omalizumab. J Asthma. 2018, 55:1116-1121. 10.1080/02770903.2017.1396471
21. Li Y, Zhou C, Zhou X, Song L, Hui R: PAPP-A in cardiac and non-cardiac conditions. Clin Chim Acta. 2013, 417:67-72. 10.1016/j.cca.2012.12.006
22. Gutiérrez-Leonard H, Martínez-Lara E, Fierro-Macías AE, et al.: Pregnancy-associated plasma protein-A (PAPP-A) as a possible biomarker in patients with coronary artery disease. Ir J Med Sci. 2017, 186:597-605. 10.1007/s11845-016-1515-6
23. Hjortebjerg R, Rasmussen LM, Gude MF, et al.: Local IGF Bioactivity Associates with High PAPP-A Activity in the Pericardial Cavity of Cardiovascular Disease Patients. J Clin Endocrinol Metab. 2020, 105. 10.1210/clinem/dgaa617

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RESEARCH ARTICLE

Cervical Cerclage: An Obstetrical Dilemma

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Abstract

Introductıon: This retrospective study evaluated women in whom transvaginal cervical cerclage (TCC) was performed in a previous pregnancy but delivered without cervical intervention in the most recent pregnancy. The primary aim was to underline the importance of etiology based management protocols on favorable pregnancy outcomes in patients with a history of TCC.

Methods: We retrospectively evaluated 34 patients with at least one failed TCC for the treatment of cervical insufficiency (CI) but who gave birth without TCC in their most recent pregnancies.

Results: All patients were evaluated preconceptionally and examined for maternal risk factors. At least one risk factor was present in all cases. The autoimmune antibody positivity rate was 41.2%. Twelve patients had Hashimoto thyroiditis, two had systemic lupus erythematosus, two had pernicious anemia, and two had anti-phospholipid antibody syndrome. 32 had homozygous or heterozygous methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms, while 11 were homozygous or heterozygous for factor 5 Leiden or prothrombin-20210A gene mutations.

Conclusion: The elimination and management of risk factors for cervical ripening and dilatation are important for preventing unnecessary cervical interventions.

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Introduction

Cervical insufficiency (CI) is defined as painless cervical dilatation leading to recurrent second-trimester pregnancy losses.[1] Congenital and acquired risk factors that increase the risk of CI include the following: 1) genetic disorders leading to impaired collagen synthesis (e.g., Ehler-Danlos syndrome); 2) congenital uterine anomalies; 3) cervical trauma during labor or delivery; 4) cervical injury due to some gynecologic procedures (e.g., uterine evacuation, treatment of cervical lesions).[1,2] The preconceptional diagnosis of CI is often complicated since it is mainly based on a patient's past obstetric history, pelvic examination, and "Hegar cervical dilator test" (passage of number 8 Hegar dilator through the cervical ostium without resistance) with some limitations.[2,3] On the other hand, transvaginal ultrasonography (TVUSG) and/or a pelvic examination together with cervicovaginal fetal fibronectin measurement can be used as ancillary diagnostic methods to examine cervical length during pregnancy.[2,4,5] Cervical cerclage, vaginal pessary, and progesterone supplements are the main management options for CI.[6,7] However, all interventions are under debate.[2,6] Transvaginal cervical cerclage (TCC) is one of the most popular treatment options for CI. There are two main techniques for TCC: the McDonald procedure and the Shirodkar procedure.[8] Transabdominal cervical cerclage methods may also be performed in complicated cases, especially for patients with previous TCC failure.[9] The critical issue is differentiating real CI from untimely cervical ripening and dilatation due to various etiological reasons. For example, it was reported that vaginal and systemic infections, hereditary thrombophilia, some metabolic disorders, methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms, autoimmune disorders, and chronic inflammatory diseases are associated with early pregnancy loss, repeated miscarriage, and preterm delivery.[10-13] Thus, placental inflammation of infectious, toxic, metabolic and immunologic reasons seems to be the main cause of untimely uterine contractions and cervical ripening/dilatation that result in CI-like pregnancy losses. In such cases, preventing metabolic and immunological placental inflammation together with disease- or disorder-specific treatments are essential to satisfactory pregnancy outcomes. The prevention and management of metabolic and immunological inflammatory processes using anti-inflammatory plus anti-thrombotic agents such as low-molecular-weight heparin (LMWH), oral corticosteroids, and low-dose acetylsalicylic acid (ASA) are crucial for achieving better perinatal outcomes.[14,15] Herein, we retrospectively evaluated women in whom TCC was performed in their previous pregnancies but who gave birth without any cervical intervention in their most recent pregnancy.

Material and Methods

Women in whom TCC was performed in one or more previous pregnancies but who did not require cervical intervention in the most recent pregnancy were included in this study. We retrospectively evaluated 34 patients who experienced at least one failed TCC for the treatment of CI and/or recurrent pregnancy loss but gave birth without TCC in the most recent pregnancy (2007–2017). The required data were extracted from the Hacettepe University Hospital database.

All patients were evaluated preconceptionally and screened for autoimmune disorders, autoimmune antibody positivity, hereditary thrombophilia, metabolic disorders (hyperhomocysteinemia, folate deficiency), MTHFR polymorphisms, chronic inflammatory diseases, genital tract inflammation, coagulation disorders, and anemia. Patients were allowed to get pregnant after the detection and management of their medical problems that were the risk factors for early pregnancy losses and/or recurrent miscarriages.

The patients were registered in a special antenatal care program during their pregnancies, and necessary laboratory tests such as complete blood count, clinical urine test, blood sugar, liver function tests, C-reactive protein, complement components 3 and 4, activated protein-C resistance, anti-thrombin III activity, protein-S activity, lupus anticoagulant, and von Willebrand factor antigen were performed during the course of follow-up. LMWH (enoxaparin 2000 Anti-Xa IU/0.2 mL), oral prednisone (methylprednisolone 4 mg), and aspirin (ASA 100 mg) were added to the treatment protocol in necessary cases as soon as a pregnancy was confirmed. Pregnancy follow-up consisted of serial ultrasonography to evaluate cervical changes, aneuploidy screening (combined or triple test), fetal anatomy scanning at the 20–24th gestational week, oral glucose challenge test, and nonstress test weekly (after the 28th gestational week). All medications were stopped 3 days before delivery.

The median (minimum-maximum value) patient age; gravida; number of previously failed TCC procedures; serum folate, vitamin B12, and homocysteine levels just before conception; gestational weeks at birth; infant birthweight; and 5-minute APGAR scores were used as the data that were not normally distributed. We also recorded the autoimmune antibody positivity types, related diseases/syndromes, MTHFR polymorphism type, hereditary thrombophilia type, maternal diseases, obstetrical complications such as early pregnancy bleeding, intrauterine growth retardation (IUGR), hypertensive states of pregnancy (e.g., preeclampsia, gestational hypertension), preterm labor and delivery, and ablatio placentae in affected cases.

Statistical analyses were performed by Statistical Package for the Social Sciences (SPSS® version 22.0; IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the data distribution. Normally distributed data are shown as mean and standard deviation, while non-parametric data are shown as median (minimum-maximum values). Written informed consent was obtained from all patients and the study was approved by the institutional ethics committee of Hacettepe University (GO 18/159).

Results

All pregnancies were singletons involving live babies. However, there were 16 (47%) late preterm births (34 weeks to 36 weeks, 4 days). The median patient age was 33 years (24–41 years), median gravida was 5 (4–14), median parity was 1 (0–3), median number of miscarriages was 3 (1–13), median number of living children was 1 (0–2), median number of previous failed TCC procedures was 1 (1–2), median gestational week at birth was 37 (34–39), median infant birthweight was 2800 g (2200–3850 g) and the median 5-minute APGAR score was 10 (7–10). The median serum levels of folate, vitamin B12, and homocysteine just before conception were 12 nmol/L (6.1–25.2 nmol/L), 285 ng/L (123–495 ng/mL), and 7.4 µmol/L (3.7–12.7 µmol/L), respectively. Table 1 shows the median and minimum-maximum values for the previously mentioned variables.

Table 1: The median and minimum-maximum values for variables examined in patients with a history of cervical insufficiency.

Variable	Median	Minimum-Maximum
Maternal age, years	33	24-41
Gravida	5	4-14
Parity	1	0-2
Abortion	3	1-13
Living child	1	0-2
Number of previous failed TCC procedures	1	1-2
–Gestational week at birth	37	34-39
Birthweight of the infant, g	2800	2200-3850
APGAR, 5-minute	10	7-10
Serum folate level, nmol/L	12	6.1-25.2
Serum vitamin B12 level, ng/L	285	123-495
Serum homocysteine level, µmol/L	7.4	3.7-12.7

TCC, transvaginal cervical cerclage

We have found at least one risk factor for early pregnancy loss and cervical dilatation in all cases. The autoimmune antibody positivity rate (≥1 antibodies) was 41.2% (14/34 cases) in our series. Table 2 shows the data related to the distribution of autoimmune antibodies. Antinuclear antibody (ANA) and anti-thyroid peroxidase (anti-TPO) antibody were the most frequent antibodies observed in this study (41.2% and 35.3% of cases, respectively). On the other hand, 12 patients (35.3%) had Hashimoto

thyroiditis, two (5.9%) had systemic lupus erythematosus, two (5.9%) had pernicious anemia, and two (5.9%) had anti-phospholipid antibody syndrome.

Table 2: Percentage of positive autoantibody results in patients with a history of cervical insufficiency.

Autoantibody	Percentage
ANA	14/34 (41.2%)
Anti-TPO	12/34 (35.3%)
Anti-TG	2/34 (5.9%)
aCL IgM-IgG	2/34 (5.9%)
APA	2/34 (5.9%)
Anti-dsDNA	2/34 (5.9%)

ANA, antinuclear antibody; anti-TPO, anti-thyroid peroxidase antibody; anti-TG, antithyroglobulin antibody; aCL, anticardiolipin antibody; APA, anti-parietal cell antibody; anti-dsDNA, anti-double-stranded DNA antibody

Of the 34 patients, 32 (94.1%) had one or more homo- or heterozygous MTHFR gene polymorphisms. Table 3 shows the distribution of the MTHFR polymorphisms. Eleven patients (32.4%) were homo- or heterozygous for factor 5 Leiden or prothrombin-20210A gene mutations (Table 3). Five patients (14.7%) had factor 5 Leiden heterozygous and two (3.8%) had factor 5 Leiden homozygous mutations, while one (2.9%) had a prothrombin 20210A homozygous mutation and three (8.8%) had a prothrombin 20210A heterozygous mutation.

Table 3: Percentage of mutations in patients with a history of cervical insufficiency.

Variable	Percentage
MTHFR C677T heterozygous	17/34 (50%)
MTHFR C677T homozygous	2/34 (5.9%)
MTHFR A1298C heterozygous	17/34 (50%)
MTHFR A1298C homozygous	3/34 (8.8%)
MTHFR compound heterozygous	9/34 (26.5%)
Factor 5 Leiden heterozygous	5/34 (14.7%)
Factor 5 Leiden homozygous	2/34 (5.9%)
Prothrombin 20210 A heterozygous	3/34 (8.8%)
Prothrombin 20210 A homozygous	1/34 (2.9%)

MTHFR, methylene tetrahydrofolate reductase

Discussion

TCC is a treatment option for CI. There are alternative surgical procedures in which various sutures, wires, or synthetic materials are used to strengthen the cervix. There are two main techniques for TCC: the McDonald procedure and the Shirodkar procedure.[8] TCC is considered beneficial for singleton pregnancies in women with a prior CI history and short cervical length (≤25 mm on TVUSG).[16] It can be applied electively (at 12–14 weeks of gestation based on the previous CI history), ultrasound-indicated (cervical length ≤ 25 mm on TVUSG at 16–23 weeks of gestation in patients with a previous CI history), or based on pelvic examination findings.[17] However, there are contraindications for TCC such as a fetal anomaly incompatible with life, maternal/fetal infections, active bleeding, active preterm labor, preterm premature rupture of the membranes (PPROM), or

fetal demise.[2] The role of TCC in multiple pregnancies and in patients with a short cervical length in the absence of previous CI is controversial.[2] The TCC procedure may feature complications such as PPROM, intraamniotic infection, suture migration, and bleeding.[18] However, a recent meta-analysis reported favorable outcomes for emergency TCC in singleton and twin pregnancies.[19] Mentioned study includes the data of 3239 women and indicated an overall survival rate of 74% with similar findings for both singleton and twin pregnancies. The main findings of the study revealed that emergency TCC was superior to expectant management.[19] Thus, TCC seems to be an effective treatment modality in appropriately selected cases.

We believe that a wide spectrum of etiological factors causes CI. Müllerian canal abnormalities and some other related anomalies, connective tissue disorders (organ-specific and/or systemic), sequelae due to infectious problems of the cervix and genital tract, cervical injury due to gynecological operations, and birth trauma are the most commonly blamed etiological factors.[20] The general trend in defining CI is to assert an association between CI and a mechanical defect.[1,2]

On the other hand, CI might be an instant condition of the developmental pathobiological events over the course of infectious, toxic, metabolic, and immunological inflammation (e.g., autoimmune antibody positivity and related disorders, metabolic disorders such as hyperhomocysteinemia, MTHFR polymorphisms, hereditary thrombophilia, and chronic inflammatory diseases) of the maternal–fetal interface causing untimely uterine contractions.[14,15] As reported previously, the amniotic fluid levels of proinflammatory cytokines such as interleukin 1α (IL-1α), IL-1ß, IL-6, and tumor necrosis factor-α are higher in CI patients.[21]

Autoimmune antibody positivity and related diseases, chronic inflammatory diseases, metabolic disorders (hyperhomocysteinemia, folate deficiency), enzyme pathway disorders (MTHFR polymorphisms), and hereditary thrombophilia are all associated with obstetrical complications such as miscarriage and preterm labor.[12,13] Toxic metabolites (e.g., hyperhomocysteinemia), autoimmune antibodies, cell degradation products, and inflammatory cytokines are most likely responsible for the injury of the vascular structures of the placenta and the cellular components of the maternal–fetal interface, resulting in placental inflammation and untimely uterine contractions that simulate CI-like symptoms.[14,22,23] It is critical to differentiate between cervical changes and CI without using unnecessary interventions. In this study, 41.2% (14/34), 94.1% (32/34), and 32.3% (11/34) of patients had autoimmune antibody positivity (≥1 antibodies), reduced MTHFR activity, hyperhomocysteinemia ,and hereditary thrombophilia, respectively. We demonstrated at least one etiological (metabolic and/or immunological) risk factor for thrombotic events and maternal–fetal interface inflammation in our patients. However, there were 16 (47%) preterm deliveries (all late preterm), most likely due to underlying medical pathologies despite intensive medical care. Miscarriage, preeclampsia, eclampsia, or placental abruption were not observed in any of our patients.

LMWH is reportedly beneficial in the management of various obstetrical complications such as recurrent miscarriage, IUGR, preterm labor, PPROM, and preeclampsia.[10,12,22] LMWH has antithrombotic and anti-inflammatory effects.[15,22] We have used LMWH together with ASA (and low-dose corticosteroids in necessary cases) to prevent and overcome the inflammatory and thrombotic events involved in autoimmune disorders, MTHFR polymorphisms, and hereditary thrombophilia. All of our patients who had experienced failed TCC in their previous pregnancies delivered their most recent infants without any cervical intervention. Our results demonstrate the importance of eliminating risk factors for untimely uterine contractions and avoiding unnecessary cervical operations.

It is hypothesized that inflammation may have a prominent role in CI as it has in preterm birth.[10] The coagulation cascade and thrombus formation are associated with inflammatory processes.[10] The coagulation cascade may reportedly be activated in patients with preterm labor and PPROM.[24] Furthermore, hereditary thrombophilia and MTHFR polymorphisms are also reportedly associated with untimely contractions and CI.[15] These findings are consistent with the presence of high rates of thrombophilia and MTHFR polymorphisms in our study. It was recently reported that heparin and heparin-related derivatives also have an anti-inflammatory effect.[15] Additionally, LMWH influences matrix metalloproteinases, tissue inhibitors, cadherin-E, heparin-binding epidermal growth factor, and insulin-like growth factor.[25-28]

As a result, the appropriate management of thrombotic events using low-dose LMWH and low-dose ASA may prevent inflammatory process activation.[14,15]

Although hyperhomocysteinemia is reportedly associated with various adverse pregnancy outcomes such as pregnancy loss, neural tube defects, chromosomal aneuploidies, fetal cardiac defects, preeclampsia, abruptio placentae, and IUGR,[29,30] its effect on CI and preterm birth is unclear.[12] Recent meta-analyses have also revealed that MTHFR C677T polymorphism and maternal vitamin B12 concentrations may play a pivotal role in preterm birth.[12,13] In this series, the appropriate management of patients with a methionine-restricted diet, low-dose ASA, folate–vitamin B supplementation, and low-dose LMWH seem to be the major factors in successful pregnancy outcomes.

The relationship between autoimmune antibodies and pregnancy loss has been investigated by many researchers.[31-33] The high impaired implantation and pregnancy loss rates in women with autoimmune antibodies may be due to injury to the syncytiotrophoblasts, endovascular trophoblasts covering the tips of the spiral arteries, endothelial cells of the spiral veins, and superficial/glandular epithelial cells of the decidua (intervillous space of the placenta) induced by autoantibody inflammatory processes and the entrance of cell degradants of these tissues into the maternal circulation. These biological events result in impaired implantation and disturbed fetal perfusion.[14] The high prevalence of autoimmune antibodies in our study group was consistent with this theory; thus, low-dose methylprednisolone seems to be a good option for modulating the immune response in these patients.

All 34 patients in our study group delivered healthy babies. However, there was a high rate of preterm birth (47%), but all were late preterm deliveries. These results were more likely due to the clinical characteristic of the patients in our study (high-risk pregnancies with poor obstetrical histories). The thorough evaluation of the underlying conditions and appropriate management of the problems are important for success in cases of CI.

The main strengths of the present study were the comprehensive evaluation of the risk factors for pregnancy losses and the unique hypothesis. However, relatively number of cases, single center experience and retrospective design were the main limitations.

In conclusion, the careful evaluation and accurate diagnosis of CI are key issues that contribute to the successful medical management of early pregnancy problems. The elimination and management of risk factors for cervical ripening and dilatation are also important for avoiding unnecessary cervical interventions.

References

1. Padua L, Coraci D, Erra C, Pazzaglia C, Paolasso I, Loreti C, et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. Lancet Neurol. 2016;15(12):1273-84.
2. Geoghegan JM, Clark DI, Bainbridge LC, Smith C, Hubbard R. Risk factors in carpal tunnel syndrome. J Hand Surg Br. 2004;29(4):315-20.
3. Spahn G, Wollny J, Hartmann B, Schiele R, Hofmann GO. [Metaanalysis for the evaluation of risk factors for carpal tunnel syndrome (CTS) Part II. Occupational risk factors]. Z Orthop Unfall. 2012;150(5):516-24.
4. El-Helaly M, Balkhy HH, Vallenius L. Carpal tunnel syndrome among laboratory technicians in relation to personal and ergonomic factors at work. J Occup Health. 2017;59(6):513-20.
5. Alhusain FA, Almohrij M, Althukeir F, Alshater A, Alghamdi B, Masuadi E, et al. Prevalence of carpal tunnel syndrome symptoms among dentists working in Riyadh. Ann Saudi Med. 2019;39(2):104-11.
6. Sears ED, Swiatek PR, Hou H, Chung KC. Utilization of Preoperative Electrodiagnostic Studies for Carpal Tunnel Syndrome: An Analysis of National Practice Patterns. J Hand Surg Am. 2016;41(6):665-72.e1.
7. Wong SM, Griffith JF, Hui AC, Tang A, Wong KS. Discriminatory sonographic criteria for the diagnosis of carpal tunnel syndrome. Arthritis Rheum. 2002;46(7):1914-21.
8. Tulipan JE, Ilyas AM. Carpal Tunnel Syndrome Surgery: What You Should Know. Plast Reconstr Surg Glob Open. 2020;8(3):e2692.
9. Wiesler ER, Chloros GD, Cartwright MS, Smith BP, Rushing J, Walker FO. The use of diagnostic ultrasound in carpal tunnel syndrome. J Hand Surg Am. 2006;31(5):726-32.
10. Hagberg M, Morgenstern H, Kelsh M. Impact of occupations and job tasks on the prevalence of carpal tunnel syndrome. Scand J Work Environ Health. 1992;18(6):337-45.
11. Kozak A, Schedlbauer G, Wirth T, Euler U, Westermann C, Nienhaus A. Association between work-related biomechanical risk factors and the occurrence of carpal tunnel syndrome: an overview of systematic reviews and a meta-analysis of current research. BMC Musculoskelet Disord. 2015;16:231.

12. Khan A. Prevalence Of Carpel Tunnel Syndrome In The Dentists Working In Karachi. Pakistan Oral and Dental Journal. 2014.
13. Shiri R, Pourmemari MH, Falah-Hassani K, Viikari-Juntura E. The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies. Obes Rev. 2015;16(12):1094-104.
14. Lam N, Thurston A. Association of obesity, gender, age and occupation with carpal tunnel syndrome. Aust N Z J Surg. 1998;68(3):190-3.
15. Nathan PA, Istvan JA, Meadows KD. A longitudinal study of predictors of research-defined carpal tunnel syndrome in industrial workers: findings at 17 years. J Hand Surg Br. 2005;30(6):593-8.
16. Lakshminarayanan K, Shah R, Li Z-M. Sex-related differences in carpal arch morphology. PLoS One. 2019;14(5):e0217425.
17. Haghighat A, Khosrawi S, Kelishadi A, Sajadieh S, Badrian H. Prevalence of clinical findings of carpal tunnel syndrome in Isfahanian dentists. Adv Biomed Res. 2012;1:13.
18. McDiarmid M, Oliver M, Ruser J, Gucer P. Male and female rate differences in carpal tunnel syndrome injuries: personal attributes or job tasks? Environ Res. 2000;83(1):23-32.
19. Stevens JC, Sun S, Beard CM, O'Fallon WM, Kurland LT. Carpal tunnel syndrome in Rochester, Minnesota, 1961 to 1980. Neurology. 1988;38(1):134-8.
20. Wipperman J, Goerl K. Carpal Tunnel Syndrome: Diagnosis and Management. Am Fam Physician. 2016;94(12):993-9.
21. Viikari-Juntura E, Silverstein B. Role of physical load factors in carpal tunnel syndrome. Scand J Work Environ Health. 1999;25(3):163-85.
22. Palmer KT, Harris EC, Coggon D. Carpal tunnel syndrome and its relation to occupation: a systematic literature review. Occup Med (Lond). 2007;57(1):57-66.
23. Reinstein L. Hand dominance in carpal tunnel syndrome. Arch Phys Med Rehabil. 1981;62(5):202-3.
24. Fowler JR, Gaughan JP, Ilyas AM. The sensitivity and specificity of ultrasound for the diagnosis of carpal tunnel syndrome: a meta-analysis. Clin Orthop Relat Res. 2011;469(4):1089-94.
25. Crasto JA, Scott ME, Fowler JR. Ultrasound Measurement of the Cross-Sectional Area of the Median Nerve: The Effect of Teaching on Measurement Accuracy. Hand (N Y). 2019;14(2):155-62.

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RESEARCH ARTICLE

Evaluation Of Humeral Cortical Index In Patients Over 65 Years With Proximal Humerus Fractures

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Abstract

Introductıon: The aim of our study is to evaluate the effect of humeral cortical index (CI) on proximal humerus fracture (PHF) risk in patients over 65 years.

Methods: Patients over 65 years who had PHF due to injury being a fall from less than standing height and were treated surgically between January 2019 and December 2023 were included in group 1. Patients over 65 years who applied to the hospital and had a shoulder anterior-posterior radiography were included in group 2. Neer classification was used to classify PHF. CI measurements were performed for all patients.

Results: In group 1, 54 male and 36 female patient were evaluated. In group 1, 42 right and 48 left humeral CI measurements were performed. The average age of group 1 was 72.87±6.65. In group 2, 49 male and 37 female patient were evaluated. The average age of group 2 was 70.9 ±4.79. No significant difference was determined between group 1 and group 2 for gender, age and side. (p=0.684, p=0.236, p=0.128 respectively). For group 1, the mean humeral CI was 0.304±0.06 and 0.380 ±0.07 for group 2. A significant difference was determined between group1 and group 2 for humeral CI. (p>0,001) No significant difference was determined between Neer type 2 patients and Neer type 3-4 patients for age, gender and humeral CI. (p=0.373, p=0.15, p=0.451 respectively) The risk of PHF increased 3.2 times in patients with humeral CI lower than 0.3267.

Conclusion: Humeral CI is a good parameter in determining the risk of PHF in the population over 65 years. However, humeral CI does not affect the severity of PHF.

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Introduction

Proximal humerus fractures (PHF) are one of the most common fractures of the upper extremity, especially in the elderly population.[1] And 70% of all PHF occur in osteoporotic patients.[1,2] Recent studies have shown that PHFs are increasing in the elderly population and a 250% increase in the proximal humerus fractures incidence is expected in the next 30 years for the population over 75 years.[3,4] In elderly population, PHF is the third most common fracture.[5,6] Most of the patients can be treated conservatively.[7] PHF is more common in women in the elderly population.[8] This may be explained by poor bone quality and increased risk of falling.[9] It has been claimed that osteoporotic proximal humerus fractures are more complex fractures.[10]

Fragility fractures occur after low-energy trauma, usually after falling from standing height or less. Fragility fractures are associated with osteoporosis.[11] Osteoporosis causes decreased bone density and bone quality. Therefore, it increases the risk of fragility fractures. Bone quality is affected by cortical and trabecular bone structure and bone turnover. Trabecular bone loss and cortical thinning are predisposing for fragility fractures. Fractures in the trabecular bone site generally result of defects in the cortical bones.[12]

Previous studies have shown that changes in anteroposterior radiographs of long bones can be used to evaluate bone quality.[13] Thickness of cortex, shape of medullary canal and width of canal at diaphyseal part evaluated are some of the parameters used in bone quality evaluation in anterior posterior radiographs. Different indices have been defined to evaluate bone quality. One of them is cortical index(CI).

In our study, we evaluated the humeral CI. We hypothesized that PHF occurs more frequently in patients with lower humeral CI. The aim of our study is to evaluate the effect of humeral CI on PHF risk in patients over 65 years

Material and Methods

Approval for the study was granted by the institutional review board of the authors' affiliated institutions (Project number: TABED 1/177/2024, Date: 08.05.2024). All of the researchers signed the most recent version of the Helsinki Declaration.

In this retrospective study, between January 2019 and December 2023, medical records of our institution were reviewed and patients who underwent open reduction and internal fixation for PHF were included in the study. And patients who applied to the hospital and had anterior-posterior shoulder radiography were included in the study. All patients included in the study were over 65 years.

Patients under 65 years, patients with bilateral PHF, multiple fractures, old PHF, pathological fractures, malignancy, neurovascular deficits and cerebrovascular disease were excluded from the study.

Patients who had PHF due to injury being a fall from less than standing height and were treated surgically were evaluated in group 1. Patients over 65 years who applied to the hospital and had a shoulder anterior-posterior radiography were evaluated in group 2. Demographic characteristics of the patients were evaluated. Such as gender, side age…

In our study, the Neer classification was used to classify PHF. In this classification, the proximal humerus is divided into 4 main parts: the humeral head, the greater tuberosity, the lesser tuberosity and the humeral shaft.[14,15] These segments are considered part if there is more than 1 cm displacement or more than 45 degrees of angulation. Neer classification is useful in the evaluation and investigation of PHF.[16] However, it also has limitations such as poor inter-observer agreement and difficulty in evaluation on radiography.[17]

Cortical index (CI) measurements were performed for all patients in group 1 and group 2. CI was measured 5cm below of the surgical neck.[18] CI was determined by proportioning the difference between the outer diameter and the inner diameter of the humerus to the outer diameter of the humerus at 5 cm below of the humeral surgical neck.

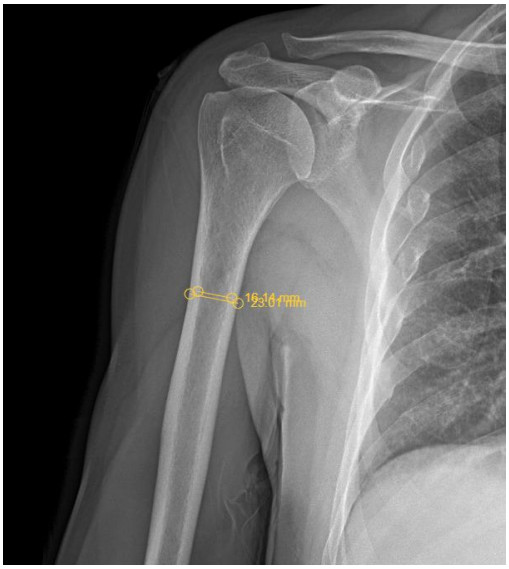

Figure 1 : Cortical index measurement

Results

Ninety-three patients were operated for PHF. Three patients whose follow-up data could not be obtained were excluded from the study. In group 1, 54 male and 36 female patient were evaluated. In group 1, 42 right and 48 left humeral CI measurements were performed. The average age of group 1 was 72.87±6.65. Eighty-six patients were included in group 2. In group 2, 49 male and 37 female patient were evaluated. The average age of group 2 was 70.9 ±4.79. In group 2, 50 right and 36 left humeral CI measurements were performed. No significant difference was determined between group 1 and group 2 for gender, age and side. (p=0.684, p=0.236, p=0.128 respectively). For group 1, the mean humeral CI was 0.304±0.06 and 0.380 ±0.07 for group 2. A significant difference was determined between group1 and group 2 for humeral CI. (p>0,001) (Table 1)

Table 1: Demographic characteristics of the patients

	Group 1 (n=90)	Group 2 (n=86)	P value
Gender			0.684
Female	54; 60%	49; 50.3%	
Male	36; 40%	37; 35.7%	
Age	72.87±6.65	66.9 ±4.79	0.236
Side			0.128
Right	42; 46.7%	50; 58.1%	
Left	48; 53.3%	36; 41.9%	
Humeral CI	0.304±0.06	0.380 ±0.07	0.001

CI: cortical index

PHFs were classified according to the Neer classification. In group 1, 65 of the patients were type 2, 25 of the patients were type 3 and type 4. The mean age of patients with Neer type 2 was 72.48±6.56. And the average age of patients with Neer type 3-4 was 73.88±6.91. The mean humeral CI was 0.301±0.06 for group 1 and 0.312 ±0.06 for group 2. Thirty-six female and twenty-nine patients had Neer type 2 PHF. And 18 female and 7 male had Neer type 3-4 PHF. No significant difference was determined between Neer type 2 patients and Neer type 3-4 patients for age, gender and humeral CI. (p=0.373, p=0.15, p=0.451 respectively) (Table 2)

Table 2: The effect of age, gender and humeral CI on Neer classification

	Neer type 2 (n=65)	Neer type 3-4 (n=25)	P value
Gender			0.15
Female	36; 55.4%	18; 72%	
Male	29; 44.6%	7; 28%	
Age	72.48±6.56	73.88 ±6.91	0.373
Humeral CI	0.301±0.06	0.312 ±0.06	0.451

CI: cortical index

All patients were evaluated and the cut-off value for humeral CI was determined as 0.3267. The risk of PHF increased 3.2 times in patients with humeral CI lower than 0.3267.

Discussion

In the current study, we determined that humeral CI is a good parameter in determining the risk of PHF in the population over 65 years. The risk of PHF increased 3.2 times in patients with humeral CI lower than 0.3267. However, there is no relationship between humeral CI and severity of PHF.

All over the world, life expectancy is increasing with the development of health care. In the United States, life expectancy was 69.9 in 1959. But it increased to 78.9 in 2016.[19] Khatip et al showed that PHF incidence increased %28 from 1990 to 2010. No significant increase in the incidence of PHF was determined in patients under 65 years, but a significant increase was determined in patients over 65 years.[20] The increase of the incidence is associated with the aging of the population. Han et al demonstrated that in elderly population, the most common used treatment for PHF is nonoperative treatment. And the most common used treatment in patients undergoing surgery is open reduction and internal fixation (ORIF). In our study, patients who underwent ORIF due to PHF were evaluated.

Cortical thickness is an important parameter for evaluating bone quality. Tingart et al. determined a strong relationship between cortical thickness of the proximal humerus and bone mineral density.[21] Hepp et al. used the cortical index to determine the risk of reoperation in PHF treated with locking plate fixation. They determined a correlation between cortical thickness and bone mineral density measured by dual-energy X-ray absorptiometry (DXA) scan.[22] Spross et al. used the deltoid tuberosity index to evaluate patients' risk of osteoporosis.[23]

The deltoid tuberosity index was compared with the cortical index and it was determined that there was a correlation between the two measurement methods. In our study, we compared the cortical index of patients with PHF and patients without fracture in the population over 65 years. And we observed that the cortical index of patients with PHF was significantly lower.

There are different studies indicating the risk of osteoporosis or PHF using different measurement methods in the proximal humerus. Hepp et al. determined 0.4 as the cut-off cortical index value for PHF.[22] In another study, it was stated that a cortical index value ≤ 0.378 was a predictor of osteoporosis.[24] In the current study, we observed that the risk of PHF increased 3.2 times in patients with humeral CI lower than 0.3267. However, there is no relationship between humeral CI and PHF Neer classification types.

There are different studies, evaluating the low CI and PHF relationship. The fact that PHF is more common in patients with low CI suggests that a more complex fracture may occur in patients with lower CI. Osterhoff et al. reported in their study that there was no relationship between CI and severity of PHF in the elderly patient population.[25] In our study, trauma mechanism of the patients was falling from less than standing height. And there was no relationship between humeral CI and severity of PHF like Oserhoff et al.'s study. There are studies in the literature indicating that more complex PHF is seen in older patients.[10] In our study, the severity of PHF is not affected by age in elderly population.

Our study have some limitations. Firstly, the sample size of our study was small. Secondly, we did not use any positioning tool while taking radiographs. Thirdly, the body mass index (BMI) of the patients was not evaluated. The fact that radiography is cheaper than other imaging methods makes our study cost effective. The relationship between cortical index and PHF can be better clarified with further studies and larger patient groups.

Conclusion

Humeral CI is a good parameter in determining the risk of PHF in the population over 65 years. The risk of PHF increased 3.2 times in patients with humeral CI lower than 0.3267. However, humeral CI does not affect the severity of PHF.

References

1. Palvanen M, Kannus P, Niemi S, Parkkari J. Update in the epidemiology of proximal humeral fractures. Clin Orthop Relat Res 2006;442:87–92.
2. Bell J-E, Leung BC, Spratt KF et al. Trends and variation in incidence, surgical treatment, and repeat surgery of proximal humeral fractures in the elderly. J Bone Joint Surg Am 2011;93:121–131.
3. Obrant KJ, Bengne´r U, Johnell O, Nilsson BE, Sernbo I. Increasing age-adjusted risk of fragility fractures: a sign of increasing osteoporosis in successive generations? Calcif Tissue Int 1989;44:157–167.
4. Resch H. Proximal humeral fractures: current controversies. J Shoulder Elbow Surg 2011;20:827–832.
5. Yang GY, Xiang M, Chen H, Hu XC. Short-term clinical outcome of proximal humeral fractures using Multiloc proximal humeral nail. Chin J Orthop, 2016, 36: 103–112.
6. Passaretti D, Candela V, Sessa P, Gumina S. Epidemiology of proximal humeral fractures: a detailed survey of 711 patients in a metropolitan area. J Shoulder Elbow Surg, 2017, 26: 2117–2124.
7. Xiang M, Hu XC, Jiang CY. Pay attention to the whole concept and improve the diagnosis and treatment of proximal humeral fracture. Chin J Orthop, 2017, 37: 1313–1317.
8. Maravic M, Le Bihan C, Landais P, Fardellone P. Incidence and cost of osteoporotic fractures in France during 2001. A methodological approach by the national hospital database. Osteoporos Int 2005;16:1475–1480
9. Lee S, Dargent-Molina P, Bre´art G. EPIDOS Group. Epidemiologie de l'Osteoporose Study. Risk factors for fractures of the proximal humerus: results from the EPIDOS prospective study. J Bone Miner Res 2002;17:817–825
10. Court-Brown C, Garg A, McQueen M. The epidemiology of proximal humeral fractures. Acta Orthop Scand 2001;72:365–371
11. Kavuri V, Bowden B, Kumar N, Cerynik D. Complications Associated with Locking Plate of Proximal Humerus Fractures. Indian J Orthop. 2018 Mar-Apr;52(2):108-116
12. Bell KL, Loveridge N, Power J et al. Intracapsular hip fracture: increased cortical remodeling in the thinned and porous anterior region of the femoral neck. Osteoporos Int 1999;10:248–257
13. Baumgartner R, Heeren N, Quast D et al. Is the cortical thickness index a valid parameter to assess

bone mineral density in geriatric patients with hip fractures? Arch Orthop Trauma Surg 2015;135:805–810
14. Neer CS., II Displaced proximal humeral fractures. I. Classification and evaluation. J Bone Joint Surg [Am] 1970;52-A:1077-1089.
15. Carofino BC, Leopold SS. Classifications in brief: the Neer classification for proximal humerus fractures. Clin Orthop Relat Res 2013;471:39-43.
16. Matsumura N, Furuhata R, Seto T, Takada Y, Shirasawa H, Oki S, Kawano Y, Shiono S. Reproducibility of the modified Neer classification defining displacement with respect to the humeral head fragment for proximal humeral fractures. J Orthop Surg Res. 2020 Sep 23;15(1):438.
17. Brorson S, Hróbjartsson A. Training improves agreement among doctors using the Neer system for proximal humeral fractures in a systematic review. J Clin Epidemiol 2008;61:7-16.
18. Skedros JG, Mears CS, Burkhead WZ. Ultimate fracture load of cadaver proximal humeri correlates more strongly with mean combined cortical thickness than with areal cortical index, DEXA density, or canal-to-calcar ratio. Bone Joint Res. 2017 Jan;6(1):1-7.
19. Woolf S.H., Schoomaker H. Life expectancy and Mortality rates in the United States, 1959-2017. JAMA. 2019;322:1996–2016.
20. Khatib O., Onyekwelu I., Zuckerman J.D. The incidence of proximal humeral fractures in New York State from 1990 through 2010 with an emphasis on operative management in patients aged 65 years or older. J Shoulder Elbow Surg. 2014;23:1356–1362.
21. Tingart, M. J., Apreleva, M., von Stechow, D., Zurakowski, D. The cortical thickness of the proximal humeral diaphysis predicts bone mineral density of the proximal humerus. Journal of Bone and Joint Surgery British, 2003;85(4), 611–617.
22. Hepp, P., Theopold, J., Osterhoff, G., Marquass, B., Voigt, C. Bone quality measured by radiogrammetric parameter “cortical index” and reoperations after locking plate osteosynthesis in patients sustaining proximal humerus fractures. Archives of Orthopedic and Trauma Surgery, 2009;129(9), 1251–1259.
23. Spross, C., Kaestle, N., Benninger, E., Fornaro, J., Erhardt, J., Zdravkovic, V., et al. Deltoid tuberosity index: a simple radiographic tool to assess local bone quality in proximal humerus fractures. Clinical Orthopaedics and Related Research, 2015;473(9), 3038–3045.
24. Jain S, Arora S, Gupta S, Sharma S, Bansal N, Ranjan S. Assessment of Bone Quality Using Radiogrammetric Parameters of Proximal Humerus in India: Defining the Osteoporotic Fracture Risk Limit Value and its Reliability. Indian J Orthop. 2020 Aug 9;54(Suppl 2):307-315.
25. Osterhoff G, Diederichs G, Tami A, Theopold J, Josten C, Hepp P. Influence of trabecular microstructure and cortical index on the complexity of proximal humeral fractures. Arch Orthop Trauma Surg. 2012 Apr;132(4):509-15.

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RESEARCH ARTICLE

Perinatal outcomes of choroid plexus cysts in a high-risk pregnant population: A tertiary center experience

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Abstract

Introductıon: The objective of this study was to present the results of fetuses followed up for choroid plexus cysts(CPC) in our clinic and to provide an additional benefit to the existing literature.

Methods: This is a retrospective cohort study conducted in Ankara Bilkent City Hospital perinatology clinic. All pregnant women who were followed up with a antenatally diagnosed choroid plexus cyst between 2021 and 2023 were included in the study. Demographic characteristics, prenatal ultrasound findings, non-invasive screening test results, invasive diagnostic test results, clinical management and postnatal outcomes were evaluated and compared between unilateral CPC group and bilateral CPC group.

Results: A comparison between unilateral and bilateral groups revealed no significant differences in maternal age, gravidity, parity, or number of abortions. However, the week of diagnosis was found to be smaller in the group with bilateral choroid plexus cysts (p=0.004). Patients undergoing invasive testing were higher in the bilateral CPC group, although these differences were not statistically significant. There was no statistically significant difference between the groups in terms of pregnancy termination rate, gestational week at delivery, neonatal weight, NICU admission, and APGAR scores. The group with additional anomalies exhibited a higher rate of high-risk screening tests, a higher rate of anomaly detection in invasive tests, and a higher rate of pregnancy termination. Nevertheless, these differences were not statistically significant

Conclusion: In conclusion, fetal choroid plexus cysts represent a risk factor for aneuploidy when associated anomalies are present.

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Introduction

The choroid plexus begins to develop at approximately six to seven weeks of gestation and fills approximately 75 percent of the lateral ventricular cavity by 9 weeks of gestation. Choroid plexus cysts (CPCs) are pseudocysts in the fetal choroid plexus.[1] They are diagnosed in approximately 1% of fetuses in the first and second trimesters of pregnancy during routine prenatal ultrasound scans.[2,3] The typical sonographic appearance is that of smoothly circumscribed, anechoic structures. Cysts may be unilateral, bilateral, bilobulated, or multiple.[4] Approximately 90% of cysts disappear after 28 weeks of gestation, and only a few show progressive enlargement.[5] In the absence of additional central nervous system abnormalities or other systemic abnormalities and risk factors for chromosomal aneuploidy, isolated choroid plexus cysts are considered a variant of normal. The shape, size, or laterality of the choroid plexus cyst is considered to be of no clinical significance. Fetuses with additional anomalies are at increased risk for chromosomal abnormalities, especially trisomy 18.

Several studies have demonstrated that patients with fetal isolated choroid plexus cysts exhibit favorable outcomes and no abnormalities in long-term follow-up after birth. A systematic review of several studies of children with a history of isolated choroid plexus cysts followed up until adolescence revealed no association with adverse health and neurodevelopmental outcomes.[6,7] However, due to the limited number of cases, the potential for selection bias, the lack of a clear definition, and the absence of a control group in these studies, the long-term prognosis remains uncertain. Furthermore, studies and case reports published in the last 20 years have indicated that CPCs may be associated with an increased risk of verbal learning difficulties and suboptimal neurodevelopment.[8,9]

The objective of this study was to present the results of fetuses followed up for choroid plexus cysts in our clinic and to provide an additional benefit to the existing literature.

Material and Methods

This retrospective cohort study was conducted on all consecutive prenatally detected choroid plexus cyst cases followed in Ankara Bilkent City Hospital's perinatology clinic between January 2021- August 2023. The study protocol was approved by the ethics committee with the reference number E2-23-5192 and all participants gave written consent. Non-invasive screening test results, invasive diagnostic test results, demographic features, prenatal ultrasound findings, and postnatal outcomes were reported.

All ultrasound assessments were made with Voluson E10 with a 2-9 Mhz abdominal convex probe by the same expert perinatologist (D.S.). The diagnostic criterion for choroid plexus cyst was the presence of a cyst with a diameter >5mm within the choroid plexus that could be detected by ultrasound. The first fetal ultrasound screening was performed at 14th-18th week of gestation and more ultrasound screenings were performed 2 weeks intervally until the time of delivery. Fetuses with major central nervous system anomalies were excluded.

The cases were initially stratified into two groups: fetuses with unilateral and bilateral choroid plexus cysts. A comparative analysis was conducted between these two groups, focusing on maternal characteristics, the presence of chromosomal abnormalities, and neonatal outcomes. Subsequently, the cases were divided into those with and without additional structural anomalies, and similar comparisons were made between these groups.

The statistical analysis was performed by SPSS 22 (IBM Corp., NY). Kolmogrov-Smirnov test was used to assess whether the data is normally distributed. Mean and standard deviation values were used for normally distributed continuous variables. Whereas, median and range values were used to present continuous variables without normal distribution. Categorical variables were presented as numbers and percentages.

Results

A total of 60 patients were included in the study. A total of 32 patients presented with a unilateral choroid plexus cyst (CPC), while 28 patients had bilateral CPC. In addition, 46 patients exhibited additional anomalies, while 14 patients presented with CPC as an isolated finding.

In the comparison between unilateral and bilateral groups, no significant difference was observed in terms of maternal age, gravidity, parity and number of abortions, whereas the week of diagnosis was found to be smaller in the group with bilateral choroid plexus cyst (p=0.004). The rate of high-risk in the first and second trimester aneuploidy screening test and the rate of aneuploidy detection in patients undergoing invasive testing were higher in the bilateral CPC group, although these differences were not statistically significant.

There was no statistically significant difference between the groups in terms of pregnancy termination rate, gestational week at delivery, neonatal weight, NICU admission, and APGAR scores. Table 1 presents a summary of the comparison of maternal characteristics, screening test and invasive test results, and obstetric outcomes in cases with unilateral and bilateral choroid plexus cysts.

Table 1. The comparison of maternal characteristics, screening test and invasive test results, and obstetric outcomes in cases with unilateral and bilateral choroid plexus cysts

	Unilateral (n=32) Mean ± SD	Bilateral (n=28) Mean ± SD	P
Age	30 ± 6.3	31.6 ±5.6	0.3
Gravidity	2.3 ± 1.2	2.1 ± 1.09	0.52
Parity	1.2 ±1.1	0.89±0.83	0.2
Abortus	0.5±0.9	0.6±0.9	0.45
Gestational age at diagnosis	20.2±5.3	16.9±3.2	**0.004**
Additional anomaly	67.9%	84.4%	0.13
High risk on first trimester aneuploidy scan	9.4%	21.4%	0.37
High risk on second trimester aneuploidy scan	0%	21.4%	0.019
Aneuploidy at invasive test result	18.8%	35.7%	0.29
TOP	3.6%	6.3%	0.45
NICU admission	23.3%	22.1%	0.92
Gestational age at birth	36.2±5.1	35.8±4.9	0.76
Newborn weight	2813±992	2636±804	0.45
APGAR 1	6.7±1.7	6.1±1.8	0.26
APGAR 5	8.2±1.3	7.6±1.8	0.16

$p<0.05$ accepted as statistically significant.
TOP: termination of pregnancy. NICU: neonatal intensive care unit.

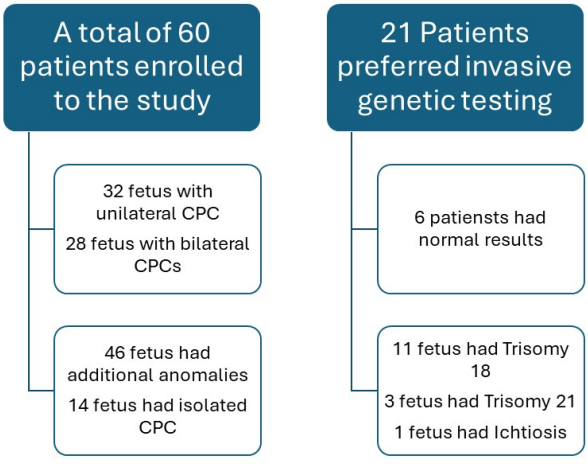
When the groups with and without additional anomalies were compared, no significant differences were observed between the groups in terms of maternal characteristics and neonatal outcomes. However, the group with additional anomalies exhibited a higher rate of high-risk screening tests, a higher rate of anomaly detection in invasive tests, and a higher rate of pregnancy termination. Nevertheless, these differences were not statistically significant. The results of the comparison between the groups with and without additional anomalies are presented in Table 2.

Table 2 The comparison of maternal characteristics, screening test and invasive test results, and obstetric outcomes between the groups with and without additional anomalies

	No additional anomaly (n=14) Mean ± SD	With additional anomaly (n=46) Mean ± SD	P
Age	29.2±4.9	31.2±6.3	0.29
Gravidity	2.4±1.2	2.2±1.1	0.6
Parity	1±0.9	1±1	0.98
Abortus	0.8±1.2	0.5±0.7	0.32
Gestational age at diagnosis	17±4	18±4	0.48
High risk on first trimester aneuploidy scan	7.1%	17.4%	0.26
High risk on second trimester aneuploidy scan	8.7%	14.3%	0.81
Aneuploidy at invasive test result	14.3%	30.4%	0.11
TOP	4.3%	7.1%	0.51
NICU admission	22.7%	23.1%	0.97
Gestational age at birth	34.5±5.8	36.5±4.7	0.19
Newborn weight	2509±938	2798±896	0.3
APGAR 1	6.7±1.6	6.3±1.8	0.51
APGAR 5	8.1±1	7.8±1.7	0.6

A total of 21 patients underwent invasive testing. Six patients exhibited a normal karyotype, 11 had trisomy 18, three had trisomy 21, and one had ichthyosis. One patient underwent cell-free DNA testing, which yielded a result of trisomy 21. However, the patient declined amniocentesis.

A flowchart illustrating the ultrasound features and invasive findings of choroid plexus cysts in Figure 1.



In addition, the following anomalies were observed: ventriculomegaly in seven fetuses, renal pelviectasis in three fetuses, left heart hypoplasia in two fetuses, bilateral clubfoot in two fetuses, cleft lip and palate in two fetuses, single umbilical artery in two fetuses, corpus callosum dysgenesis in two fetuses, and nasal bone hypoplasia in two fetuses. One fetus exhibited an atrioventricular septal defect, one had a double outlet right ventricle, one had radial aplasia and hemivertebra, one had cataracts, one had megacystis, one had arrhythmia, one had a mega cisterna magna, and one had ambiguous genitalia.

Discussion

Fetal choroid plexus cysts are formed when cerebrospinal fluid is trapped in the choroid plexus and are typically identified during the second trimester ultrasound examination. Choroid plexus cysts are not considered to be a brain anomaly. However, various studies have demonstrated that they may be associated with aneuploidies.

When identified as a solitary finding, it is advised that choroid plexus cysts be regarded as a benign phenomenon. In a study in which 12,672 patients were screened and 336 choroid plexus cysts were detected, it was reported that the presence of additional structural abnormalities was observed in all cases with aneuploidy. It was determined that amniocentesis was not necessary in patients without additional anomalies.[6] In a separate study, in which ultrasound findings of fetuses with trisomy 18 were analyzed, choroid plexus cysts were detected in approximately half of the cases. However, in no case was this finding isolated.[10] A systematic review was conducted to examine the neurodevelopmental outcomes of children who were followed with isolated choroid plexus cysts and delivered at birth. The results demonstrated that there were no significant neurodevelopmental effects in these cases.[11] In a separate study examining the relationship between trisomy 18 and choroid plexus cysts, the analysis concluded that in order to identify one case of trisomy 18 in cases with isolated choroid plexus cysts, 477 fetuses with a normal karyotype would require amniocentesis. In consideration of the established risk of fetal loss associated with amniocentesis, it was estimated that two normal fetuses would be lost in order to diagnose one fetus with trisomy 18.[12]

In the present study, although the rate of aneuploidy detection by amniocentesis was higher in fetuses with additional anomalies compared to isolated CPC cases, this difference was not statistically significant. This result is partially consistent with the findings of previous studies in the literature. As the study was based on data from a perinatology clinic, the majority of patients were from the high-risk population. Consequently, the majority of cases exhibited associated anomalies. The lack of statistical significance may be attributed to the relatively small sample size and the fact that additional anomalies were not classified as major or minor structural anomalies.

Choroid plexus cysts may be single or multiple, unilateral or bilateral, septate or simple cysts, and typically measure less than 10 mm in diameter. These cysts, which have been demonstrated to be associated with aneuploidy in various studies, manifest in diverse forms, prompting the inquiry into the relationship between the characteristics of the cysts and aneuploidy.

A study of 435 CPC cases revealed that the aneuploidy rates of unilateral and bilateral CPC cases were comparable, although slightly higher in the bilateral group.[13] However, in a patient with no additional risk factors and only sonographic findings of bilateral large choroid plexus cysts, trisomy 18 was diagnosed by amniocentesis.[14] Similarly, a case report describes a patient with trisomy 21 and bilateral choroid plexus cysts as the only ultrasound finding.[15] Nevertheless, it is generally believed that choroid plexus cysts do not increase the risk of Down syndrome when detected as an isolated finding.[16,17] In a study of significant importance in this field, it was found that the presence of bilateral cysts had no effect on the risk of aneuploidy.[18] In the present study, the rate of aneuploidy detection by invasive testing was found to be higher in the bilateral CPC group than in the unilateral CPC group. However, this difference was not found to be statistically significant. The higher rate of aneuploidy detection in the bilateral CPC group may be attributed to the higher prevalence of concomitant anomalies and the higher rate of high-risk detection in screening tests. A comparison of isolated cases of CPC would have yielded more significant results in this regard. However, given that the patients in our study group were high-risk pregnant women, the majority of them exhibited associated anomalies.

In conclusion, fetal choroid plexus cysts represent a risk factor for aneuploidy when associated anomalies are present. Consequently, when such a cyst is

identified, a comprehensive anatomical examination and a meticulous evaluation of the patient's previous risk of aneuploidy should be conducted. In the event that genetic diagnosis is deemed necessary, patients should be referred for such testing. In instances where it is confirmed that the cyst is isolated, it is similarly crucial to avoid exacerbating the distress of the family.

The principal limitation of our study is its retrospective design and the relatively small number of patients included. However, the study also has notable strengths, including the evaluation of the relationship between bilaterality and the presence of concomitant anomalies in a single investigation.

References

1. Kraus I, Jirásek JE. Some observations of the structure of the choroid plexus and its cysts. Prenat Diagn. 2002;22(13):1223-1228. doi:10.1002/pd.486
2. Hurt L, Wright M, Dunstan F, et al. Prevalence of defined ultrasound findings of unknown significance at the second trimester fetal anomaly scan and their association with adverse pregnancy outcomes: the Welsh study of mothers and babies population-based cohort. Prenat Diagn. 2016;36(1):40-48. doi:10.1002/pd.4708
3. Demasio K, Canterino J, Ananth C, Fernandez C, Smulian J, Vintzileos A. Isolated choroid plexus cyst in low-risk women less than 35 years old. Am J Obstet Gynecol. 2002;187(5):1246-1249. doi:10.1067/mob.2002.127463
4. Epelman M, Daneman A, Blaser SI, et al. Differential diagnosis of intracranial cystic lesions at head US: correlation with CT and MR imaging. Radiogr Rev Publ Radiol Soc N Am Inc. 2006;26(1):173-196. doi:10.1148/rg.261055033
5. Lopez JA, Reich D. Choroid plexus cysts. J Am Board Fam Med JABFM. 2006;19(4):422-425. doi:10.3122/jabfm.19.4.422
6. Coco C, Jeanty P. Karyotyping of fetuses with isolated choroid plexus cysts is not justified in an unselected population. J Ultrasound Med Off J Am Inst Ultrasound Med. 2004;23(7):899-906. doi:10.7863/jum.2004.23.7.899
7. Bronsteen R, Lee W, Vettraino IM, Huang R, Comstock CH. Second-trimester sonography and trisomy 18: the significance of isolated choroid plexus cysts after an examination that includes the fetal hands. J Ultrasound Med Off J Am Inst Ultrasound Med. 2004;23(2):241-245. doi:10.7863/jum.2004.23.2.241
8. Bernier FP, Crawford SG, Dewey D. Developmental outcome of children who had choroid plexus cysts detected prenatally. Prenat Diagn. 2005;25(4):322-326. doi:10.1002/pd.1135
9. Leitner Y, Goez H, Gull I, et al. Antenatal diagnosis of central nervous system anomalies: can we predict prognosis? J Child Neurol. 2004;19(6):435-438. doi:10.1177/088307380401900607
10. Yeo L, Guzman ER, Day-Salvatore D, Walters C, Chavez D, Vintzileos AM. Prenatal detection of fetal trisomy 18 through abnormal sonographic features. J Ultrasound Med Off J Am Inst Ultrasound Med. 2003;22(6):581-590; quiz 591-592. doi:10.7863/jum.2003.22.6.581
11. Singal K, Adamczyk K, Hurt L, Woolner A, Paranjothy S. Isolated choroid plexus cysts and health and developmental outcomes in childhood and adolescence - A systematic review. Eur J Obstet Gynecol Reprod Biol. 2023;290:115-122. doi:10.1016/j.ejogrb.2023.09.013
12. Benacerraf BR, Harlow B, Frigoletto FD. Are choroid plexus cysts an indication for second-trimester amniocentesis? Am J Obstet Gynecol. 1990;162(4):1001-1006. doi:10.1016/0002-9378(90)91304-u
13. Beke A, Barakonyi E, Belics Z, et al. Risk of chromosome abnormalities in the presence of bilateral or unilateral choroid plexus cysts. Fetal Diagn Ther. 2008;23(3):185-191. doi:10.1159/000116739
14. Sharma A, Dadhwal V, Rana A, Chawla J. Isolated large bilateral choroid plexus cysts associated with trisomy 18. BMJ Case Rep. 2019;12(3):e229216. doi:10.1136/bcr-2019-229216
15. Rotmensch S, Luo JS, Nores JA, Dimaio MS, Hobbins JC. Bilateral choroid plexus cysts in trisomy 21. Am J Obstet Gynecol. 1992;166(2):591-592. doi:10.1016/0002-9378(92)91680-9
16. Bromley B, Lieberman R, Benacerraf BR. Choroid plexus cysts: not associated with Down syndrome. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 1996;8(4):232-235. doi:10.1046/j.1469-0705.1996.08040232.x
17. Yoder PR, Sabbagha RE, Gross SJ, Zelop CM. The second-trimester fetus with isolated choroid plexus cysts: a meta-analysis of risk of trisomies 18 and 21. Obstet Gynecol. 1999;93(5 Pt 2):869-872. doi:10.1016/s0029-7844(98)00544-4
18. Gupta JK, Cave M, Lilford RJ, et al. Clinical significance of fetal choroid plexus cysts. Lancet Lond Engl. 1995;346(8977):724-729. doi:10.1016/s0140-6736(95)91502-8

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CASE REPORT

Abdominoscrotal hydrocele: A case report of a young adult treated with laparoscopy

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Abstract

Abdominoscrotal hydrocele (ASH) is a rare condition characterized by interconnected abdominal and scrotal components, resembling the appearance of an hourglass, which can occur in both pediatric and adult populations. Although its pathophysiology remains incompletely elucidated, it involves an increase in fluid pressure within the tunica vaginalis, resulting in the progression of fluid along the inguinal canal towards the abdomen and the formation of an abdominal sac. Due to the potential for various complications such as hydronephrosis and lymphedema in the leg secondary to compression effects, early surgical intervention is generally recommended. The presentation aims to demonstrate a case of ASH successfully managed through laparoscopic excision.

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Introduction

Abdominoscrotal hydrocele (ASH) is a rare medical condition characterized by interconnected, fluid-filled scrotal and abdominal sacs, constituting approximately 0.4-3.1% of all hydroceles.[1] While ASH predominantly affects children, it can also impact adults. Despite its low incidence, it can lead to serious complications due to compression effects.[2] Surgical intervention stands out among treatment options. Laparoscopic surgery has emerged as a preferred method for ASH treatment in recent years.[3] This approach offers a minimally invasive option, resulting in reduced postoperative pain and shorter recovery times for the patient. This report aims to present a case of ASH successfully treated using laparoscopic techniques.

Case

An 18-year-old male patient presented to the urology outpatient clinic of a tertiary hospital with a complaint of left-sided scrotal swelling for the past 8 years and abdominal pain for the last 3 years. He had no other symptoms such as changes in bowel or bladder habits, and no known comorbidities. Examination revealed a left-sided scrotal hydrocele and a large swelling covering the left lower abdominal region (Figure 1).

Figure 1

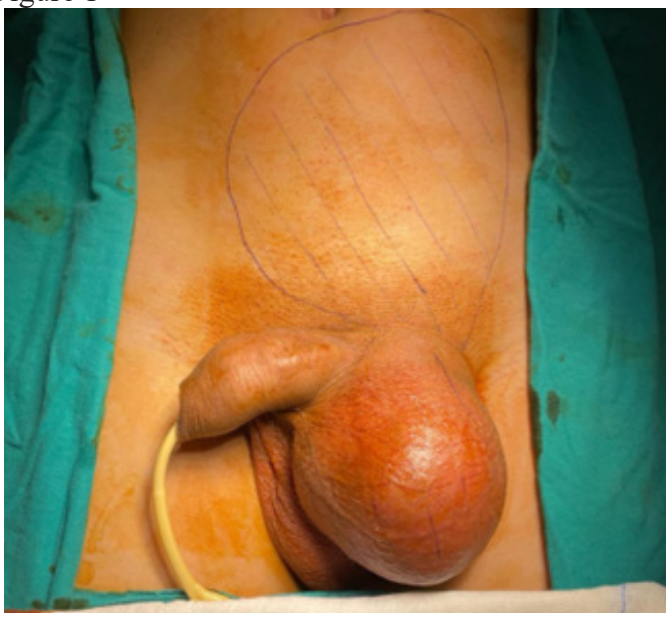

Figure 1: The marked area showed the boundaries of the hydrocele sac palpated during the physical examination.

The abdominal swelling was soft, non-tender, and had a smooth surface. Ultrasonography of the abdomen and scrotum revealed a large hypoechoic collection extending from the left lower abdomen to the left inguinoscrotal region, originating from the umbilicus. Bilateral testes appeared normal, and levels of AFP, total hCG, and LDH were within normal limits. Abdominal computed tomography showed a large hypodense retroperitoneal cystic lesion, measuring 26 x 14 cm, extending from the left side of the abdomen to the scrotum via the inguinal canal (Figure 2).

Figure 2

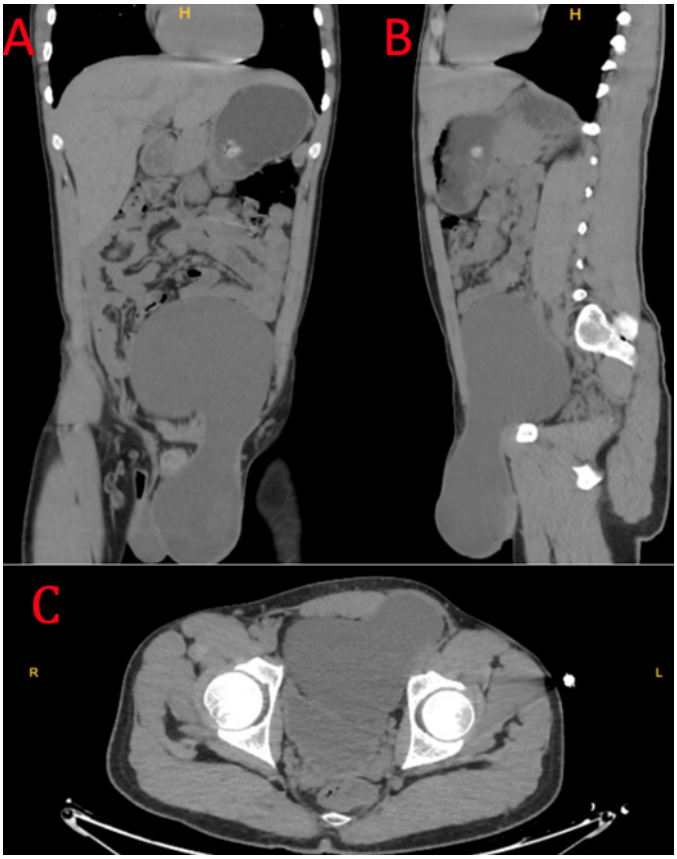

Figure 2: The hourglass appearance of the abdominoscrotal hydrocele sac in the coronal (A) and sagittal (B) section and the bladder displaced by the abdominal hydrocele sac in the transverse (C) section image of the computed tomography.

It extended anteriorly up to the anterior abdominal wall and displaced the bladder to the right side. Therefore, surgical intervention was planned. Due to its minimally invasive nature, laparoscopic technique was preferred. Pneumoperitoneum was created by entering the intraperitoneal space through an open technique from the supraumbilical region. A large retroperitoneal cystic lesion extending from the umbilicus to the inguinal canal, covering a significant portion of the left half of the abdomen, was observed (Figure 3).

Figure 3

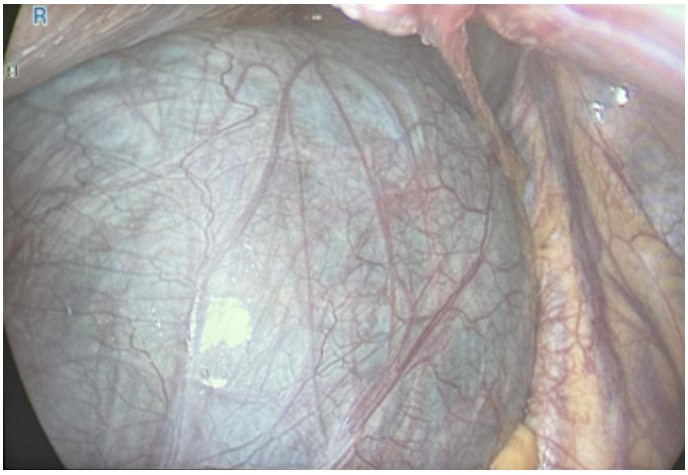

Figure 3: The laparoscopic view of the extension of the hydrocele sac into the inguinal canal.

Due to the size of the cyst and inadequate access for dissection, decompression of the cyst was decided. Using a needle inserted transcutaneously from the scrotum, 3000 mL of clear yellow fluid was aspirated. The wall of the cyst was dissected from the lateral abdominal wall, preserving testicular vascular structures and vas deferens, and separated from the spermatic cord. The scrotal portion of the cyst was excised through a subinguinal incision, completely removing the hydrocele sac. The patient was discharged without complications two days later. Histopathological examination revealed no neoplasm. There was no recurrence observed in the abdomen or scrotum during one year of follow-up.

Discussion

Hydrocele is defined as the accumulation of fluid between the visceral and parietal layers of the tunica vaginalis.[4] It occurs in different pathophysiological conditions, including primary hydrocele, secondary hydrocele, and cord hydrocele. ASH represents a rare subgroup, characterized by its connection between the abdominal component and the scrotum through a narrow neck covering the inguinal canal, resembling an hourglass appearance. It was first described by Dupuytren in 1834 as "hydrocoele en bissac".[5] This rare condition can occur in both children and adults. While the exact pathophysiology of ASH remains incompletely understood, several hypotheses exist.[6,7] The most plausible hypothesis involves an increase in intraluminal pressure within the proximal processus vaginalis associated with scrotal hydrocele, leading, in accordance with Laplace's law, to progression along the spermatic cord to the inguinal canal and expansion into the abdomen. Other hypotheses suggest upward extension of the hydrocele sac due to excessive intrascrotal pressure resulting from a one-way valve mechanism directing abdominal fluid towards the inguinal canal, causing obliteration of the processus vaginalis at a higher level.

Diagnosis is typically based on clinical examination, including palpation of a mass above the inguinal ring and observation of fluid movement between the abdomen and scrotum upon compression. The presence of the "springing back ball" sign and hourglass transillumination are diagnostic for ASH.[8] The abdominal and scrotal sacs may contain liters of fluid. Differential diagnosis may include mesenteric and enteric duplication cysts, massive hydronephrosis extending into the pelvis, bladder diverticulum, and cystic neoplasms. Imaging techniques such as ultrasonography, CT, and MRI may be utilized in the differential diagnosis.

Open scrotal surgery is commonly employed in the treatment of scrotal hydrocele. Due to its rarity, there is a lack of guideline information regarding treatment options for ASH. Complications associated with ASH, such as hydronephrosis, leg edema, testicular atrophy, and rarely, testicular and paratesticular malignancy, have been reported.[2] Although displacement of the bladder was observed in this case, the patient remained asymptomatic. Early surgical intervention is generally considered an appropriate treatment option to prevent complications resulting from mass effect on the testis and intra-abdominal organs.[9] While cases of conservative management have been reported in children, most eventually underwent surgery.[10] Spontaneous regression is not expected in adults. While initial reports described open surgical excision of scrotal and abdominal components, laparoscopic surgical options have become increasingly preferred in recent times.[3] Adhesion of the hydrocele sac to the spermatic cord due to thickening requires careful dissection during surgery.

In conclusion, ASH, although rare, is a condition that warrants clinical attention. Standardized guidelines for its treatment are lacking, necessitating a case-by-case approach. Diagnosis relies on a combination of clinical examination and imaging modalities. The use of laparoscopic technique as a minimally invasive approach may be preferred for surgical management. Further research is needed to determine optimal management strategies and guidelines for ASH.

References

1. Nagar H, Kessler A. Abdominoscrotal hydrocele in infancy: a study of 15 cases. Pediatr Surg Int. 1998;13(2-3):189-190. doi:10.1007/s003830050286
2. Gadelkareem RA. Abdominoscrotal hydrocele: A systematic review and proposed clinical grading. African Journal of Urology. 2018;24(2):83-92. doi:10.1016/j.afju.2018.01.006
3. Funatsu Y, Shono K, Hashimoto Y, Shirai T, Shono T. Laparoscopic Abdominoscrortal Hydrocele: A Case Series. Urology. 2020;145:236-242. doi:10.1016/j.urology.2020.07.032
4. Kapur P, Caty MG, Glick PL. PEDIATRIC HERNIAS AND HYDROCELES. Pediatr Clin North Am. 1998;45(4):773-789. doi:10.1016/S0031-3955(05)70044-4
5. G Dupuytren. De l'hydrocèle et de ses principales variétés. Leçons orales de clinique chirurgicale. Published online 1834.
6. Celayir AC, Akyüz Ü, Çiftlik H, Gürbüz A, Danişmend N. A critical observation about the pathogenesis of abdominoscrotal hydrocele. J Pediatr Surg. 2001;36(7):1082-1084. doi:10.1053/jpsu.2001.24760
7. Bayne A, Paduch D, Skoog SJ. Pressure, Fluid and Anatomical Characteristics of Abdominoscrotal Hydroceles in Infants. Journal of Urology. 2008;180(4S):1720-1723. doi:10.1016/j.juro.2008.04.086
8. Wlochynski T, Wassermann J, Generowicz Z. Abdominoscrotal hydrocele in childhood. J Pediatr Surg. 1993;28(2):248-250. doi:10.1016/S0022-3468(05)80286-6
9. Doudt AD, Kehoe JE, Ignacio RC, Christman MS. Abdominoscrotal hydrocele: A systematic review. J Pediatr Surg. 2016;51(9):1561-1564. doi:10.1016/j.jpedsurg.2016.06.012
10. Ceccanti S, de Vito C, Migliara G, Cozzi DA. Early Surgery Versus Watchful Waiting Strategy for Infantile Abdominoscrotal Hydrocele. J Pediatr Surg. 2023;58(11):2238-2243. doi:10.1016/j.jpedsurg.2023.05.020

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CASE REPORT

Add-on Erythromycin and Tacrolimus Treatment for Primary Sjogren's Syndrome-Related Immune Thrombocytopenia: A Case Report

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Abstract

A 64-year-old woman with primary Sjogren's syndrome (SjS) was admitted to our hospital for nasal bleeding, oral bleeding, and purpura on her entire body. On this admission, laboratory findings were as follows: white blood cell counts, 8,910 /μL; hemoglobin, 9.9 g/dL; and platelet (PLT) counts, 0.1×10^4/μL. Although the anti-PLT antibodies were positive, other autoimmune antibodies including anti-deoxyribonucleic acid antibodies were negative. No immunoglobulin (Ig)M antibodies for cytomegalovirus and Parvovirus B19, and no IgG antibodies for Helicobacter pylori, were detected. No abnormal findings suggestive of infection were identified in the systemic examination. A bone marrow aspiration smear revealed normal bone marrow. Based on these findings, the patient was diagnosed with primary SjS-related immune thrombocytopenia (ITP). The patient initially received intravenous immunoglobulin, methyl prednisolone (PSL) pulse therapy, and subsequent high dose PSL without significant improvement. Therefore, eltrombopag was added. Subsequently, erythromycin (EM) was also added, considering its immunomodulatory effects. After initiating the EM treatment, the PLT counts increased. Therefore, the PSL dosage was reduced. However, the PLT counts gradually decreased. Instead of increasing the PSL dosage again, tacrolimus (TAC) was successfully added. Consequently, the PSL dosage could be successfully reduced. This case suggests that EM and TAC can be effective alternatives when conventional immunosuppressants fail to improve primary SjS-related ITP.

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Introduction

Sjogren's syndrome (SjS) is a systemic autoimmune disease characterized by a wide spectrum of clinical manifestations. Immune thrombocytopenia (ITP) is a common clinical manifestation of SjS and causes hemorrhagic events. The mechanism of ITP in SjS is due to anti-platelet (PLT) autoantibody-induced peripheral PLT destruction and splenic sequestration, as well as reduced PLT production by impaired megakaryocytes caused by anti-PLT autoantibodies.[1] Corticosteroids supplemented with immunoglobulin (Ig) are the first-line treatments for SjS-related ITP, while second-line treatments including danazol, cyclosporin A, azathioprine, eltrombopag (ELT), and rituximab have been proposed. However, clinical trials evaluating their efficacy and safety in patients with SjS-related ITP are not documented.[1] Erythromycin (EM), a macrolide (MAC), provides not only anti-bacterial activities but also immunomodulatory effects. Similarly, tacrolimus (TAC), a calcineurin inhibitor and MAC, also provides immunomodulatory effects. Recently, successful cases of ITP using these two drugs have been reported. Herein, we report a case of refractory primary SjS-related ITP treated using EM and TAC.

Case

A 64-year-old woman with primary SjS which was not treated, was admitted to our hospital for nasal bleeding, oral bleeding, and purpura on her entire body. She was diagnosed with primary SjS at the age of 53 years old, based on xerophthalmia, xerostomia, positive results for the Shirmer test and anti-Sjogren's syndrome antigen A antibodies, and abnormal salivary gland scintigraphy. When she visited our hospital for a routine consultation 3 months ago, her PLT count was $20.7\times10^4/\mu L$. This time, laboratory findings were as follows: white blood cell counts, 8,910 /μL (basophils, 0.1%; eosinophils, 0.3%; neutrophils, 74.3%; lymphocytes, 22.6%; and monocytes, 2.7%); hemoglobin, 9.9 g/dL; PLT counts, $0.1\times10^4/\mu L$; C-reactive protein, 0.32 mg/dL; IgG, 3,721 mg/dL; IgM, 244 mg/dL; and IgA, 408 mg/dL. Although the anti-PLT antibodies were positive, other autoimmune antibodies such as anti-deoxyribonucleic acid and anti-cardiolipin IgG antibodies were negative. Moreover, no IgM antibodies for cytomegalovirus and Parvovirus B19, and no IgG antibodies for Helicobacter pylori, were detected. Prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrin degradation products were all within normal levels. A bone marrow aspiration smear revealed normal bone marrow with a nucleated cell count of $15.1\times10^4/\mu L$ and a megakaryocyte count of 53/μL without dysplasia or hemophagocytosis. Furthermore, the number of megakaryocytes was adequate in the specimen (Figure 1). No abnormal findings suggestive of infection were identified in the systemic examination, including the chest X-ray film and urinalysis. Based on these findings, the patient was diagnosed with primary SjS-related ITP. The clinical course is shown in (Figure 2).

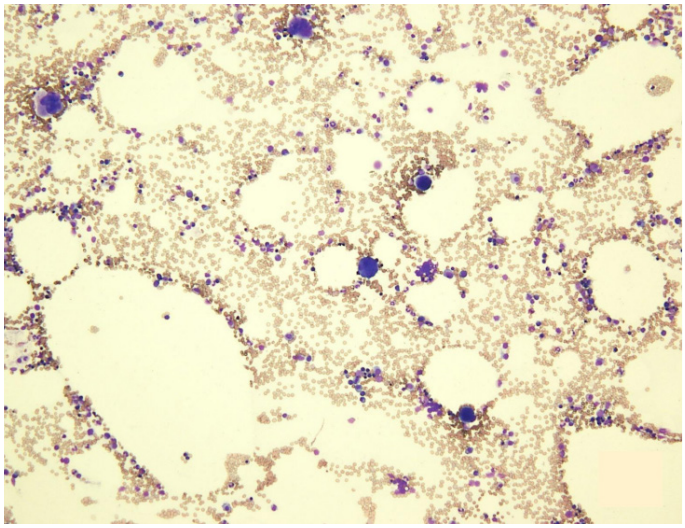

Figure 1. Bone marrow aspiration smear reveals sufficient numbers of megakaryocytes (May-Giemsa stain, magnification ×100).

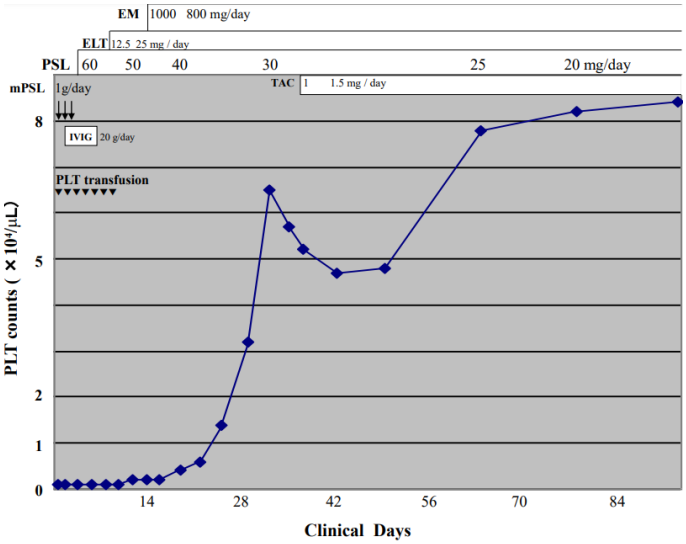

Figure 2. Laboratory data and prescribed agents on clinical days.
PLT: platelet, mPSL: methyl prednisolone, PSL: prednisolone, IVIG: intravenous immunoglobulin, ELT: elthrombopag, EM: erythromycin, TAC: tacrolimus

On the first day of admission, she received PLT transfusion and intravenous methyl prednisolone (PSL) (1,000 mg/day) for 3 days, followed by PSL (60 mg/day) for 7 days, and then PSL (50 mg/day) for 7 days. On the second day, she was treated with intravenous immunoglobulin (IVIG) (20 g/day) for 5 days. During this clinical course, she received PLT transfusions several times. However, the PLT counts did not increase and remained at 0.1–0.2 $\times 10^4/\mu L$. Seven days after initiating the IVIG treatment, ELT (12.5 mg/day), a thrombopoietin-receptor agonist, was added. However, the PLT counts did not increase; therefore, after 7 days of ELT treatment, the dosage was doubled. Considering the immunomodulatory effects of MACs,[2] intravenous EM (0.5 g, twice daily) for 7 days and subsequently oral EM (200 mg, four times daily) for the long-term were added after obtaining informed consent. Five days after initiating the EM treatment, the PLT counts increased to $0.4\times10^4/\mu L$. Concurrently, the dosage of PSL was reduced to 40 mg/day. Subsequently, the PLT counts gradually increased. By 18 days after initiating the EM treatment, the PLT counts had increased to $6.5\times10^4/\mu L$. Therefore, the PSL dosage was reduced to 30 mg/day. However, after 6 days of treatment with PSL (30 mg/day), the PLT counts decreased to 5.2 $\times 10^4/\mu L$. Instead of increasing the PSL dosage again, TAC (1 mg/day) was added. However, after 6 days of TAC (1 mg/day) treatment, the PLT counts decreased to $4.7\times10^4/\mu L$. Subsequently, the TAC dosage was increased to 1.5 mg/day. Three weeks after initiating TAC (1.5 mg/day) treatment, the PLT counts increased to 7.8 $\times 10^4/\mu L$. Therefore, the PSL dosage was reduced to 25 mg/day. Two weeks after starting PSL (25 mg/day) treatment, the PLT counts increased 8.2 $\times 10^4/\mu L$. Therefore, the PSL dosage was further reduced to 20 mg/day. The trough levels of TAC (1.5 mg/day) were 6.5 ng/mL.

Discussion

In this current case with hemorrhagic events, the patient initially received IVIG, methyl PSL pulse therapy, and subsequent high dose PSL without significant improvement. Due to the insufficient effectiveness of these combined treatments, ELT was added. Subsequently EM was also added, considering its immunomodulatory effects. The addition of EM treatment was considered effective; however, it takes two weeks to confirm the effectiveness of ELT treatment. Therefore, the improvement in PLT counts observed with PSL (40 mg/day) may be attributed to the effects of EM and/or ELT. MACs have immunomodulatory and anti-inflammatory effects by increasing the apoptosis of activated lymphocytes, thereby reducing inflammation. MACs, such as clarithromycin and azithromycin have been reported to modulate the function of dendritic cells, which are crucial antigen-presenting cells playing a central role in initiating and regulating immune responses. Additionally, MACs seem to suppress the production of proinflammatory cytokines by T cells.[2] In our previous reports, we have reported several cases of primary ITP showing increased PLT counts following MACs treatment.[3-5] The improvement of ITP in these cases might be attributed to the immunomodulatory effects of MACs. Based on these findings, the immunomodulatory effects of EM may have contributed to the improvement in PLT counts in this case. During the clinical course, the PLT counts gradually decreased while the patient was on PSL (30 mg/day) in combination with ELT and EM treatment. Instead of increasing the PSL dosage again, TAC was successfully added in this case. As mentioned earlier, TAC is a calcineurin inhibitor and also belongs to the class of MAC. Because calcineurin is a critical phosphatase in T cell receptor signaling, TAC can restrain the activation and differentiation of helper T cells. Additionally, TAC has been proven to inhibit the differentiation of T follicular helper cells and suppress B-cell function.[6] TAC also inhibits the production and release of tumor necrosis factor-α, interferon (IFN)-γ, and interleukin (IL)-2.[7] In a study of TAC treatment for primary SjS-related ITP, Xu et al. recruited 23 patients with refractory primary SjS-related ITP and administered 2 or 3 mg/day of TAC in addition to conventional treatments such as glucocorticoids, IVIG, hydroxychloroquine, and others. Four weeks after initiating TAC treatment, 2 patients (8.7%) achieved a complete response showing PLT counts of over $10\times10^4/\mu L$ without bleeding, 15 patients (65.2%) achieved a partial response with PLT counts of over $3\times10^4/\mu L$ but under $10\times10^4/\mu L$ without bleeding or PLT counts at least doubled compared to before treatment, and the remaining 6 patients (26.1%) did not respond to TAC treatment. Additionally, they measured several cytokines, including IL-2, Il-4, and IFN-γ. Consequently, they found that the effect of TAC may be related to reduced expression of T helper cell type 1 cytokine.[6]

In this case, TAC at 1.5 mg/day was sufficiently effective. MACs are known to suppress TAC metabolism by inhibiting cytochrome P450 3A4, the-

reby increasing TAC blood concentrations.[8] Suzuki et al.[9] measured TAC blood concentrations in patients with rheumatoid arthritis and observed that the trough levels of TAC in the 1, 2, and 3 mg/day groups were 2.96, 4.29, and 8.32 ng/mL, respectively, although these levels varied widely among individuals within the groups. We regarded the optimal trough levels of TAC as 5.0–10.0 ng/mL. Actually, the trough levels of TAC (1.5 mg/day) in this case were 6.5 ng/mL, indicating that EM may have increased TAC blood concentrations, resulting in the reduction of expensive TAC dosages. However, repeated monitoring of TAC levels is necessary to prevent adverse reactions.

Conclusion

This case suggests that EM and TAC can be effective alternatives when conventional immunosuppressants fail to improve primary SjS-related ITP.

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Declaration of interest

The author declares no conflicts of interest associated with this article.

References

1. Xu L, Zhang Y, Lin N, Song X, Dai Q. Eltrombopag improves refractory thrombocytopenia in patients with Sjögren's syndrome. Sci Prog. 2022;105(2). https// doi: 10.1177/00368504221102786
2. Altenburg J, De Graaff CS, Van Der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics–part 1: biological mechanisms. Respiration. 2010 Dec 1;81(1):67-74. https://doi: 10.1159/000320319
3. Ohe M, Hashino S. Successful treatment with erythromycin for idiopathic thrombocytopenic purpura. Korean J Hematol. 2011; 46:139-142. https://doi:10.5045/kjh.2011.46.2.139
4. Ohe M, Hashino S. Successful treatment of primary immune thrombocytopenia in aged patients using clarithromycin. J Formos Med Assoc. 2014; 113:197-198. https://doi:10.1016/j.jfma.2011.08.035
5. Ohe M, Furuya K, Goudarzi H. Immune Thrombocytopenia Treated with Intravenous Erythromycin. Gazi Med J. 2021 Sep 9;32(4):577-579. https://doi: 10.12996/gmj.2021.129
6. Xu R, Yan Q, Gong Y, et al. Tacrolimus therapy in primary Sjögren's syndrome with refractory immune thrombocytopenia: a retrospective study. Clin Exp Rheumatol. 2022 Dec;40(12):2268-2274. https://doi: 10.55563/clinexprheumatol/5c7l01. Epub 2022 Sep 20. PMID: 36135951.
7. Du Y, Yang C, Chen M, et al. Tacrolimus is effective in relapsed/refractory autoimmune cytopenias: results of a single-center retrospective study. Hematology. 2020 Jan 1;25(1):478-483. https://doi: 10.1080/16078454.2020.1852763
8. Ohe M. A Case of Rheumatoid Arthritis accompanied by Organizing Pneumonia Successfully Treated with Prednisolone, Clarithromycin and Tacrolimus. Korean J Clin Pharm. 2017 Sep 30;27(3):195-197. https://doi: 10.24304/kjcp.2017.27.3.195
9. Suzuki K, Kameda H, Amano K, et al. Single center prospective study of tacrolimus efficacy and safety in treatment of rheumatoid arthritis. Rheumatol Int. 2009 Feb;29(4):431-436. https://doi: 10.1007/s00296-008-0833-z. Epub 2009 Jan 7. PMID: 19127365.