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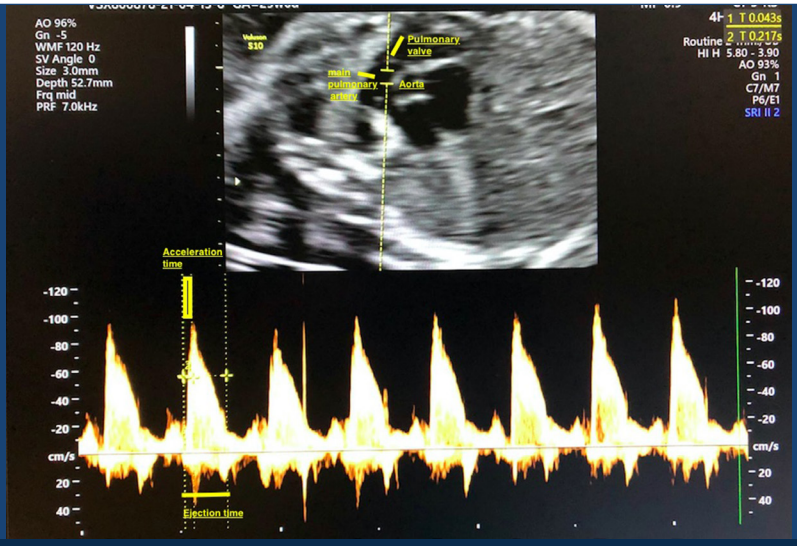

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Aims and Scope

Journal of the Turkish-German Gynecological Association is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December. The publication language of the journal is English. Manuscripts are reviewed in accordance with "double-blind peer review" process for both reviewers and authors.

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All manuscripts should be accompanied by an abstract. A structured abstract is required with original articles and it should include the following subheadings: Objective, Material and Methods, Results and Conclusion. A structured abstract is not required with review articles. The abstract should be limited to 250 words for original articles and review articles.

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Below the abstract provide 3 to 5 Keywords. Abbreviations should not be used as Keywords. Keywords should be picked from the Medical Subject Headings (MeSH) list (www.nlm.nih.gov/mesh/MBrowser.html).

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State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

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Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures. Provide information on informed consent and ethics committee approval.

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Number references in Arabic numerals consecutively in the order in which they are mentioned in the text starting with number "1". Use the form of the "Uniform Requirements for Manuscript Submitted to Biomedical Journals" (http://www.amaassn.org/public/peer/wame/uniform.htm). If number of authors exceeds seven, list first 6 authors followed by et al.

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Ertan AK, Tanriverdi HA, Schmidt W. Doppler Sonography in Obstetrics. In: Kurjak A, Chervenak FA, editors. Ian Donald School Textbook of Ultrasound in Obstetrics and Gynecology. New Delhi, India: Jaypee Brothers; 2003. p. 395-421.

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the last issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2022. This issue is consisted of eight articles and two reviews that we hope you will read with interest. Also you may have the oppurtunity to watch all of the latest videos here (http://www.jtgga.org/video). Here we share some of our favorite articles that were published in this issue of the journal.

Each year, an estimated 250,000 newborn babies die in the first 28 days of life from congenital anomalies. You will read an article determining the accuracy of antenal ultrasound in the diagnosis of congenital anomalies in Malta.

Shoulder dystocia is a complication of vaginal delivery. Maternal and fetal characteristics associated with the development of shoulder dystocia have been described. You will also read an interesting study which evaluated the relationship between neonatal biacromial diameter, birth weight and shoulder dystocia.

You will also have the opportunity to read a meta-analysis form USA which reported the result of systematic evaluation of current literature on fertility sparing interventions for early-stage cervical cancer and their associated cancer related reproductive and obstetric outcomes.

Dear Esteemed Readers,

J Turk Ger Gynecol Assoc is included in many indexes including the Emerging Sources Citation Index. Clarivate Plc, on July 26, 2022, announced that in the 2023 release of the Journal Citation Reports™, all Web of Science Core Collection™ journals will get a Journal Impact Factor (JIF)™. This will make full transparency possible to the articles and citations that contribute to impact.

The Journal Citation Indicator (JCI) represents the average category-normalized citation impact for papers published in the prior three-year period. As we announced earlier our journal is included in the JCI, a new metric offered by Web of Science, and its score has increased from 0.37 to 0.43. JTGGA became the third-quarter journal according to JCI data.

We received more than 202 article submissions in 2022, we have already published more than 32 articles, although some of our articles are still under evaluation. Our published papers represent the breadth of the obstetrics and gynecology. We would like to take this opportunity to thank everyone who contributed to our journal last year. We are grateful to our authors, reviewers, and readers.

I would like to wish you a happy new year in 2022 and we are looking forward to receiving your valuable submissions, thank you in advance for your contributions.

Sincerely,

Prof. Cihat Ünlü, M.D.
Editor in Chief of J Turk Ger Gynecol Assoc
President of TGGF

The accuracy of antenatal ultrasound screening in Malta: a population-based study

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Abstract

Objective: To analyse the accuracy of antenatal ultrasound screening in Malta, comparing detection rates within the private and public sectors, and with the rest of Europe. To assess local trends in accuracy for each organ system.

Material and Methods: Ethics approval was obtained to gather routinely collected data from the national congenital anomalies registry between 2016 and 2018. This was analysed to determine local antenatal ultrasound accuracy rates and trends. Electronic medical appointment record data was also used to indirectly determine whether a significant difference existed in the detection of antenatal anomalies in mothers scanned privately and those scanned within the public sector. χ^2-for-trend was used to analyse changes in the accuracy rates. European Surveillance of Congenital Anomalies (EUROCAT) data was used to compare scanning accuracy in Malta and other EUROCAT centres.

Results: The local rate of undetected congenital anomalies was 62.0% for public scans and 83.9% for private scans. Local trends over the three-year period showed an improvement in accuracy rates in detecting isolated syndromes ($p=0.05$), anomalies of the renal system ($p=0.02$) and craniofacial anomalies ($p=0.05$). Malta's overall performance was similar to other EUROCAT centres.

Conclusion: Scans carried out within the public sector are more accurate than private scans, and Malta's overall performance was similar to other EUROCAT centres. (J Turk Ger Gynecol Assoc 2022; 23: 222-32)

Keywords: Prenatal diagnosis, ultrasonography, pregnancy outcome, maternal health services

Received: 09 May, 2022 **Accepted:** 06 September, 2022

Introduction

Congenital anomalies are relatively common, occurring in 2-3% of all births. Anomalies constitute a major cause of perinatal morbidity and mortality, with lasting effects on those who survive, as well as on their families, in the form of physical and emotional trauma (1). Ultrasound is the ideal modality for the antenatal detection of many anomalies, since it is safe and highly effective, albeit user and equipment-grade dependent (1).

Antenatal ultrasound scanning has now become a routine procedure and an integral part of antenatal care universally. In most countries worldwide, screening is carried out in all pregnancies as the great majority of abnormal foetuses are born to mothers with no apparent risk factors (2). Ultrasound is also used to monitor foetal growth, multiple pregnancies, and so on (3).

A nuchal scan is carried out at 12 weeks of gestation since, at this time, the majority of the foetal organs are well developed and may be visualised (4). In Malta, the nuchal scan is the earliest routine antenatal ultrasound scan, typically carried out at 10 to 14^{+6} weeks gestation. Foetal organs are scrutinised for anomalies and foetal growth measured (5). This scan may also be used in conjunction with other antenatal tests to confirm an antenatal diagnosis of trisomy 21 (Down syndrome) (4).

The anomaly scan is a later ultrasound scan, performed routinely at around 20 weeks of gestation (5). In all studies, the

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ability to detect anomalies depends on many factors, such as operator ability, the ultrasound machine being used, the foetal organ being analysed, and even the body mass index (BMI) of the mother (6).

Benefits of antenatal ultrasound scanning include promoting improved antenatal practice and perhaps further encourage expectant mothers to attend their routine antenatal clinics. Psychological benefits, in the form of maternal-fetal connection, have also been adduced, albeit in higher-income countries (7). It has also been suggested that seeing one's child via ultrasound may help promote healthy behaviour, such as smoking cessation (7). Antenatal diagnosis may also allow expectant parents to prepare for the eventual birth of a disabled child (8). In addition, the early diagnoses of foetal anomalies may allow paediatricians, paediatric surgeons, and neonatologists, as well as the obstetric specialists, to prepare for the eventual medical and surgical needs at birth. It can also trigger a more detailed screening of the foetus as well as genetically related family members. Furthermore, the method and timing of delivery can be optimised.

Malta is an independent archipelago located south of Sicily in the Mediterranean Sea with a population of approximately half a million. Malta has only one main public hospital, giving the authors the unique opportunity to carry out a population study. Free National Health Care is available, modelled on the British system, but patients may also elect to attend private, fee-paying clinics. Antenatal ultrasound scans are no exception and can be carried out in private obstetric clinics, or in the country's regional centre. All mothers whose foetus is found to have an abnormality on an ultrasound scan carried out in the private sector are referred to the state hospital for a second ultrasound scan. This is carried out by the obstetrics and gynaecology outpatient department and further follow-up is organised as necessary. Termination of pregnancy is currently illegal in Malta.

This study was carried out to analyse the accuracy of the antenatal ultrasound services provided in Malta.

Material and Methods

The study was approved by Ethics Committee of Malta Faculty of Medicine and Surgery Research Ethics Committee (approval number: FRECMDS_1819_100).

Case recruitment

Recruitment of local cases

Cases recruited for this study included all cases of babies diagnosed with congenital anomalies detectable by antenatal ultrasound screening, born between January 2016 and December 2018. This list of cases was based on inclusion criteria adopted by the country's local congenital anomalies registry. This data is routinely collected by the registry and was complete up to the end of this period. The variables used from the registry dataset were gender, gestation, date of birth, whether antenatal ultrasound scanning was done, what anomalies were found postnatally, whether said anomalies were detected antenatally, and which type of antenatal test was positive first.

EUROCAT data

The EUROCAT network is a European network of population-based registries for the epidemiological surveillance of congenital anomalies. Data obtained included all cases of babies with congenital anomalies detectable by antenatal ultrasound screening, born between January 2015 and December 2019. This was done by accessing the publicly available EUROCAT website (9). EUROCAT data extract started from 2015 through to 2019 and it was thus decided to use all data available. The EUROCAT centres from which data was obtained were as follows: Cork and Kerry, French West Indies, Hainaut, Malta, Netherlands, Northern England, Odense, Pleven, Saxony-Anhalt, Tuscany, Valencian Region, Vaud, Wessex and Zagreb.

Inclusion and exclusion criteria

Inclusion and exclusion criteria for local congenital anomalies registry cases

All cases of registered anomalies were collected, irrespective of maternal nationality, gender of child and whether assisted conception was used or not. Cases excluded from the data set included those in which pre-natal ultrasound scans were not done, or in cases where this could not be traced. Cases in which a scan was logged as performed, but the results were not available, were also excluded. Cases where any anomaly found postnatally could not have been detectable on antenatal ultrasound or would have been considered part of the normal foetal anatomy [e.g., patent ductus arteriosus (PDA)] at the time of antenatal scanning were also excluded. Furthermore, cases in which the first positive pre-natal test showing an anomaly was identified by other methods and not by ultrasound were also excluded (e.g., chromosomal defect picked by chromosomal analysis following amniocentesis before an ultrasound scan detected an abnormality).

Inclusion and exclusion criteria for EUROCAT data

Cases excluded were those in which the patient was diagnosed with a condition in which no children with the same pathology were born in Malta. This was done because this data was specifically collected for the purpose of accuracy comparison between Malta and the other EUROCAT centres.

Local data collection

Ultrasound machines in the Maltese state service

To-date, there is no central electronic record system available for storing data obtained from antenatal ultrasound, apart from the data recorded and stored on the ultrasound machines themselves, which is eventually overwritten once the machine hard-drives reach maximum data capacity. Nevertheless, electronic attendance records are created on the hospital electronic medical record software (iSoft Clinical Manager, https://dxc.com/us/en/industries/healthcare), whenever a patient attends an appointment for an ultrasound at the state hospital. This information was utilised to ascertain whether a patient actually attended the state hospital gynaecology outpatients department. Scans performed for the purposes of the antenatal nuchal and anomaly scans as provided by the state hospital, were carried out using one of two General Electric (https://www.ge.com/) Voluson S10 BT18 ultrasound machines, capable of carrying out 3D and 4D ultrasounds (10). Each machine is equipped with three different transducer probes:

1. General Electric RAB6-RS broadband electronic curved array transducer running at 2-8 MHz.
2. General Electric C1-5-RS wide band convex array probe running at 2-5 MHz.
3. General Electric RIC5-9A-RS endocavity probe running at 4-10 MHz.

A Philips IE33 echo machine, with the Philips C5-1 PureWave probe/transducer, was available for foetal echocardiograms (https://www.philips.com/global).

Ultrasound machines in the private sector

The ultrasound units and probes utilised in private clinics vary widely and information relating to the make and models of these ultrasound scanners was not available. Since data from ultrasound records in private sector was not directly available, an indirect method of data calculation was employed. State hospital electronic medical records were accessed via iSoft Clinical Manager software, and a list of mothers within the local congenital anomaly registry dataset who presented within the gestational period for an outpatient antenatal obstetric ultrasound scan at the state hospital was created. The remaining mothers in the local congenital anomaly registry dataset who had not presented for a state hospital ultrasound, but did have an ultrasound done at some point during the pregnancy (as per the congenital anomaly registry information), were thus assumed to have done their ultrasound privately. Some bias may have occurred due to differences in the case mix of mothers attending private and state hospital clinics.

Local ultrasound accuracy data collection

Once all the required ethical and data protection approvals were obtained, data was obtained from the local congenital anomalies registry that contained data on each baby born with a list of their congenital anomaly(s). Using data from this registry, for each anomaly listed, data on whether an antenatal ultrasound diagnosis was made for each anomaly was collected and, if so, whether the diagnosis was partially correct or completely correct. For the purposes of this study, anomalies that were marked as partially correct and completely correct were taken as successfully detected.

Assessment of where local scans were performed

The attendance of gravid mothers for an antenatal ultrasound scan at the state hospital obstetrics and gynecology outpatient department was determined by accessing the electronic public hospital medical record system. This made it possible to identify whether an anomaly was missed by a non-state hospital clinic or by the state hospital antenatal ultrasound clinic. This methodology was based on the assumption that any one mother either had her scans done privately or within the public sector. If the local congenital anomalies registry were to list a congenital anomaly as not detected during antenatal ultrasound screening, and the mother did not have an episode registered at the state hospital, then the case must have been missed at a non-state hospital clinic. On the other hand, if the local congenital anomalies registry listed a congenital anomaly as not detected during antenatal ultrasound screening and the mother had confirmed attendance at the state hospital antenatal ultrasound clinic as per her electronic medical record, then the anomaly must have been missed during state hospital screening. As per typical local practice protocols, abnormal scans in private practice typically result in a referral to the state hospital for a second follow-up scan, and for the purposes of this study, such mothers were considered to have had a scan only at the state hospital. In view of this limitation, results were represented as percentage of cases not detected, rather than detected, in order to minimise the risk of under-estimating the performance of private clinics. This was done because babies with anomalies that were not detected privately would not have been referred to the state hospital for a follow up scan.

EUROCAT data

Data pertaining to the antenatal ultrasound detection rates is openly available on the EUROCAT website (9). The anomalies analysed for antenatal detection by EUROCAT were anencephaly and similar defects, spina bifida, hydrocephalus, transposition of the great arteries (TGA), hypoplastic left heart, cleft lip with or without cleft palate, diaphragmatic hernia,

gastroschisis, omphalocoele, bilateral renal agenesis and Potter's syndrome, posterior urethral valves and/or prune belly, limb reduction defects, club foot, chromosomal abnormalities in general, Down syndrome, Patau syndrome and Edwards syndrome.

Statistical analysis

Local accuracy by organ system was assessed as follows. The data on accuracy rates for antenatal ultrasound screening was classified by organ system. The percentage of congenital anomalies missed by antenatal ultrasound for congenital malformations involving the central nervous system (CNS), face, lung, heart, musculoskeletal system, craniofacial system, gastrointestinal system, the renal system, and syndromes were subsequently analysed separately. χ^2-for-trend testing was carried out to elucidate any statistically significant trends in scan accuracy for each organ system over the 3-year period. This was done using formulae made by the authors within Microsoft Excel software (https://www.microsoft.com/en-mt).

Local accuracy trend by organ system

The overall trend in antenatal ultrasound screening detection over the three study years, 2016, 2017 and 2018, was also noted for each organ system and for syndromes.

Public vs. private sector accuracy was calculated and expressed as a percentage.

EUROCAT data

The number of cases detected on ultrasound antenatally within the EUROCAT database and the percentage that this represented was retrieved and compared with the local figures for the same three-year period. Simple proportion was utilised to calculate the total number of postnatal cases that were found, and subsequently, the number of cases that were not detected. This was carried out for each group according to the underlying pathology.

Results

A total of 335 mothers were obtained from the local congenital anomalies registry, which included births affected by congenital anomalies from the beginning of 2016 to the end of 2018. The maternal age ranged from 16 to 46 years. A total of 338 babies were delivered with congenital anomalies during this period, 202 of which were male and 136 of which were female. Gestational lengths ranged from 26 weeks up to 41 weeks. The local birth rate decreased over the 3-year period, with a rate of 9.90 per 1,000 persons in 2016, 9.25 in 2017 and 9.15 in 2018.

Local exclusions

Twelve patients were removed in view of incomplete data. Another 6 patients were removed since their reported anomalies were deemed to be normal foetal findings. These were isolated patent foramen ovale and PDA. Another 30 cases labelled atrial septal defect (ASD) were also removed from the analysis, since it is nearly impossible to differentiate an ASD from the physiological foramen ovale on antenatal scans (11).

Single cases of Crigler-Najjar syndrome, Bartter syndrome, gangliosidosis and two cases of cutis aplasia, three cases of congenital hypothyroidism and one case of severe hearing loss were excluded, since these conditions cannot be antenatally detected by ultrasound.

EUROCAT exclusions

Patau syndrome and bilateral renal agenesis plus Potter's syndrome were not analysed as Malta did not have any cases of these pathologies during the period, 2015-2019.

Local accuracy overall (public and private)

Antenatally detected cardiac anomalies (Table 1) included TGA, tetralogy of Fallot, tricuspid atresia, cor triatriatum, pulmonary valve stenosis, congenital hypertrophic cardiomyopathy, perimembranous and muscular ventricular septal defect, hypoplastic left heart, Ebstein anomaly, coarctation of the aorta, hypoplastic abdominal aorta, atrioventricular septal defect, truncus arteriosus, aortic valve stenosis, pulmonary atresia, total anomalous pulmonary venous drainage, bicuspid aortic valve, double outlet left ventricle, mitral valve regurgitation, hypoplastic aortic arch, ASD, dysplastic aortic valve, right sided aortic arch, atrial isomerism, vascular ring around the trachea and congenital dilated cardiomyopathy. There were no significant trends in antenatal cardiac anomaly diagnosis rates during the 3-year period.

Renal defects detected included were penoscrotal, proximal shaft, midshaft, distal shaft, glanular, perineal and subcoronal hypospadias, fused renal ectopia, hydronephrosis, pulviureteric junction stenosis, webbed penis, pelvic kidney, duplex kidneys, chordee, atrophic kidneys, horseshoe kidney, renal agenesis, webbed scrotum, hydroureter, micropenis, renal cystic dysplasia, bifid scrotum, and posterior urethral valves. A statistically significant negative trend in the percentage of cases missed was observed (Table 1).

Musculoskeletal defects included congenital hip dislocation, duplication of various digits, structural talipes equinovarus, myopathies, achondroplasia, hamartomata involving the digits, hypoplastic digits, congenital dislocation of the knee, natal teeth, asymmetrical limb shortening, arthrogryposis, overriding digits, abnormalities of the vertebrae, clinodactyly, dysplastic hands, dysplastic/bifid ribs, brachydactyly, thoracic dystrophy,

Sprengel deformity, scoliosis, fixed knee flexion, and rotated hip (Table 1) and there were no significant trends in diagnosis rates.

With regards to craniofacial defects, a significant negative trend in the percentage of cases missed was detected (Table 1). Facial abnormalities included cleft lip and palate of various grades, facial dysmorphia, micrognathia, high arched palate, microtia, low set ears, accessory auricles, choanal atresia, facial hypertelorism, microphthalmia, mid-facial hypoplasia, and coloboma.

There were no significant trends in the antenatal detection rate of CNS defects (Table 1) and congenital anomalies identified were hydrocephalus, myelomeningocoele, anencephaly, microcephaly, severe holoprosencephaly, partial and complete agenesis of the corpus callosum, plagiocephaly, turricephaly (due to maternal bicornuate uterus), colpocephaly, sub-ependymal cysts, craniosynostosis, Dandy-Walker variant, pontine and cerebellar hypoplasia, neurofibromatosis type-1, Chiari-1 malformation, hypoplasia of the anterior pituitary and bilateral choroid plexus cysts.

With regards to defects affecting the lungs and thorax, no significant trends were identified, and these defects were lung aplasia, a cystic lesion in the sub-cutaneous layers of the right side of the chest, a cystic mass in the right upper lung lobe, and premature hypoplastic lung (one of which was associated with a left sided severe pulmonary artery malformation).

There were no significant trends in gastrointestinal cases either (Table 1) and the anomalies included gastroschisis, Hirschsprung disease, congenital hepatomegaly with hepatic fibrosis, diaphragmatic hernia, omphalocoele, displaced anus, oesophageal atresia, trachea-oesophageal fistula, imperforate anus, congenital volvulus, duodenal stenosis, jejunal-ileal atresia, and obstruction secondary to an annular pancreas.

With regard to syndromes, a significant negative trend in the percentage of cases missed was noted, indicating an improvement in the antenatal US detection of certain syndromes (Table 1). The syndromes were: Down, DiGeorge, Edwards, Poland syndrome with characteristic absent right pectoralis, 3p deletion, dextrocardia with complete situs inversus, Pentalogy of Cantrell, Neu Laxova, and CHARGE syndrome.

Local accuracy of out of hospital scans

A total of 199 anomalies were present in patients who did not have an antenatal ultrasound appointment logged at the local state hospital. The trend in the miss rate over the three-year period was not significant (Table 2A).

Local accuracy of hospital scans

A total of 284 anomalies were present in patients who did have an antenatal ultrasound appointment logged at the local state hospital. The trend in the not detected rate over the three-year period was not significant (Table 2B).

Hospital vs. private

Private sector scans had a higher non-detection rate than the state hospital scans (Table 3).

Malta vs. EUROCAT

There were no statistically significant differences in the number of antenatal anomalies detected and not detected between Malta and the rest of the EUROCAT centres (Table 4).

Discussion

Timely antenatal diagnosis and appropriate, repeated parental counselling is associated with lower levels of parental anxiety at birth (12). Early diagnoses and appropriate preparation may at least soften the blow dealt by such a turbulent and upsetting period in parents' lives.

Private vs. hospital scan accuracy

A notable discrepancy existed between the accuracy rates obtained in non-state hospital clinics and state hospital clinics (Table 3). This may be due to the use of ultrasound machines in some non-state hospital clinics, which perhaps do not meet the same specifications as those used in the state hospital. It may also be due to the use of machines which may not be equipped with the ideal set of ultrasound probes needed to perform a range of antenatal ultrasound scans. Finally, it may also be due to more rigorous maintenance of the ultrasound equipment used within state hospital clinics as opposed to equipment used in some non-state hospital clinics. It is also possible that obstetricians carrying out antenatal ultrasound scans within the state hospital have more experience than some of those carrying out scans solely in the private sector. They may also have more training pertaining specifically to carrying out effective antenatal ultrasound scans.

Malta vs. EUROCAT

Accuracy rates were not significantly different on comparing Malta and the other EUROCAT centres. This suggests that at least some of the factors that hinder ultrasound accuracy locally may also be present in other antenatal clinics abroad.

Declining congenital anomaly rates

The total number of postnatally detected cases decreased over the three-year period under study. This suggests that the incidence of various congenital anomalies was decreasing. Another possibility is that parents may in fact be notified of a serious antenatal anomaly during a routine antenatal anomaly

Table 1. Local trends in scan accuracy for each organ system

	Heart				**Renal**				**Musculoskeletal**			
	2016	**2017**	**2018**	**Overall**	**2016**	**2017**	**2018**	**Overall**	**2016**	**2017**	**2018**	**Overall**
Not detected	41	42	24	107	31	15	18	64	27	14	20	61
Detected	14	14	14	42	12	11	20	43	6	4	2	12
Total	55	56	38	149	43	26	38	107	33	18	22	73
(%) not detected	74.5	75	63.2	71.8	72.1	57.7	47.4	59.8	81.8	77.8	90.9	83.6
Upper 95% CI for overall (%) not detected	78.7				69.0				90.9			
Lower 95% CI for overall (%) not detected	63.8				49.9				72.7			
χ^2-for-trend	2.52				5.16				0.66			
p	0.11				0.02				0.42			
	Craniofacial				**Central nervous system**				**Lung**			
	2016	**2017**	**2018**	**Overall**	**2016**	**2017**	**2018**	**Overall**	**2016**	**2017**	**2018**	**Overall**
Not detected	23	14	4	41	3	10	5	18	2	1	0	3
Detected	1	2	2	5	9	4	3	16	0	2	0	2
Total	24	16	6	46	12	14	8	34	2	3	0	5
(%) not detected	95.8	87.5	66.7	89.1	25.0	71.4	62.5	52.9	100	33.3	-	60.0
Upper 95% CI for overall (%) not detected	95.9				69.8				92.7			
Lower 95% CI for overall (%) not detected	76.5				35.4				17.0			
χ^2-for-trend	3.93				3.48				2.22			
p	0.05				0.06				0.14			
	Gastrointestinal tract				**Isolated syndrome**							
	2016	**2017**	**2018**	**Overall**	**2016**	**2017**	**2018**	**Overall**				
Not detected	3	3	7	13	16	12	8	36				
Detected	7	2	5	14	1	1	4	6				
Total	10	5	12	27	17	13	12	42				
(%) not detected	30	60	58.3	48.2	94.1	92.3	66.7	85.7				
Upper 95% CI for overall (%) not detected	67.7				94.1							
Lower 95% CI for overall (%) not detected	29.2				85.7							
χ^2-for-trend	1.69				3.97							
p	0.19				0.05							
CI: Confidence interval												

Table 2A. The accuracy rates of antenatal ultrasound screening in non-state hospital clinics between 2016 and 2018, including trend analysis

Non-state hospital clinics	2016	2017	2018	Overall	Trend analysis
Not detected	93	35	39	167	χ^2-for-trend=2.52 p=0.11
Detected	15	4	13	32	
Total	108	39	52	199	
(%) not detected	86.1	89.7	75.0	83.9	
Upper 95% CI for overall (%) not detected	88.6				
Lower 95% CI for overall (%) not detected	77.9				
CI: Confidence interval					

Table 2B. The accuracy rates of antenatal ultrasound screening in state hospital clinics between 2016 and 2018, including trend analysis

State hospital clinics	2016	2017	2018	Overall	Trend analysis
Not detected	53	76	47	176	χ^2-for-trend=0.30 p=0.58
Detected	35	36	37	108	
Total	88	112	84	284	
(%) not detected	60.2	67.9	56.0	62.0	
Upper 95% CI for overall (%) not detected	67.6				
Lower 95% CI for overall (%) not detected	56.0				
CI: Confidence interval					

Table 3. Comparing the accuracy of state hospital scans and non-state hospital scans

	Not detected overall	Detected overall	(%) not detected
State hospital	176	108	62.0
Non-state hospital	167	32	83.9

scan, at which point they may decide to travel overseas, as abortion is illegal in Malta, and proceed with termination of the pregnancy of their own accord. This would result in a decrease in the total number of postnatally detected congenital anomalies listed within the local congenital anomalies registry per annum since a baby is only listed in said registry upon being born. According to the non-profit organisation *Doctors for Choice Malta*, it is possible for people residing in Malta to carry out termination of pregnancy by either travelling overseas to Italy, the Netherlands or the United Kingdom and having the procedure done at a dedicated abortion clinic, or by purchasing abortifacient tablets over the internet (13).

Accurate statistics pertaining to the number of people residing in Malta who carry out termination of pregnancy at the time of writing were unavailable. It may be reasonable to assume that a proportion of abortions are carried out solely in view of the successful detection of a severe congenital anomaly, which is known to be associated with high degrees of morbidity, mortality, and reduction in quality of life. With this assumption in mind, such abortions could lead to an underestimation of the total number of babies born in Malta with severe congenital anomalies. If this were the case, this may also result in an overestimation of the percentage of anomalies not detected by antenatal ultrasonography, as in cases such as these, antenatal ultrasound would have indeed made a correct diagnosis, but this would never be recorded in the local congenital anomalies registry. According to data published by the country's local directorate of health and research information, a decline in birth rate in Malta occurred during the three-year period under study (14,15). If a significant decline in the national birth rate were to be caused mainly by increased rates of abortion secondary to the detection of severe congenital anomalies on ultrasound and such events would most likely be under-reported, this would most likely hinder the ability of the local congenital anomaly registry to provide accurate representations pertaining to the incidence of congenital anomalies occurring during births in Malta. Subsequently, any attempt to calculate the accuracy of antenatal screening programs in Malta would be less representative of the true situation.

Maternal BMI and scan accuracy

Maternal obesity can be detrimental to ultrasound accuracy. Malta is known to have some of the highest obesity rates in Europe, with 35.65% of the Maltese population classified as overweight and 34.10% classified as obese from 2014 to 2016 (16). In 2015, 23.8% of pregnant women were noted to be overweight, and 13.7% were noted to be obese (17). According

to this data, in 2015, over a third of the population of pregnant women in Malta were above the normal range for healthy body weight. Thus, it may be possible that this factor heavily impacted the local performance of antenatal ultrasound screening.

It has also been shown that obese pregnant women are more likely to give birth to children with congenital anomalies, such as neural tube defects, cardiac defects, gastrointestinal defects, hypospadias, and limb reduction defects. It has been postulated that the typical metabolic disturbances that come with obesity, which include increased serum triglycerides, uric acid, oestrogens, and serum insulin, may have their own teratogenic effects (18). It is well known that performing antenatal ultrasound scans on obese women is technically challenging. It has been suggested that foetal component visualisation rates drop by 14.5% if the maternal BMI is higher than the 90th centile, with the heart and spine being the most difficult to visualise. A linear correlation has been established between the rate of hindered sonographic visualisation and increasing degrees of maternal obesity (18). Carrying out the anomaly scan at a later date than usual in cases of maternal obesity was seen to improve visualisation rates, but not significantly. It has thus been suggested that significant maternal obesity as a specific indication for dedicated foetal echocardiography and possibly even early transvaginal

Table 4. EUROCAT data on the number of cases not detected and detected for the various congenital anomalies

	Anencephaly		**Spina bifida**		**Hydrocephalus**	
	Malta	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**
Number detected	4	567	3	572	9	519
Number not detected	0	440	1	560	3	535
Observed χ^2	3.09		0.95		3.15	
p	0.08		0.33		0.08	
	Transposition of the great arteries		**Hypoplastic left heart**		**Cleft palate**	
	Malta	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**
Number detected	1	383	3	294	7	801
Number not detected	4	486	0	328	3	1034
Observed χ^2	1.17		3.33		2.81	
p	0.28		0.07		0.09	
	Congenital diaphragmatic hernia		**Gastroschisis**		**Omphalocoele**	
	Malta	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**
Number detected	4	272	2	286	2	285
Number not detected	1	409	1	297	2	280
Observed χ^2	3.31		0.37		0.00	
p	0.07		0.54		0.99	
	Posterior urethral valve/prune belly syndrome		**Limb reduction**		**Club foot**	
	Malta	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**
Number detected	3	164	5	393	11	1144
Number not detected	0	144	4	622	17	1583
Observed χ^2	2.61		1.06		0.08	
p	0.11		0.30		0.78	
	Chromosomal		**Trisomy 21**		**All anomalies**	
	Malta	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**	**Malta**	**Rest of EUROCAT**
Number detected	7	2890	7	1331	131	13239
Number not detected	36	8786	30	4849	307	37256
Observed χ^2	1.64		0.15		3.05	
p	0.20		0.70		0.08	

EUROCAT: European Surveillance of Congenital Anomalies

anomaly scanning. This would of course be difficult in view of the high numbers of mothers that are obese. It would also mean that each mother with a high BMI would require more time for her scan, with resultant longer waiting lists and higher costs (18). The greater the distance over which the ultrasound waves must travel (increased in maternal obesity), the higher the degree of energy absorption and dispersion of ultrasound wave energy into the surrounding tissues. This results in weaker ultrasound wave signals and a greater degree of backscatter (18).

It would appear that it is worth using high-end ultrasound machines, especially in light of the high proportion of mothers with high BMI in Malta. Nevertheless, such sophisticated machinery would need to be operated correctly, highlighting the importance of operator experience and skill.

Another factor that complicates further the performance of antenatal ultrasound in obese mothers, is the increasing incidence of multiple pregnancies, especially in those who opt to use assisted reproductive methods. Multiple pregnancies hinder the availability of useful acoustic windows via which one may assess the foetus. Furthermore, infertility secondary to hormonal and metabolic issues is more common in obese mothers and having to manage a mother with high BMI with multiple pregnancy is not uncommon (18).

The high acoustic impedance of the foetal skeletal structures means that the gross visualisation of the foetal skeleton is typically possible in spite of maternal obesity. However, low impedance foetal structures, such as the cerebellum, extremities, lips, kidneys, and heart, are not as easy to visualise. It is recommended that the extremities are best visualised during a transvaginal scan at 12 to 15 weeks' gestation. It may sometimes even be possible to visualise the heart during this scan (18).

Challenges

In Malta in 2016-18, there was currently no IT data record system in place to allow publication of ultrasound reports online, unlike other medical investigation results that are all online. Data collection was thus challenging. Antenatal ultrasound reports and/or images could only be found on the ultrasound machines themselves, or on printed reports within the patient's paper-based file. Clearly, there is room for improvement in this regard.

Recommendations

It may be beneficial to have an IT-based system on which all antenatal scan data, whether carried out privately or within Mata's State Hospital, could be published and accessed by relevant healthcare professionals. Having all the data on one unified database archiving and communications system would provide the caring obstetrician or paediatrician secure, password protected access to any relevant images or measurements pertaining to the foetus. The use of this system could be extended as part of the formation of a dedicated foeto-maternal unit. Apart from the advantages that this would provide to the obstetric, neonatal, and paediatric teams, this would also streamline the data collection process required for future audits, research, and local congenital anomaly registry data collection. A similar system is already in place for imaging used in other departments of medicine and surgery.

With regards to privately run clinics which offer antenatal ultrasound scans, it may prove beneficial to ensure effective regulation of such services by ensuring that personnel operating the ultrasound units are experienced and certified, and that the machines and probes themselves are updated according to internationally recognised standards and designed for obstetric use.

It would be useful to repeat this study in the future, perhaps once data collection sources become more streamlined as highlighted above, over a longer period of time. This would allow further accuracy rate trending to be carried out, providing more information regarding the quality of the local antenatal screening service moving forward.

Study limitations

Due to the fact that Malta has a relatively small population, data pertaining to rare diseases and their incidence within the Maltese islands was not as abundant as data relating to such conditions in larger EUROCAT centres. For the rarer subset of congenital anomalies, this made it difficult to judge Malta's antenatal ultrasound screening performance against that of overseas centres.

In view of the data available, it was not possible to obtain a list of every type of private clinic each mother attended during the antenatal period, and these were thus analysed "collectively". During the data collection process, it was assumed that if a mother attended an appointment for an antenatal scan with the state hospital, as per her electronic medical record, then it may be assumed that she did not attend a non-state hospital (private) clinic for an antenatal scan. Thus, if a mother was logged as having attended a scan within the state hospital, and anomalies affecting her foetus were logged as detected antenatally, then the credit for the positive antenatal diagnosis was given to the state hospital clinic. Nevertheless, it may be that the mother was indeed referred for a scan within the state hospital in the first place because an anomaly was successfully detected during a scan at a non-state hospital obstetrics clinic. In this case, it followed that the non-state hospital clinic may also have been credited as having successfully picked up the anomaly antenatally. This would risk underestimating the

accuracy of antenatal scans performed privately. However, the opposite is also true, in that if a patient was logged as having attended an appointment within the state hospital, and the anomaly was not detected, that same patient may have still attended a non-state hospital clinic, which also did not detect the anomaly. It was therefore decided to collect and process data in terms of anomalies not detected rather than anomalies detected. Subsequently, the overall risk would be of underestimating the number of anomalies not detected by non-state hospital clinics. This is because if an anomaly was not detected in a non-state hospital clinic, then that patient will not be referred to the state hospital for further scanning anyway. In spite of this, a significant difference in accuracy rates was still detected when comparing state hospital and non-state hospital scans, with non-state hospital clinics underperforming in comparison to state hospital clinics.

Finally, there exists a lacuna in the research data collected in view of the fact that the local congenital anomaly registry only registers babies who are delivered from 22 weeks gestation onwards. This means that data pertaining to foetuses who may have been diagnosed antenatally prior to 22 weeks gestation with a serious congenital anomaly and then aborted overseas, was missing from the registry.

Conclusion

The difference between the performance of private and state hospital sectors in terms of antenatal ultrasound screening in Malta was significant. In this study, for major congenital anomalies, Malta's antenatal ultrasound screening service performed similarly to antenatal ultrasound screening centres contributing to EUROCAT. Overall trends do not indicate a reduction in the miss rate over the three-year period for non-state hospital or state hospital clinics, although the detection of isolated syndromes, craniofacial anomalies and renal anomalies was seen to improve significantly during the study period. The three organ systems that had the best accuracy rates were the gastrointestinal system, the CNS, and the renal system. The congenital anomalies that had the worst accuracy rates were those associated with the musculoskeletal system, the craniofacial system and those related to congenital syndromes, although miss rates were seen to be significantly down-trending for craniofacial anomalies and syndromes.

Ethical Committee Approval: *The study was approved by the University of Malta Faculty of Medicine and Surgery Research Ethics Committee (approval number: FRECMDS_1819_100).*

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Surgical treatment of endometrioid endometrial carcinoma - laparotomy versus laparoscopy

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Abstract

Objective: Recent publications have raised doubts about the oncological safety of a laparoscopic approach in the treatment of endometrial cancer. The aim of this study was to investigate the beneficial aspects of laparoscopy versus laparotomy in patients with endometrial cancer, and present oncological outcomes.

Material and Methods: A retrospective study of patients who underwent surgery for the treatment of endometrioid endometrial cancer was performed. Surgical outcomes and complications in patients who were treated by laparoscopy or open surgery were compared. The patients were followed for 5-years. Patients' characteristics, tumor stage, complications rate and oncologic outcome were analyzed.

Results: A total of 151 patients were included. The laparoscopy (n=80) and laparotomy (n=71) groups were homogeneous in regards of demographic data and tumor stage. Median average blood loss (1.31 vs. 1.92 g/dL), the mean duration of hospitalization (5.73 vs. 12.25 days), intraoperative (0 vs. 6%), and severe postoperative complications (5.1 vs. 14.3%) were significantly lower in the laparoscopy group. The numbers of pelvic or para-aortic lymph nodes removed during systematic lymphadenectomy were similar in both groups. Women who underwent laparoscopy and those who underwent laparotomy had similar five-year recurrence-free survival rates (88.7% vs. 91.5%, p=0.864), as well as similar overall five-year survival rates (91.2% vs. 97.2%, p=0.094).

Conclusion: The oncological outcome of laparoscopy was similar to that of laparotomy in the treatment of patients with endometrial cancer. However, surgical outcomes and morbidity rates were significantly better in patients treated by laparoscopy. Clinical trials are essential to evaluate the oncological efficacy of laparoscopy in patients with endometrial cancer. (J Turk Ger Gynecol Assoc 2022; 23: 233-40)

Keywords: Endometrial cancer, laparotomy, laparoscopy, complications, oncological outcome

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Introduction

Endometrial carcinoma is the most common cancer of the female genital organs and the fourth most common malignant disease in women (1). As endometrial carcinoma is frequently accompanied by the early symptom of vaginal bleeding, the disease is diagnosed in an early stage in more than 75% of patients (2,3). This explains the favorable prognosis of the disease, which accounts for no more than 2.5 % of all cancer-related deaths, with five-year survival rates reported to range from 80% to 85% (1). However, due to the increasing number of women over the age of 60 years in the general population, the incidence of the disease is expected to rise (4). The disease rate is expected to increase by 1-2% every year, which makes this type of cancer a matter of concern for gynecologists (1).

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Surgery is the primary treatment for patients with early endometrial cancer (5). Various studies have shown that the advantages of laparoscopic surgery over open surgery include a lower rate of postoperative adhesions, a shorter hospital stay, fewer postoperative complications, less pain, and better quality of life due to faster recovery (6-11). Furthermore, several studies have concluded that minimally invasive surgery provides similar oncological outcomes and is associated with lesser morbidity compared to laparotomy (12,13). Minimally invasive surgery was included in the majority of the existing guidelines throughout the world for the treatment of endometrial cancer (14,15). Given the option of the laparoscopic approach, primary surgery is performed by laparoscopy in the large majority of hospitals. However, minimally invasive treatment of malignant diseases, such as cervical cancer, has been controversial in the last few years (16). A randomized international multicenter study on cervical cancer published by Ramirez and co-workers revealed that radical endoscopic surgery was associated with a significantly higher risk of recurrence and mortality compared to the open procedure (16). Despite the numerous explanations offered for this phenomenon, including the use of a uterine manipulator and the method of colpotomy, the reasons for the unfavorable effects of the minimally invasive approach are not clear. Tumor exposure may be a likely reason for high recurrence rates after minimally invasive surgery.

Knowledge of the exact factors that worsen the outcome is of utmost importance in order to devise innovative programs that will overcome these obstacles and provide all benefits of minimally invasive surgery for comprehensive and sustainable treatment of cancer patients. Until this problem has been solved, we may need to take a step backward in oncologic surgery and review the surgical access for endometrial cancer. In our department patients with endometrioid endometrial cancer were treated by either a laparoscopic procedure or open surgery. The aims of the investigation were to determine the advantages and disadvantages of both surgical approaches in terms of oncological safety and surgical outcome.

Material and Methods

At a single tertiary university center, a retrospective analysis of patients with histologically confirmed endometrioid endometrial cancer, presenting from 2006 to 2016, was performed. Using the hospital information system, the patients' medical records were collected and analysed. Data collected included intra- and post-operative parameters, such as complication rates, the radicality of lymphadenectomy, blood loss, the duration of surgery and the duration of hospitalization, for all patients with endometrioid endometrial cancer, treated by the laparoscopic procedure or open surgery. The five-year oncological outcome was analyzed.

Patients without well documented histopathological results were excluded. Intra- and post-operative data, as well as clinical parameters were analyzed. The majority of operations until 2010 were performed by the open approach. Laparoscopic access was used on a standard basis after this time. Patients were divided by technique into those that underwent surgery by laparoscopy [laparoscopy group = (LSC group)], and those patients operated by laparotomy [laparotomy group = (LAP group)]. The study was in compliance with the Helsinki Declaration and was approved by the Ethics Committee of the University of Luebeck (approval number: 18-229A, date: 16.08.2018). Informed consent was obtained. Patients with primary metastasis or International Federation of Gynecology and Obstetrics (FIGO) stage 4 disease, or cancer of non-endometrioid histology, such as a serous or clear cell carcinoma, or patients with incomplete resection (R1), were not included in the study.

All patients underwent hysterectomy and bilateral adenectomy. Depending on tumor stage, peritoneal biopsies or pelvic and para-aortic lymphadenectomy were performed. Frozen sections were used to estimate the depth of myometrial invasion intraoperatively. Pelvic and para-aortic lymphadenectomy was performed in cases of myometrial invasion of 50% or more (17,18). The uterus was sent to an experienced pathologist and evaluated both macroscopically and microscopically. Cancer was categorized according to the FIGO staging system. In keeping with our clinical protocols, which concur with the German guidelines (17), patients were given a single-shot intravenous antibiotic intra-operatively and low-dose heparin post-operatively.

A pre-operative score was used to assess the risk of the surgical access due to previous operations. One point was assigned for each laparoscopy in the patient's medical history, and two points for each laparotomy, whether transverse or longitudinal. Postoperative complications were classified according to the Clavien-Dindo classification (19). Grade 1 and 2 complications were rated mild, and grades 3-5 complications severe. Postoperative complications were recorded until one month after the operation. Patients were followed up for at least five years postoperatively on the basis of the hospital information system or by letter. Follow-up data included the location of recurrence, recurrence-free survival rates, and overall survival rates. Local recurrence was defined as disease in the vaginal vault or lesser pelvis, whereas distant metastasis included disease in the lungs, lymph nodes, or liver.

Statistical analysis

Statistical analysis was performed by IBM SPSS Statistics for Windows, version 21.0 (IBM Inc., Armonk, NY, USA). Qualitative variables were described by frequency (percentage) and

compared between groups using the chi-square test or Fisher's exact test, as appropriate. Normal distribution of data was assessed using a one-sample Kolmogorov-Smirnov test. Quantitative variables were expressed as the mean and standard deviation or median. The Mann-Whitney U test and Student's t-test were also used. P-values less than or equal to 0.05 were considered statistically significant.

Results

There were a total of 151 cases, of which 80 patients were included in the LSC group and 71 patients were included in the LAP group. The mean age of patients in the LSC and LAP groups were 63.75±12 years and 64.93±13 years, respectively (p=0.633). The groups did not differ significantly in terms of their physical constitution or American Society of Anesthesiology (ASA) classification. Sociodemographic parameters are presented in Table 1. The applied pre-operative score yielded no significant difference between groups in the number of previous abdominal procedures.

Intra-operative parameters are shown in Table 2. Pelvic lymphadenectomy was performed in 42 patients in the LSC group and 46 patients in the LAP group. The mean duration of the operation was 171.48±94 minutes in the LSC group and 176.32±84 minutes in the LAP group (p=0.335). Median blood loss, measured by the difference between pre- and post-operative hemoglobin (Hb) levels, differed significantly between the groups (Table 2). Mean blood loss was 121.3 mL in the LSC group and 286.4 mL in the LAP group (p<0.001). Injuries to intra-abdominal organs occurred exclusively in the LAP group; these consisted of three perforations of the bladder and one injury to the small bowel.

As shown in Table 2, the groups were homogeneous in regard of tumor stage. The majority of patients were operated on at FIGO stage 1 in both groups (80% in the LSC group and 73.2% in the LAP group). Cancer grades did not differ significantly between groups: a little more than 60% of the cancers were grade 1 tumors in both groups. On average, 16.2±11 pelvic lymph nodes were removed by laparoscopy and 18.1±14 by laparotomy (p=0.092). Furthermore, 12.5±8 para-aortic lymph nodes were removed by laparoscopy and 12.1±5.4 lymph nodes by laparotomy (p=0.510). Positive pelvic lymph nodes were found in seven (8.75%) patients who underwent laparoscopic surgery and six (8.45%) who underwent open surgery (p=0.484).

Postoperative data are shown in Table 3. Patients in the LSC group were hospitalized on average 5.73 days postoperatively. In comparison, patients who underwent laparotomy were hospitalized for 12.25 days after the operation (p<0.001). According to the Clavien-Dindo classification, significantly more grade 3b complications occurred in the LAP group (10%; n=7)

Table 1. Demographic data and surgery groups

Parameters	LAP (n=71)	LSC (n=80)	Total	p-value
Age (years)	64.93±13.28	63.75±12.52	64.30±12.86	0.673†
BMI (kg/m²)	29.7319±6.33	30.6538±9.23	30.2245±8.00	0.978†
ASA I	10 (14.5%)	4 (5.1%)	14 (9.5%)	0.051††
ASA II	31 (44.9%)	41 (51.9%)	72 (48.6%)	0.397††
ASA III	27 (39.1%)	33 (41.8%)	60 (40.5%)	0.744††
ASA IV	1 (1.4%)	1 (1.3%)	2 (1.4%)	1.000†††
Mean no. of pregnancies	2.19±1.66	1.62±1.27	1.89±1.49	0.046†
Mean no. of births	1.86±1.45	1.44±1.22	1.64±1.35	0.091†
Premenopausal	12 (16.9%)	12 (15.2%)	24 (16.0%)	0.775††
Postmenopausal	59 (83.1%)	67 (84.8%)	126 (84.0%)	0.775††
Smoking	15 (21.4%)	15 (20.0%)	30 (20.7%)	0.832††
Pre-operative score 6	2 (2.8%)	0 (0.0%)	2 (1.3%)	0.219†††
Pre-operative score 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Pre-operative score 4	2 (2.8%)	4 (5.0%)	6 (4.0%)	0.685†††
Pre-operative score 3	1 (1.4%)	3 (3.8%)	4 (2.6%)	0.623†††
Pre-operative score 2	5 (7.0%)	6 (7.5%)	11 (7.3%)	0.914††
Pre-operative score 1	5 (7.0%)	14 (17.5%)	19 (12.6%)	0.053††
Pre-operative score 0	56 (78.9%)	53 (66.3%)	109 (72.2%)	0.084††

(n) indicates the number of patients in each subgroup who reported for evaluation.
LAP: Laparotomy group, LSC: Laparoscopy group, BMI: Body mass index, ASA: American Society of Anesthesiologists Physical Class System, †Mann-Whitney U test, ††chi-square test, †††Fisher's exact test

than in the LSC group (0%; n=0) (p=0.004). More numerous high-grade complications (grades 3a to 5) occurred in patients of the LAP group compared to the LSC group (p=0.045).

The LSC and LAP groups had similar five-year disease-free survival rates (88.7% vs. 91.5%, respectively). Disease recurrence was noted in nine patients in the LSC group and six patients in the LAP group (Figure 1). Local recurrence was observed in five patients (four in the LSC group and one in the LAP group), whereas distant metastases were registered in two patients (0 in the LSC group and two in LAP group). The remaining patients had both local and distant disease recurrence. The five-year survival rate did not differ significantly: 91.2% vs. 97.2% in the LSC and LAP groups, respectively. Seven patients in the LSC group and two in the LAP group died. Adjuvant therapy (radiation with or without chemotherapy) was applied to a similar extent in both groups. Median disease-free survival was 14.83±11 months in the LSC group and 15.33±5 months in the LAP group; overall survival rates were 25.00±15 and 32.00±30 months, respectively.

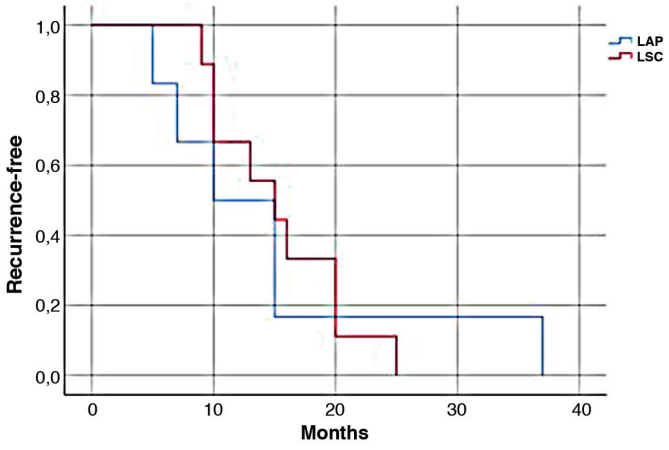

Figure 1. Five-year disease-free survival rates with reference to the surgical procedure (laparotomy vs. laparoscopy) in 151 patients with endometrioid endometrial cancer (p=0.864)

Discussion

The treatment of endometrioid endometrial cancer by the laparoscopic approach is associated with fewer intraoperative and postoperative complications than treatment by open surgery. Blood loss was significantly lower and the duration of hospitalization shorter in the laparoscopic group. Five-year disease-free survival rates and overall five-year survival rates were similar in both groups.

The laparoscopic approach is used to an increasing extent, especially in early stages of cancer. Tumor stage and lymphadenectomy rates were similar in both groups. The published literature reports more frequent use of open surgery than laparoscopy in patients with higher FIGO stages of disease (20-22). According to international data, minimally invasive surgery has been performed in 1.88-4.75% of patients with FIGO stage 3A, and in 0-1.54% of patients with FIGO stage 3B disease (21,23). These rates are somewhat lower than those registered in the present study (8.8%). The mean age and body mass index of our patients are in line with published data for endometrial

Table 2. Intraoperative parameters and tumor stage

Parameters	LAP (n=71)	LSC (n=80)	Total	p-value
Duration of operation (minute)	173.73±76.52	182.53±90.18	178.38±83.84	0.806†
Lymphadenectomy	46 (65.7%)	42 (53.2%)	88 (59.1%)	0.120††
Weight of uterus (g)	142.5	104	-	-
Size of tumor (mm)	34.33±25.67	32.59±18.00	33.58±22.55	0.974†
Invasion depth (mm)	8.56±7.63	5.91±5.46	7.43±6.88	0.099†
Intraoperative blood loss Hb loss; (g/dL)	1.923±1.34	1.317±1.15	1.582±1.27	0.005†
Bladder injury	3 (4.5%)	0 (0.0%)	3 (2.1%)	0.094†††
Ureter injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Bowel injury	1 (1.5%)	0 (0.0%)	1 (0.7%)	0.459†††
FIGO I	52 (73.2%)	64 (80.0%)	116 (76.8%)	0.326††
FIGO II	9 (12.9%)	7 (8.8%)	16 (10.7%)	0.416††
FIGO III	6 (8.5%)	7 (8.8%)	13 (8.6%)	0.948††
Grade 1	43 (61.4%)	50 (62.5%)	93 (62.0%)	0.893††
Grade 2	19 (27.1%)	16 (20.0%)	35 (23.3%)	0.302††
Grade 3	8 (11.4%)	14 (17.5%)	22 (14.7%)	0.294††

(n) indicates the number of patients in each subgroup who reported for evaluation.
LAP: Laparotomy group, LSC: Laparoscopy group, FIGO: International Federation of Gynecology and Obstetrics, †Mann-Whitney U test, ††chi-square test, †††Fisher's exact test

cancer. Our groups were also homogeneous in regard of their ASA scores. In contrast, Schramm et al. (24) reported a poor constitutional status in 55.9% of their 254 patients (ASA score of 3 or 4). A comparison of the present study with previous reports is hindered by these differences (24).

In line with published data, there was a higher median average blood loss in the LAP group than in the LSC group (1.9 vs. 1.3 g/dL). Lu et al. (6) analyzed 272 patients with endometrial cancer prospectively, and noted a statistically significant reduction of blood loss when using the laparoscopic approach compared to the open approach (median blood loss, 86 vs. 419 mL). In a meta-analysis of three randomized controlled trials, comprising 313 patients, laparoscopy was associated with a large and statistically significant reduction in blood loss compared to laparotomy (mean difference, 106.82 mL) (12). However, in our study, blood loss was estimated by the surgeon and determined by the difference in Hb levels before and after surgery.

As expected, the duration of hospital stays was longer in the LAP group than in the LSC group (12.25 days vs. 5.73). However, the mean average duration of hospitalization after laparotomy, as reported in the published literature (3.2 to 8.2 days), is shorter than that registered in the present study. The significantly longer postoperative stay of our patients may be due to the fact that FIGO stage 3 disease was not included in many studies. Moreover, the duration and total flow rate of intraperitoneal drains were significantly greater in women undergoing open surgery, as was the quantity of drainage in 24 hours. However, since the number of resected pelvic lymph nodes did not differ significantly between groups, the higher flow rate in drains may have been due to the traumatic nature of open surgery.

The mean duration of the operation was only five minutes shorter in the LSC than in the LAP group (171 vs. 176 minutes). This is in contrast to Kyrgiou et al. (25), who reported a longer time taken for laparoscopic surgery compared with the open approach (150 vs. 105 minutes). Lu et al. (6) mentioned a shorter median operating time in the LSC group compared with the LAP group (211 minutes vs. 261 minutes, $p<0.01$). Published data concerning the average duration of laparoscopic procedures for endometrial carcinoma range from 75.8 to 287 minutes, and for open surgery between 79 and 247.8 minutes (20,23,26,27). The large variation in the duration of surgery may be explained by the fact that patients with different FIGO stages, who underwent different operative procedures, were evaluated in these studies.

In general, sufficient and similar numbers of pelvic and para-aortic lymph nodes were removed in both our patient groups. The published literature reports a wide range of resected pelvic lymph nodes by the laparoscopic approach (8.86 to 24.1) or by laparotomy (6.1 to 30.8). Open surgery appears to be more radical in regard of lymphadenectomy (28,29). However, the role and the extent of lymphadenectomy remain a debated issue in the scientific community. The German guidelines recommend the removal of at least 15 pelvic and 10 para-aortic lymph nodes for surgical staging and for selecting the appropriate adjuvant therapy, but provide no data about a potential survival benefit (15). Systematic lymphadenectomy may cause intra- and post-operative complications. According to the GOG 244 trial, systematic lymphadenectomy has a negative impact on quality of life in the majority of patients (30). An update of scientific evidence may well cause clinicians to depart from the policy

Table 3. Postoperative parameters and complication rates

Parameters	LAP (n=71)	LSC (n=80)	Total	p-value
Postoperative days in hospital (d)	12.25±6.40	5.73±3.75	8.72±6.07	<0.001†
Drainage duration (d)	5.91±3.99	3.86±1.80	4.82±3.18	0.003†
Drainage quantity (mL)	1160	370	-	-
Clavien-Dindo 1	48 (68.6%)	69 (87.3%)	117 (78.5%)	0.005††
Clavien-Dindo 2	12 (17.1%)	6 (7.6%)	18 (12.1%)	0.074††
Clavien-Dindo 3a	0 (0.0%)	4 (5.1%)	4 (2.7%)	0.123†††
Clavien-Dindo 3b	7 (10.0%)	0 (0.0%)	7 (4.7%)	0.004†††
Clavien-Dindo 4a	3 (4.3%)	0 (0.0%)	3 (2.0%)	0.101†††
Clavien-Dindo 4b	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Clavien-Dindo 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Clavien-Dindo (mild) Grades 1 and 2	60 (85.7%)	75 (94.9%)	135 (90.6%)	0.054††
Clavien-Dindo (severe) Grades 3a-5	10 (14.3%)	4 (5.1%)	14 (9.4%)	0.045††

(n) indicates the number of patients in each subgroup who reported for evaluation.
LAP: Laparotomy group, LSC: Laparoscopy group, †Mann-Whitney U test, ††chi-square test, †††Fisher's exact test

of "everything or nothing" to the acceptance of "less is more", as currently used in breast surgery. This would also signify a departure from purely technical advancements in surgery, towards the achievement of a beneficial oncological outcome for patients.

Despite the larger number of patients with higher FIGO stages of disease, no patient in the LSC group experienced intra-operative injury. In contrast, 4.2% of patients in the open surgery group had bladder injuries and 1.4% had a bowel injury. Complications in the urinary tract in patients with endometrial cancer range from 0.3% to 4.65%, and bowel injuries range between 0.85% and 13.1% (21,31). In a study performed by Cheng et al. (32) comprising 120 patients, obese women with endometrial cancer who underwent laparoscopic surgery had significantly fewer intra-operative and postoperative complication than those who were treated by laparotomy (5.0% vs. 16.7% and 6.7% vs. 20.0%, respectively). Favero et al. (33) noted lower complication rates for laparoscopic surgery compared with open surgery (18% vs. 36%) in patients with type 2 endometrial cancer. We noted similar results for complications based on Clavien-Dindo classification: the LAP group experienced both mild and severe complications significantly more frequently than the LSC group.

The published literature contains meager and very heterogeneous information about postoperative complications according to Clavien-Dindo classification. First-degree complication rates are 25.5-96%, and severe complication rates 5-51.7% (31). However, the above-mentioned data prove that the laparoscopic approach is a safe option for the treatment of endometrial cancer.

We registered no significant difference in disease recurrence rates between LSC (11.3%) and LAP (8.5%). Local recurrences were more common in the LSC group (4 vs. 1), and distant recurrent disease was more common in the LAP group (2 vs. 0). However, reliable statements in this regard are hindered by the fact that most of the recurrences were local as well as distant, and the number of cases was small. In a prospective study with a median follow-up period of 68 months, Lu et al. (6) reported similar results for both groups: recurrence rates were 4.6% for patients treated by the laparoscopic approach versus 5.0% for those treated by open surgery. However, the duration of follow-up varied between 2 and 153 months. Slightly higher recurrence rates were reported by Walker et al. after a three-year follow-up; 11.4% in the LSC group versus 10.2% in the LAP group. We conclude that recurrence rates in patients with endometrial cancer are not related to the open or laparoscopic surgical approach. However, it would be appropriate to analyze locoregional and distant recurrent disease in a large patient population after minimally invasive surgery for endometrial tumors outside the uterus.

A Cochrane meta-analysis of six large studies, assessing 3,993 individuals, yielded no significant difference in overall survival between women who underwent laparoscopy and those who underwent laparotomy (12). Analogous to our data, the 4.5-year overall survival rate was 92.0% in the LSC group and 92.4% in the LAP group. In a randomized clinical trial comprising 122 patients, Tozzi et al. (34) registered overall survival rates of 83% in the LSC group versus 86.5% the LAP group after a median follow-up of 44 months. Our study, one of the few to report overall five-year survival rates, revealed slightly lower overall survival (91.2% vs 97.2%) and median overall survival rates (25 vs. 32 months) for LSC compared to LAP, but the difference was not significant. In fact, the use of minimally invasive surgery in cancer patients is a very controversial issue, especially in cases of advanced endometrial cancer with tumor outside the uterus (14). However, patients older than 60 years of age who underwent laparoscopic staging for uterine cancer had significantly reduced morbidity rates (35). A multivariate analysis of the oncologic outcome in regard of tumor stage, age, and physical status may serve as a basis for devising individual therapy concepts for patients.

Study limitations

The potential limitations of the present analysis include its retrospective design and the absence of randomization. Moreover, the data were derived from a single center. The strengths of the present investigation are the inclusion of homogenous groups, the analysis of postoperative complications according to the Clavien-Dindo classification, and the long duration of follow-up, which permitted analysis of five-year outcomes.

Conclusion

These data highlight the superiority of the laparoscopic approach over open surgery for the treatment of endometrioid endometrial cancer in terms of overall morbidity, intraoperative complications, blood loss, post-surgical recovery, as well as the incidence and severity of postoperative complications in this population. Both approaches permitted a systematic pelvic and para-aortic lymphadenectomy with a sufficient amount of resected lymph nodes. The laparoscopic approach appears to be as safe as the conventional open technique, but provides a better surgical outcome and might therefore be more beneficial for the patient.

Ethics Committee Approval: *The study was in compliance with the Helsinki Declaration and was approved by the Ethics Committee of the University of Luebeck (approval number: 18-229A, date: 16.08.2018).*

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The effect of biacromial and bideltoid distance on shoulder dystocia and birth weight in newborns

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Abstract

Objective: To evaluate the relationship between neonatal biacromial and bideltoid diameter (BDD), birth weight and shoulder dystocia (SD).

Material and Methods: This was a prospective observational study conducted on 161 pregnancies who applied to Private Lokman Hekim Hospital for follow-up between February 2021 and August 2021. Maternal height, weight, parity, and presence of SD in the second stage of labor were evaluated in the patients included in the study. The weight, height, head circumference, biacromial and BDD measurements of newborn babies were taken within the first two hours after birth. The primary purpose of the study was to evaluate the relationship between the biacromial and BDD and SD. The secondary purpose of the study was to evaluate the relationship between the biacromial and BDD and macrosomia.

Results: The mean age and post-pregnancy body mass index of the participants were 31.3±4.4 years and 29.0±4.0 kg/m^2, respectively, and 42.9% (n=69) delivered vaginally. The incidence of macrosomia was 6.8% (n=11) in all women and the incidence of SD was 7.2% (n=5) in women who had vaginal deliveries. The mean biacromial diameter (BAD) was 12.4±1.0 cm and the mean BDD was 18.2±1.7 cm. A correlation rate of 0.373 was found between SD and the BAD, and 0.484 between SD and the BDD. The correlation coefficients between macrosomia and the biacromial and BDD were 0.213 and 0.420, respectively. In cases in which the BDD was ≥21 cm, the sensitivity for SD was 100%, the specificity was 90.63%, and the accuracy was 91.30%. The cut-off point for the BAD was ≥14 cm, and the sensitivity and specificity for SD was 63.64% and 89.33%, respectively. The highest correlation for SD was obtained in cases in which there was a history of SD (0.648).

Conclusion: The relationship between neonatal biacromial and BDD, and macrosomia and SD were significant. There was no difference between the correlation values of the two measurements in terms of SD. However, the correlation coefficient of the BDD was greater for macrosomia. (J Turk Ger Gynecol Assoc 2022; 23: 241-8)

Keywords: Neonatal shoulder width, macrosomia, shoulder dystocia, delivery

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Introduction

Shoulder dystocia (SD) can be defined as difficulty or failure to deliver the fetal shoulders after delivery of the fetal head. It has different definitions according to the time required for the trunk to be delivered after the fetal head has emerged or the need for auxiliary maneuvers (1,2). According to the first definition, SD is seen at a rate of about 2-3% in all deliveries (1). It occurs unpredictably at birth and is a medicolegal problem due to its consequences in newborns (2).

The most common and known risk for SD is macrosomia. Macrosomia can be defined as a birth weight above the 90th percentile or over 4000-4500 g according to gestational age (3). In addition to many maternal factors, such as maternal weight before pregnancy, weight gain during pregnancy, increasing parity, and fetal factors, such as fetal sex, genetic and environmental factors also have an effect on macrosomia (4). It is important to detect macrosomia in the antenatal period, since maternal and fetal complications, SD risk and need for cesarean section increase with macrosomia (5). However, although it is known that it is more common in macrosomic infants, it is also seen in non-macrosomic infants, making the antenatal detection of SD difficult (1). Therefore, studies have

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been performed to investigate antenatal parameters other than fetal weight to predict SD (6,7).

In anthropometric evaluations performed on newborns, the fetal shoulder circumference was found to be significantly larger in pregnancies complicated with SD when compared to cases without SD (8). However, measurement of the shoulder circumference is difficult in antenatal ultrasonographic evaluation. To obtain information about the shoulder circumference, fetal biacromial diameter (BAD) measurement was investigated. Calculations were made for BAD based on different measurements taken from the fetus, but it was reported that the correlation of fetal measurements with actual postnatal measurements was not accurate (9). Since SD arises as a result of incompatibility between fetal BAD and maternal pelvic outlet, the relationship between neonatal BAD and bideltoid diameter (BDD) and SD was investigated herein. The primary purpose of the study was to evaluate the relationship between BAD and BDD with SD, and the secondary purpose was to evaluate the relationship between BAD and BDD in cases of macrosomia.

Material and Methods

This study was a prospective, cross-sectional study conducted with 161 patients who came to Private Lokman Hekim Hospital pregnancy outpatient clinic between 02.2021 and 08.2021.

Following the approval of the Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/013, date: 19.01.2021), full term singleton pregnancies without fetal anomaly, regardless of parity and previous delivery type, were included in the study. Patients with a history of type 1 or type 2 diabetes mellitus, gestational diabetes, antepartum hemorrhage, intrauterine growth restriction, intrauterine exitus and musculoskeletal pathology that may cause complications during normal delivery were not included in the study.

The purpose of the study and what would be done within the scope of the study were explained to all the patients, and written consent was obtained from participants. The study was conducted in accordance with the Principles of the Helsinki Declaration. Information about age, parity, height, pre-pregnancy and birth weight, macrosomia and SD history of previous deliveries were obtained from all the participants. Body mass index (BMI) was calculated in kg/m^2.

Mode of delivery, need for episiotomy, vacuum-assisted delivery, presence of SD, and maneuvers to release the affected shoulder were recorded. The presence of SD was accepted as any case in which the contraction that came after the uterine contraction leading to the delivery of the fetal head, and pushing by the mother, was insufficient for the delivery of the shoulders (1).

The weight, height, and head circumference of all newborns were recorded by the neonatal nurse. The neonatal weight was measured with a digital scale with a sensitivity of ±50 g (Medika plus, Turkey). A birth weight of 4000 g and above was accepted as macrosomia. The baby's head circumference was measured from the glabella to the occiput with an inflexible tape measure and recorded in the nearest whole cm. The baby's height was measured with an inflexible tape measure between the tip of the head and the heel while the baby was in the supine position on a flat surface and was recorded as the nearest whole cm. BAD and BDD was measured with an inflexible tape measure when the baby was in the supine position on a flat surface and recorded in cm by the author in accordance with the definition of Şener and Alpa (10). These definitions are: distance between the outermost parts of the acromial processes for BAD; and the distance between the origin of the most prominent point of the deltoid muscles for BDD (10). In all the measurements, the average of three consecutive measurements was taken.

Delivery was performed using the McRoberts' maneuver (hyperflexing the mother's legs tightly to her abdomen) in three of the SD cases and using the Rubin's 1 maneuver (the rotation of anterior shoulder under pubic symphysis by giving suprapubic pressure) following the McRoberts' maneuver in the other two (1). All the newborns were delivered without any complications, such as clavicle fracture and brachial plexus paralysis. All the newborns were examined by a pediatrician within the first hour after delivery and were found to be normal.

Statistical analysis

For the statistical analysis and calculations, IBM SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) and MS-Excel 2016 (Microsoft, Redmond, VA, USA) programs were used. Statistical significance level was accepted as $p<0.05$. Qualitative data were expressed as the frequency and percentage. Quantitative data were summarized as the median (quartile 1-3), minimum, maximum, and mean ± standard deviation. To compare between the patients with and without SD (or macrosomia), the categorical variables were analyzed using the Fisher's exact test and the numeric variables were analyzed using the Mann-Whitney U test. The point biserial, phi, and Cramer V correlation coefficients were calculated with a 95% confidence interval (CI) to measure the relationship between SD (or macrosomia) and a continuous, a binary (or more than two category) variable. If the CI for the correlation coefficient includes zero, then the relevant coefficient is meaningless. Correlation coefficient values were interpreted as: 0.00-0.29 negligible; 0.30-0.49 low; 0.50-0.69 moderate; 0.70-0.89 high; and 0.90-1.00 very high correlation (11). The "cocor" R package was used to test significance for

the difference between two correlations with one common variable (12). The receiver operating characteristic (ROC) curves were constructed to determine the cut-off points using the Youden index. The sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy value of the BAD and BDD for detecting SD (or macrosomia) were obtained.

Results

Descriptive information and birth data of the 161 women included in the study are given in Table 1. The incidence of macrosomia was 6.8% (n=11) in the whole cohort. The mean, median and minimum-maximum values are given Table 2. The mean age and post-pregnancy BMI of the participants were 31.3±4.4 years and 29.0±4.0 kg/m^2, respectively, and 42.9% (n=69) delivered vaginally. SD was observed only in women who had vaginal deliveries and the incidence of SD was 7.2% (5/69). The mean BAD was 12.4±1.0 (minimum: 10, maximum: 14) cm, and the mean BDD was 18.2±1.7 (minimum: 14, maximum: 23) cm. The correlation between gender and BAD was -0.066 (95% CI: -0.22 to 0.09; p=0.407) and between gender and BDD was -0.024 (95% CI: -0.18 to 0.13; p=0.766); neither were significant.

Results regarding the comparison of maternal and neonatal clinical information that may be associated with SD risk are given in Table 3. SD was observed only for women who had vaginal deliveries, so the SD results included only these women's findings. Presence of a history of SD, a history of macrosomia, high birth weight of the baby, high BAD, high BDD, large baby head circumference, high maternal BMI value, and low maternal height/infant weight ratio were observed in cases with SD (p<0.05). The highest correlation was with a history of SD (0.648). The correlation coefficient was 0.373 between the incidence of SD and BAD, and 0.484 between the incidence of SD and BDD. When the relevant coefficients were compared, there was no significant difference in relation to SD (p=0.264).

The results regarding the comparison of the maternal and neonatal clinical information that may be associated with macrosomia are given in Table 4. Macrosomia was observed in babies born by both delivery methods, and there was no difference in terms of the delivery rate of those with macrosomia (45.5% vs. 54.5% of macrosomic neonates were born by caesarean section and vaginal delivery, respectively). There was no difference between the parity, number of pregnancies, type of delivery, sex, maternal height variables, and macrosomia groups (p>0.05). When the correlations were examined, the correlation between macrosomia and history of dystocia was 0.584. The correlation coefficients between macrosomia and BAD and BDD variables were 0.213 and 0.420, respectively. There was a significant difference between these two coefficients (p=0.004).

Table 1. The descriptive statistics of the maternal and neonatal characteristics (n=161)

Variable	n (%)	Variable	n (%)
Parity		**Biacromial diameter (cm)**	
Primiparous	73 (45.3)	10 - <12	29 (18.0)
Multiparous	88 (54.7)	12 - <14	109 (67.7)
History of dystocia#		14 - <16	23 (14.3)
Yes	4 (5.8)	**Bideltoid diameter (cm)**	
No	65 (94.2)	14 - <16	8 (5.0)
History of macrosomia		16 - <18	51 (31.6)
Yes (>4000 gr)	15 (9.3)	18 - <20	75 (46.6)
No	146 (90.7)	20 - <22	22 (13.7)
Shoulder dystocia#		22 - <24	5 (3.1)
Yes	5 (7.2)	**Delivery method**	
No	64 (92.8)	Vaginal delivery	69 (42.9)
Macrosomia		Caesarean section	92 (57.1)
Yes (>4000 gr)	11 (6.8)	**Gender**	
No	150 (93.2)	Boy	82 (50.9)
Vacuum-assisted delivery#		Girl	79 (49.1)
Yes	5 (3.1)	**Episiotomy#**	
No	64 (39.8)	Yes	25 (36.2)
		No	44 (63.8)

#(n=69) on women who have vaginal delivery

In this cohort, SD developed in 1 (1.6%) of 63 non-macrosomic infants and 4 (66.7%) of 6 macrosomic infants (p<0.05). Macrosomia was seen in 4 (80.0%) of 5 infants with SD and 2 of 64 (3.1%) infants without SD.

The ROC analysis results for BAD and BDD on SD development and the incidence of macrosomia are given in Table 5. The areas under the curve (AUC) for both cases were shown in Figure 1a, b. ROC analysis of the association of BAD, BDD and SD gave AUC values of 0.930 and 0.966, respectively (p=0.001 and p<0.001). The sensitivity rate according to the cut-off point determined for both variables was 1.00 (100.00%). A cut-off of ≥21 cm for BDD yielded a sensitivity for SD of 100%, the specificity was 90.63% and the accuracy was 91.30%. Similarly, for macrosomia, a significant cut-off point was identified for both variables (p<0.05). The cut-off point for the BAD was ≥14 cm, and the sensitivity and specificity for SD was 63.64% and 89.33%, respectively.

Table 2. The minimum, maximum, median and mean values of variables (n=161)

Variable	Minimum; maximum	Median (Q_1-Q_3)	Mean ± SD
Birthweight (g)	2235; 4590	3350 (3065-3620)	3349.7±436.3
Biacromial diameter (cm)	10; 14	12 (12-13)	12.4±1.0
Bideltoid diameter (cm)	14; 23	18 (17-19)	18.2±1.7
Head circumference (cm)	31; 39	35 (34-36)	34.9±1.5
Neonatal length (cm)	42; 56	50 (49-51)	50.0±2.0
Maternal age (years)	20; 42	31 (28-34)	31.3±4.4
Non-pregnant weight (kg)	46; 97	64 (57-70)	64.3±10.9
Prepartum weight (kg)	57; 115	76 (70-86)	78.7±11.8
Weight gain (kg)	3; 35	14 (10.5-17)	14.4±5.4
Maternal height (cm)	148; 178	165 (160.5-168)	164.6±5.2
Maternal BMI (kg/m^2)	20; 42.2	28.2 (26.2-31.6)	29.0±4.0
Maternal height/infant weight ratio	0.04; 0.08	0.049 (0.046-0.053)	0.05±0.01
Infant weight/maternal BMI ratio	68.9; 181.32	116.83 (105.11-129.32)	116.96±18.48

Data are presented as frequency (percentage) for categorical variables and minimum; maximum, median (Q1-Q3), mean ± SD for numeric variables.
SD: Standard deviation, BMI: Body mass index, Q_1-Q_3: Quartile 1-Quartile 3

Table 3. The maternal and neonatal characteristics of patients with and without SD#

Variable	Without SD, (n=64)	With SD, (n=5)	p*	r** (95% CI lower; upper bound)
Parity (multiparous)	39 (60.9)	4 (80.0)	0.643	0.102 (-0.138; 0.331)
History of dystocia#	1 (1.6)	3 (60.0)	**0.001**	0.648 (0.486; 0.767)
History of macrosomia	4 (6.3)	3 (60.0)	**0.006**	0.462 (0.253; 0.630)
Gender (girl)	29 (45.3)	3 (60.0)	0.657	0.076 (-0.164; 0.307)
Birthweight (g)	3365 (3117.5-3603.8)	4140 (3847.5; 4345)	**<0.001**	0.496 (0.294; 0.656)
Biacromial diameter (cm)	13 (12; 13)	14 (14; 14)	**<0.001**	0.373 (0.150; 0.560)
Bideltoid diameter (cm)	18 (17; 19)	21 (21; 22.5)	**<0.001**	0.484 (0.279; 0.647)
Head circumference (cm)	34 (34; 36)	36 (35; 37.5)	**0.031**	0.285 (0.052; 0.489)
Neonatal length (cm)	50 (49; 51.8)	51 (50; 53)	0.181	0.153 (-0.087; 0.376)
Maternal age (years)	32 (28; 34)	31 (29.5; 36)	0.711	0.050 (-0.189; 0.283)
Weight gain (kg)	13 (10; 15)	14 (11.5; 25)	0.261	0.196 (-0.043; 0.414)
Maternal BMI (kg/m^2)	27.4 (26.2-30.4)	30.8 (29.9-33.8)	**0.019**	0.254 (0.018; 0.463)
Maternal BMI (>30 kg/m^2)	20 (31.3)	4 (80.0)	**0.046**	0.265 (0.030; 0.472)
Maternal height (<155 cm)	2 (3.1)	1 (20.0)	0.205	0.215 (-0.023; 0.43)
Maternal height/infant weight ratio	0.049 (0.047-0.053)	0.042 (0.039-0.043)	**<0.001**	-0.398 (-0.58; -0.178)
Infant weight/maternal BMI ratio	120.69 (109.54-131.68)	138.47 (113.97-142.59)	0.189	0.168 (-0.072; 0.389)

#(n=69) on women who have vaginal delivery. Data are presented as frequency (percentage) and median (Quartile 1-Quartile 3). *The Fisher's exact test and Mann-Whitney U test are used to compare groups with respect to categorical and numeric variables, respectively. Bold values denote statistical significance at the p<0.05 level. **The point biserial, phi and Cramer's V correlation coefficient are calculated with their 95% CI.
SD: Shoulder dystocia, CI: Confidence interval, BMI: Body mass index

Post-hoc power results: The effect sizes from the non-parametric approaches for the BAD and the BDD variables were determined as d=0.87 and 0.93 for SD and as 0.42 and 0.80 for macrosomia, respectively. The post-hoc power values calculated, based on the determined effect size, 0.05 type 1 error, two tails, and sample size were 0.44, 0.49, 0.26, and 0.70. The post-hoc power was found to be low in all three cases, except for the BDD variable in macrosomia.

Discussion

Despite the use of advanced technological facilities, it is still a troublesome situation for clinicians in terms of the difficulty in predicting macrosomia and SD in obstetric practice and the medicolegal problems it may create (2). SD occurs as a result of incompatibility between fetal BAD and maternal pelvis and is more common in macrosomic infants (1). The relationship between newborn weight and SD has been reported to be significant previously (p<0.001) (13). In the present study, 1 (1.6%) of 63 non-macrosomic infants and 4 (66.7%) of 6 macrosomic infants had SD and the correlation coefficient between macrosomia and SD was found to be 0.496. Although different results have been obtained in studies due to the lack of a standard definition, the rate of SD is reported to be around 3% (1) and the rate of macrosomia around 7.74% (3). In the cohort of the present study the SD rate was 7.2% in women who had vaginal deliveries and the macrosomia rate was 6.8%

Table 4. The maternal and neonatal characteristics of patients with and without macrosomia

Variable	Without macrosomia (n=150)	With macrosomia, (n=11)	p*	r** (95% CI lower; upper bound)
Parity (multiparous)	81 (54.0)	7 (63.6)	0.755	0.049 (-0.106; 0.202)
History of dystocia#	1 (1.6)	3 (50.0)	**0.001**	0.584 (0.403; 0.721)
History of macrosomia	9 (6.0)	6 (54.5)	**<0.001**	0.421 (0.285; 0.54)
Delivery method (VD)	63 (42.0)	6 (54.5)	0.532	0.064 (-0.092; 0.217)
Gender (girl)	74 (49.3)	5 (45.5)	>0.999	-0.02 (-0.174; 0.135)
Biacromial diameter (cm)	12 (12; 13)	14 (12; 14)	**0.010**	0.213 (0.06; 0.356)
Bideltoid diameter (cm)	18 (17; 19)	21 (20; 22)	**<0.001**	0.42 (0.284; 0.54)
Head circumference (cm)	35 (34; 36)	36 (36; 38)	**<0.001**	0.319 (0.173; 0.451)
Neonatal length (cm)	50 (49; 51)	53 (51; 53)	**<0.001**	0.347 (0.203; 0.476)
Maternal age (years)	31 (28; 34)	35 (31; 36)	**0.018**	0.175 (0.021; 0.321)
Weight gain (kg)	14 (10; 16)	20 (13; 24)	**0.010**	0.254 (0.103; 0.393)
Maternal BMI (kg/m^2)	27.93 (26.10; 31.59)	30.82 (30.10; 34.06)	**0.009**	0.168 (0.014; 0.315)
Maternal BMI (>30 kg/m^2)	52 (34.7)	9 (81.8)	**0.003**	0.245 (0.094; 0.385)
Maternal height (<155 cm)	4 (2.7)	0 (0.0)	**>0.999**	-0.043 (-0.196; 0.112)
Maternal height/infant-weight ratio	0.05 (0.047; 0.054)	0.039 (0.037; 0.041)	**<0.001**	-0.441 (-0.558; -0.307)
Infant weight/maternal BMI ratio	115.97 (104.54; 128.41)	138.47 (128.00; 142.85)	**<0.001**	0.285 (0.136; 0.421)

#(n=69) on women who have vaginal delivery. Data are presented as frequency (percentage) and median (Quartile 1-Quartile 3). *The Fisher's exact test and Mann-Whitney U test are used to compare groups with respect to categorical and numeric variables, respectively. Bold values denote statistical significance at the p<0.05 level. **The point biserial, phi and Cramer's V correlation coefficient are calculated with their 95% CI.
VD: Vaginal delivery, CI: Confidence interval, BMI: Body mass index

Table 5. Predictive value of biacromial and bideltoid diameter for prediction of SD and macrosomia at birth

	Variable (cm)	AUC (95% CI lower; upper bound)	Cut-off point	p	Sen., (%)	Spe., (%)	PPV, (%)	NPV, (%)	Accuracy, (%)
Shoulder dystocia	Biacromial diameter	0.930 (0.866; 0.993)	≥14	**0.001**	100.00	85.94	35.71	100.00	86.96
	Bideltoid diameter	0.966 (0.922; 0.999)	≥21	**<0.001**	100.00	90.63	45.46	100.00	91.30
Macrosomia	Biacromial diameter	0.723 (0.522; 0.925)	≥14	**0.014**	63.64	89.33	30.44	97.10	87.58
	Bideltoid diameter	0.916 (0.854; 0.978)	≥20	**<0.001**	81.82	88.00	33.33	98.51	87.58

(n=69) for shoulder dystocia and (n=161) for macrosomia.
AUC: Area under the curve, CI: Confidence interval, Sen.: Sensitivity, Spe.: Specificity, PPV: Positive predictive value, NPV: Negative predictive value SD: Shoulder dystocia

for all women, which was consistent with other studies. It was also observed that the relationship of both macrosomia and SD risk with neonatal BAD and BDD was significant (p<0.001).

Factors that contribute to macrosomia are expected to increase the risk of SD. There are studies showing that the risk of macrosomia and SD increases with increasing parity. A weight gain of 100 to 150 g can be observed in each pregnancy due to an increase in parity, which increases the risk of macrosomia in the long run. However, multiparity is not a major risk factor for macrosomia compared to other factors (4). Consistent with these results, no significant relationship was found between parity and macrosomia in our study. However, although there was a statistically significant relationship between multiparity and SD risk in previous studies (p=0.006) (14), no such relationship was found in the present study. Similarly, macrosomia was more common in male fetuses than female fetuses due to the fact that male fetuses are generally approximately 150 g heavier than female fetuses (4). However, no statistically significant relationship was found between sex and macrosomia or SD. Maternal obesity is associated with 4-12 times increase in the probability of macrosomia (4). In addition, previous studies have found a significant relationship between maternal obesity and SD (p<0.001) (14). Our results were consistent with this as the risk of macrosomia and SD in cases in which the maternal BMI was >30 kg/m^2 was significant (p=0.003 and p=0.046, respectively).

In anthropometric studies evaluating the risk of SD in non-macrosomic newborns, it was observed that the risk of SD increased with a low maternal height-newborn weight ratio (14). In keeping with this, the ratio of maternal height-newborn weight was lower in cases with SD in our study. As another anthropometric value, a high newborn weight-maternal BMI ratio also increased the risk of SD (p<0.001) (14). However, in the current study, no statistically significant relationship was found between the ratio of newborn weight-maternal BMI and SD. It has been reported that the risk of SD increased, especially in cases in which the maternal height was <1.55 m (p=0.03) (14), although we found no such association, possibly because of differences in sample populations or sample sizes.

In another study conducted by Bahar (15) on newborns with and without SD, but with similar birth weight, SD risk indicators were evaluated. These authors reported that the presence of a history of SD increased the risk of subsequent birth SD by six-fold, and our findings were consistent with this. In the same study, while no difference was observed between the case and control groups with regard to the newborn head and chest circumference measurements, a statistically significant difference was found between the case and control groups with regard to BAD and head circumference/BAD ratio. The BAD was 15.16 cm in the case group and 14.61 cm in the control group (p<0.001) (15).

In a study conducted by Winn et al. (9) in order to investigate the relationship between newborn BAD and some fetal measurements, it was stated that the strongest correlation with newborn BAD was with fetal chest circumference (r=0.67, p=0.003), followed by arm circumference. Winn et al. (9) reported mean BAD to be 15.5 (±0.9) cm, and that newborn BAD measurement was equal to half of the shoulder circumference. Another study was conducted by Youssef et al. (7) to evaluate the effect of fetal BAD measurement on the prediction of macrosomia. In the ROC analysis of fetal BAD and abdominal circumference in predicting macrosomia and SD

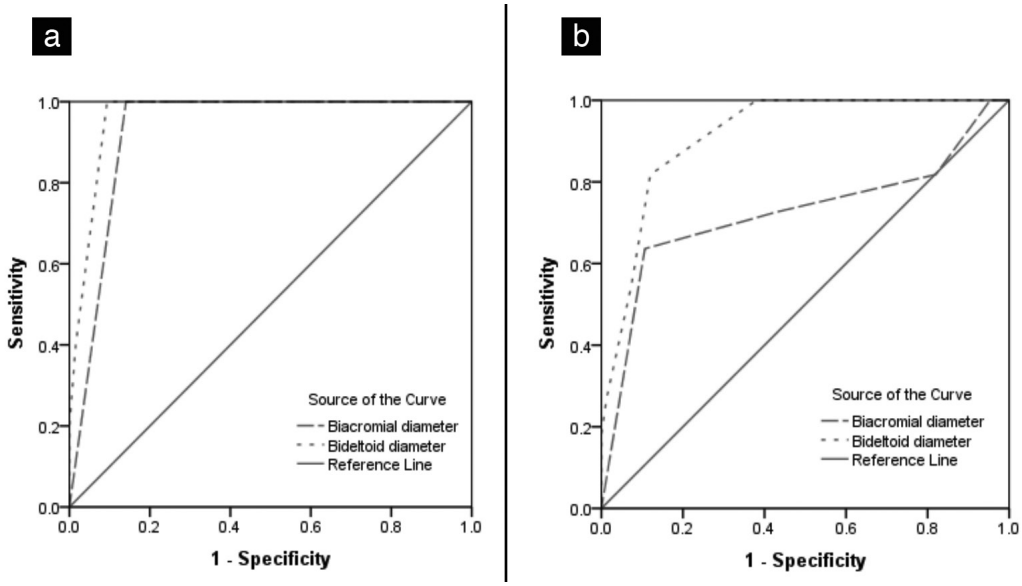

Figure 1. (a,b) Receiver operating characteristic curve analysis of the predictive value of biacromial diameter and bideltoid diameter for prediction of shoulder dystocia and macrosomia at birth, respectively

risk, the AUC was found to be >0.90 in all of the results. When the cut-off value for fetal BAD was taken as 15.4 cm, the PPV for macrosomia was 88.4%, sensitivity was 96.4%, and accuracy was 96.4% (7).

In a study conducted on 2,222 cases in which factors that may be associated with neonatal BAD and SD were evaluated, maternal weight gain, gestational week, BAD and birth weight were determined as predisposing factors for SD. No relationship was found between maternal age, parity, pre-pregnancy weight, maternal height, infant sex, and SD. Significant correlations were found between newborn BAD and parity, non-pregnant weight, weight gain during pregnancy, maternal height, fasting and one-hour glucose values, gestational week, and newborn weight. The strongest correlation was reported between newborn BAD and birth weight ($r=0.59$, $p<0.001$). In that study, the mean BAD was 122.1 mm, and if it was >140 mm, it was considered as the 90th percentile. Again, in that study, the newborn BAD measurement was found to be significantly higher in cases with SD (13).

In the current study, the AUC values for SD and BAD and BDD were 0.930 and 0.966, respectively. The sensitivity rate according to the cut-off point that was determined for both variables was 1.00 (100.00%). For BDD the best cut-off determined for BDD was ≥21 cm. Similarly for macrosomia, a significant cut-off point was determined for both variables ($p<0.05$). The optimal cut-off point for BAD was ≥14 cm, while the optimal cut-off point for BDD was ≥20 cm. We suggest that the relationship between BAD and BDD in predicting the risk of SD and macrosomia makes it important to take these measurements in the antenatal period.

Study limitations

As the definition of SD varies according to the knowledge and skills of the physician, evaluations on this subject are generally subjective. The small sample size was the most important limitation of the study, which is why we preferred non-parametric methods in the analysis phase to minimize the effect of low sample size and imbalance in groups. However, there is a need for much larger, multi-center studies to better investigate the relationships identified in this study, particularly antenatal measurements for predictive purposes.

Conclusion

We have shown in that there is a significant relationship between neonatal BAD and BDD measurements and SD and macrosomia, and that the relationship between BDD and macrosomia is relatively strong. There is a need for future studies that will further explore BAD and BDD measurements in the antenatal period to predict complications.

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Informed Consent: *The purpose of the study and what would be done within the scope of the study were explained to all the patients, and written consent was obtained from participants.*

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Surgical and Medical Practices: E.T., Concept: E.T., P.D., Design: E.T., P.D., Data Collection or Processing: E.T., Analysis or Interpretation: E.T., P.D., Literature Search: E.T., Writing: E.T., P.D.

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Fetal pulmonary artery Doppler parameters in pregnancies complicated with intrahepatic cholestasis of pregnancy: a prospective case-control study

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Abstract

Objective: The primary aim of this study was to determine whether pulmonary artery acceleration time (AT) to ejection time (ET) ratio (PATET) was altered in fetuses of mothers with intrahepatic cholestasis of pregnancy (IHCP). The secondary aim was to investigate the association between fetal pulmonary artery Doppler parameters with neonatal outcomes in pregnancies complicated by IHCP.

Material and Methods: This prospective case control study was conducted in a tertiary perinatal-neonatal center. A total of 18 fetuses whose mothers' pregnancies were complicated by IHCP were included as the study group and a total of 37 fetuses of mothers with healthy pregnancies were selected as controls. Fetal pulmonary artery Doppler parameters (AT; ET; AT/ET ratio) were assessed and neonatal outcomes were evaluated.

Results: Mean pulmonary artery AT, ET and PATET were significantly different between the groups ($p=0.001$, $p=0.024$ and $p=0.003$, respectively). The mean PATET value in the IHCP group was 0.217 ± 0.029 while in the control group it was 0.180 ± 0.020. While PATET values were correlated with gestational age at birth, respiratory distress and need for neonatal intensive care admission were not correlated with PATET.

Conclusion: Higher values of PATET may be a useful biomarker of fetal lung damage, secondary to IHCP. (J Turk Ger Gynecol Assoc 2022; 23: 249-54)

Keywords: Acceleration time, ejection time, intrahepatic cholestasis, pulmonary artery

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Introduction

Intrahepatic cholestasis of pregnancy (IHCP) is the most common hepatobiliary system disease of pregnancy and generally occurs in the late second and third trimesters, with a variable incidence of between 0.4% and 5% (1). IHCP is diagnosed with new-onset pruritus, particularly in the palms and soles of the feet, and elevated maternal serum bile acids and/or liver function enzymes. Furthermore, in the latest articles it has been reported that IHCP may be predicted in the first trimester by using the ratio of aspartate aminotransferase (AST) to platelet ratio index (2). Even though IHCP is generally a benign condition that resolves in two or three weeks after delivery, it is associated with adverse perinatal and neonatal outcomes (3-6). Due to the severity of the disease, a higher incidence of obstetric complications, such as preterm delivery, meconium staining of amniotic fluid, respiratory distress, fetal bradyarrhythmia and fetal demise, has been observed (1,3). It has been suggested that the underlying pathophysiological mechanism to explain these complications is raised bile acids in fetal tissues (7). As in bile acid accumulation in fetal myocardium, chronic exposure to bile acids disrupts fetal pulmonary development and function by blocking surfactant production (1,7). Moreover, in the literature, higher bile acid

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concentration has been detected in cord blood and amniotic fluid and this is associated with lower levels of pulmonary surfactant production so that respiratory distress syndrome (RDS) may be observed more often in affected newborns (8,9). RDS which may even complicate newborns after term delivery, still remains the major cause of neonatal intensive care unit (NICU) admissions, neonatal morbidity and mortality (10). Due to the importance of RDS, prediction of respiratory complications before delivery has been proposed using a range of invasive techniques, such as assessment of lecithin/sphingomyelin ratio in amniotic fluid. However, in the last decade, pulmonary artery acceleration time (AT) to ejection time (ET) ratio (PATET) has been investigated as a non-invasive method for evaluating pulmonary lung maturation (10-13). It has been reported that a low PATET ratio is a reliable ultrasonographic parameter for assessment of fetal lung immaturity, and has been particularly studied in preterm, small-for-gestational age fetuses (10,11).

Based on published evidence, we hypothesized that the effect of IHCP on fetal lung maturation might be detected by evaluating the impact of IHCP on fetal pulmonary artery Doppler parameters. The primary aim of this study was to investigate changes in PATET in the fetuses of mothers with pregnancies complicated by IHCP and to compare these with healthy pregnancies. The secondary aim was to investigate the association between fetal pulmonary artery Doppler parameters with neonatal outcomes in pregnancies complicated by IHCP.

Material and Methods

This prospective, case-control study was conducted in a tertiary perinatal-neonatal center, between June 2020 and December 2020. The study was approved by the Institutional Review Board of University of Health Sciences Turkey, Ankara City Hospital Ethics Committee (approval number: E2-20-89). The research related to humans complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Declaration of Helsinki, and has been approved by the authors' institutional review board or equivalent committee. After verbal and written information about the study, all eligible and voluntary participants gave informed consent.

Eligibility criteria of participants included singleton pregnancies, maternal age between 17 and 45 years, having no chronic systemic diseases except for IHCP. Exclusion criteria included multiple pregnancies, preexisting maternal systemic disease, such as diabetes mellitus, chronic liver disease, hepatitis, chronic renal failure, and rheumatological disease, and maternal hepatotoxic drug use. Additionally, fetal growth restriction or macrosomia, known fetal structural malformation and/or karyotype abnormality, and pregnancies complicated with preterm delivery, premature preterm rupture of membranes, preeclampsia, or pregnancy-induced hypertension were excluded.

The gestational age was determined according to crown-rump length measurement between 11th and 14th gestational weeks. The medical records of every eligible case was reviewed and the following variables were recorded to dataset: maternal demographic characteristics (age, body mass index in kg/m^2), obstetric histories (gravidity, parity, miscarriage, living children), pregnancy associated plasma protein A MoM values that were obtained in the first trimester aneuploidy screening, maternal liver function enzymes including (AST in U/L), (alanine aminotransferase in U/L) and maternal serum bile acid values that were reported at the time of diagnosis. The birth characteristics (type of delivery, gestational age at birth, birth weight, APGAR scores first and fifth minutes), NICU admission and the parameters of umbilical cord venous blood samples to determine acidbase status of the newborns were also recorded. Neonatal acidemia at birth was defined as either pH <7.2 or base deficit ≥12 mEq/L, in agreement with the neonatology clinic.

All ultrasonographic measurements were performed using a Voluson E8 Expert ultrasound (GE Healthcare, USA) with a multi-frequency convex transducer at 3-9 mHz. After admission of participants for delivery, fetal biometric measurements (biparietal diameter, head circumference, abdominal circumference, femur length, thoracic circumference), estimated fetal weight, fetal wellbeing, amniotic fluid index, Doppler flow and velocity indices of umbilical artery, middle cerebral artery, ductus venosus and fetal main pulmonary artery flow waveforms were assessed by a single observer (B.Y.).

A standardized measurement technique, previously described by Azpurua et al. (13), was used for fetal main pulmonary artery flow waveforms. After obtaining a four-chamber view of the fetal heart, a slight probe rotation was performed to maintain the short axes view that revealed the main pulmonary artery and its branches. The sample volume gate was set between two and three millimeters and was placed above the pulmonary valve. The angle of insonation was maintained under 20 degrees. The time interval between the beginning of the ventricular systole and the first peak was defined as AT. The time interval of ventricular systole was defined as ET (Figure 1). These measurements were repeated three times and mean values were recorded. The PATET ratio was obtained by dividing the AT by the ET. Using the same flow-trace, the main pulmonary artery pulsatility and resistance indices were calculated.

Immediately after delivery, the umbilical cord was clamped bilaterally and umbilical venous blood samples from the placental side were drawn into a heparinized syringe. Umbilical

venous blood pH, partial oxygen (pO_2) and carbon dioxide (pCO_2) saturation, bicarbonate, lactic acid, and base excess were recorded.

Statistical analysis

The statistical analyses were conducted using the SPSS version 22 (IBM Inc. Armonk, NY, USA). The normality of distribution was evaluated with histograms, probability plots and Kolmogorov-Smirnov test. The quantitative data were summarized as mean ± standard deviation. Parametric comparisons were made by using the Student's t-test. For all statistical analysis, a p-value <0.05 with a 95% confidence interval was considered significant. Correlation analysis was conducted using Pearson analysis.

Results

This sample consisted of 55 cases, of which 18 were IHCP and 37 were controls. Comparison of demographic features is summarized in Table 1. There was no statistically significant difference between IHCP and control groups in terms of maternal demographic characteristics and obstetric history, with the exception of parity (p=0.02).

Umbilical artery, middle cerebral artery and pulmonary artery Doppler flow indices are summarized in Table 2. Mean pulmonary artery AT, ET, PATET and peak systolic velocity values were significantly different between the groups (p=0.001, p=0.024 and p=0.003, respectively). The mean PATET value in the IHCP group was 0.217±0.029 while in the control group it was 0.180±0.020. Mean maternal serum bile acid value was 27.8±16.3 mmol/L.

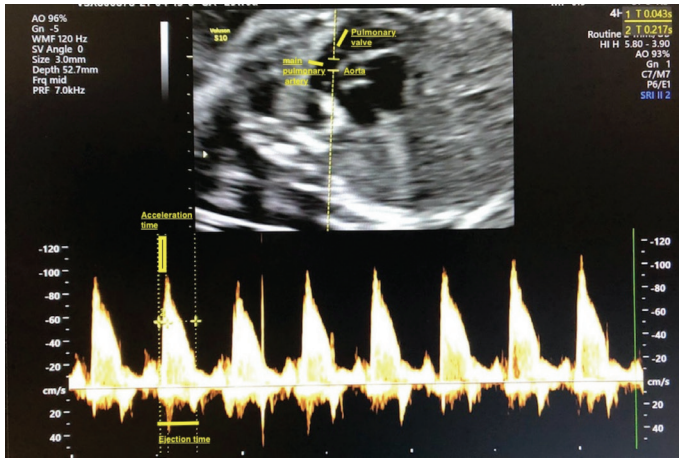

Figure 1. Fetal main pulmonary artery Doppler flow-trace

In Table 3, birth characteristics, umbilical venous blood gas analysis, NICU admission and respiratory distress values are compared. There was no difference in terms of type of delivery, administration of antenatal corticosteroid, APGAR scores at the first and fifth minutes and respiratory distress between the two groups but gestational age at birth and birthweight were significantly different (p=0.001 and p=0.034). Furthermore, significantly lower pH values and higher pCO_2 values were found in the IHC group. Acidemia was not detected in any pregnancy in either group.

In the IHCP group, 8 (44.4%) of newborns were admitted to NICU and 5 (27.7%) had respiratory distress. In comparison, 3 (8%) of newborns in the control group were admitted to NICU due to respiratory distress. When NICU admission and respiratory distress values were compared, NICU admission was significantly different (p=0.012) but respiratory distress was not (p=0.096). APGAR score at the fifth minute, gestational age at birth and respiratory distress were significantly correlated with NICU admission. Moderate negative correlations were identified for gestational age at birth (r=-0.471, p=0.001) and APGAR score at five minutes (r=-0.294, p=0.031) and a moderate positive correlation was present between respiratory distress (r=0.372, p=0.006) and NICU admission was found. While PATET values were correlated with gestational age at birth, there was no correlation with respiratory distress and NICU admission.

Discussion

In the present study, significantly higher values of PATET were found in the fetuses whose mothers' pregnancies were complicated by IHCP compared to fetuses of mothers with healthy pregnancies. Although NICU admission and respiratory distress were more frequent in the IHCP group, these were not correlated with PATET. Gestational age at birth and APGAR

Table 1. Maternal characteristics of intrahepatic cholestasis and control groups

Maternal characteristics	Intrahepatic cholestasis group, (n=18)	Control group, (n=37)	p
Age, years	27.4±6.1	27.6±5.6	0.905
Gravidity, (n)	1.5±1.1	2.2±1.1	0.064
Parity, (n)	0.3±0.8	0.9±1.1	0.020
Miscarriage, (n)	0.2±0.4	0.2±0.5	0.710
Living child, (n)	0.3±0.8	0.9±1.1	0.119
Body mass index (k/m^2)	28.6±3.9	29.6±4.5	0.441

score at the fifth minute were the most important determinants of the NICU admission and respiratory complications.

Many studies have focused on the relationship between PATET and respiratory complications, but conflicting results have been reported. Pulmonary artery AT and right ventricle ET were first assessed by Kitabatake et al. (14), and they reported that decreased values of both measurements were present in patients with pulmonary arterial hypertension. Fuke et al. (15), showed that AT/ET ratio of the branches of pulmonary artery appeared to be an accurate parameter with which to predict pulmonary hypoplasia. To date, PATET has been investigated to predict RDS, especially in premature fetuses (12-16). Few studies have investigated PATET values in late term and term fetuses and these showed an

Table 2. Comparison of main pulmonary artery, umbilical and middle cerebral artery Doppler flow indices between intrahepatic cholestasis group and control group

	Intrahepatic cholestasis group, (n=18)	Control group, (n=37)	p
MPA acceleration time milisec, ms	0.0462±0.007	0.035±0.004	<0.001
MPA ejection time milisec, ms	0.214±0.030	0.195±0.015	0.024
PATET	0.217±0.029	0.180±0.020	0.003
MPA PI	2.166±0.17	2.12±0.258	0.434
MPA RI	0.856±0.066	0.847±0.05	0.666
MPA systole/diastole	8.087±4.573	7.389±1.56	0.539
MPA PSV (cm/s)	83.1±10.06	70.6±8.95	<0.001
UA PI	0.85±0.11	0.83±0.21	0.648
UA RI	0.57±0.04	0.58±0.08	0.875
MCA PI	1.54±0.32	1.38±0.33	0.099
MCA RI	0.76±0.06	0.72±0.08	0.037

MPA: Main pulmonary artery, PATET: Pulmonary artery acceleration time-ejection time ratio, PI: Pulsatility index, PSV: Peak systolic velocity, RI: Resistance index, UA: Umbilical artery, MCA: Middle cerebral artery

Table 3. Comparisons of birth characteristics, umbilical cord venous blood gas analysis and NICU admission between intrahepatic cholestasis and control group

	Intrahepatic cholestasis group, (n=18)	Control group, (n=37)	p
Gestational age at birth, weeks	36.6±1.0	38.4±0.9	0.001
Antenatal corticosteroid, (n)	4	2	0.185
Type of delivery, (n)			
Vaginal birth	5	3	0.230
Ceaserean section	13	34	
Birthweight, (g)	2,973±422	3,221±275	0.034
APGAR 1. minute	7.1±0.6	7.5±0.5	0.070
APGAR 5. minute	8.6±0.6	8.9±0.4	0.108
Umbilical venous blood			
pH	7.29±0.05	7.33±0.06	0.016
pO_2 (mmHg)	24.3±10.4	27.1±9.7	0.359
pCO_2 (mmHg)	45.6±7.5	38.2±6.9	0.002
HCO_3 (mEq/L)	21.3±1.9	20.5±2.5	0.234
Lactate (mmol/L)	2.7±1.1	2.2±0.8	0.106
Base excess (mmol/L)	-4.3±3.7	-5.4±2.3	0.273
FO_2Hb (%)	34.8±21.6	45.8±19.9	0.111
Respiratory distress, (n)	5	3	0.096
NICU admission, (n)	8	3	0.012

NICU: Neonatal intensive care unit

inverse correlation between fetal PATET value and transient tachypnea of newborns (10,17).

In 2010, Azpurua et al. (13), reported that the AT/ET in the main pulmonary artery waveform correlated inversely with the lecithin/sphingomyelin ratio. In addition, in 2013, Kim et al. (12), demonstrated that an elevated AT/ET ratio in the fetal pulmonary artery was associated with RDS, further supporting the findings of Azpurua et al (13). Our findings are in keeping with those of Kim et al. (12) and Azpurua et al. (13) in terms of the relationship between elevated PATET and lung immaturity but contrast with many earlier studies. A possible explanation for this relationship is that fetal lung surfactant production is lower in IHCP than healthy fetuses and thus lung damage may be more likely in cases with elevated PATET.

In human fetuses the immunological response to tissue injury or microbial invasion involves both pro-inflammatory and anti-inflammatory responses. It has been shown that newborns exposed to systemic inflammation in utero have a higher frequency of neonatal morbidity, as a result of fetal inflammatory response syndrome, and is associated with multisystemic involvement (18). Fetal lung inflammation is characterized by expression of many different cytokines and the effect of inflammation is usually to stimulate surfactant production. In the literature, there are studies investigating this inflammatory process in order to clarify the etiology of IHCP and the pathophysiological pathways of bile acid-induced inflammation affecting fetal and neonatal outcomes (19-21). Herraez et al. (7) reported that accumulation of maternal bileacids triggered an inflammatory response in maternal and fetal lungs and highlighted the importance of released macrophage associated phospholipase A2 in RDS developmen.

Previous studies demonstrated that the RDS rate was approximately three times higher among the newborns whose mothers' pregnancies were complicated by IHCP (22,23). Arthuis et al. (22), also found a significant difference in intensive care unit admission rates and reported elevated biliary acid levels in this group. The NICU admission rate was higher in our study group, which is consistent with previous studies. Although respiratory distress rate (5/18) was higher in our study group, it was not different from the rate in the control group (3/37). This may be because all NICU admissions in the control group were due to respiratory distress and a lower rate of respiratory distress in all NICU admission in the study group.

To the best of our knowledge, this is the first study to evaluate PATET in fetuses whose mothers' pregnancies were complicated by IHCP. The strength of this study was its prospective nature and good design and being the first study in IHCP. The main limitation was the small sample size, because of the low incidence of IHCP and thus it was not possible to take account of severity of IHCP. Furthermore, the secondary hypothesis of this study was not testable given the results obtained.

Conclusion

Higher values of the main pulmonary artery PATET was present in fetuses whose mothers' pregnancies were complicated by IHCP. This finding may be helpful to understand the etiology of fetal lung damage, secondary to IHCP. Larger prospective studies and possibly more detailed investigation of sub-factors of PATET may further illuminate the prediction of respiratory complications in these newborns.

Ethics Committee Approval: *The study was approved by the Institutional Review Board of University of Health Sciences Turkey, Ankara City Hospital Ethics Committee (approval number: E2-20-89).*

Informed Consent: *After verbal and written information about the study, all eligible and voluntary participants gave informed consent.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: B.Y.; Concept: B.Y., A.Y., O.A.; Design: B.Y., A.Y., F.E.C.; Data Collection or Processing: B.Y., S.E.; Analysis or Interpretation: A.T., F.E.C.; Literature Search: B.Y., S.E., O.A.; Writing: B.Y., A.T.*

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The efficacy, acceptability and continuation of postpartum, post-abortive progestin-only pill: a pioneering prospective multicentric study from Turkey

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Abstract

Objective: The aim of this study was to evaluate the efficacy, side-effects and continuation rate of the desogestrel-progestin-only-pill (POP) in postpartum and post-abortive Turkish women and its relation with breast-feeding.

Material and Methods: In this prospective multicentric study women who delivered (or had surgical abortion) and wanted to receive POP for contraception were recruited to the study. The follow-up visits were scheduled at the third, sixth and ninth months.

Results: Overall A total of 7,468 women (66.5% postpartum, 33.5% post-abortive) participated in the study. The number of women who attended follow-up visits in relation to the previous visit at the third, sixth and ninth months was 944/7,468 (12.6%), 406/944 (43%) and 121/406 (29.8%) respectively. The incidence of breastfeeding at all visits was between 54.8% and 68.4%. Out of the 7,468 women recruited only 6% continued with the method at the end of the ninth month. There was a statistically significant increase in hemoglobin level at the third month compared to initial values. Oligomenorrhea, spotting and headache were the three leading side-effects. There was no pregnancy among the patients who were followed up.

Conclusion: This study demonstrated that POP was an effective postpartum and post-abortive contraceptive method that had no negative impact on breast-feeding. A change in bleeding patterns was the most common side-effect. However, the possible causes of low contraceptive maintenance rates need to be investigated. (J Turk Ger Gynecol Assoc 2022; 23: 255-62)

Keywords: Breast-feeding, contraception, progestin-only pill, postpartum, post-abortive

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Introduction

Out of 211 million pregnancies that occur globally each year, 87 million are unintended and 46 million of these might end in induced abortion while unintended pregnancies constituted 40% of all pregnancies in 2012 (1,2). Unintended pregnancies and shorter pregnancy intervals result in maternal and fetal morbidity and mortality, and also increase social and economic burden (3-5). In various studies, short intervals between pregnancies were found to be associated with increased maternal risks, such as gestational diabetes, placental abruption, and uterine rupture while fetal problems include preterm delivery, low-birth weight or small for gestational age infants (6) and thus birth-spacing is strongly advised. While the World Health Organization (WHO) recommends an interpregnancy interval (time between delivery and conception

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of subsequent pregnancy) of 24 months, the American College of Obstetricians and Gynecologists emphasises the importance of avoiding an interpregnancy interval of less than six months and advises an interpregnancy interval of longer than 18 months (7,8).

Postpartum contraception is a life-saving issue for women who opt to delay the subsequent pregnancy. It is common for contraceptive service delivery to be delayed until the routine postpartum sixth week visit. However, this practice is criticized as most women experience sexual activity before this initial postpartum visit and may even ovulate, especially if they are not breast-feeding (9). The other problem related to the postpartum sixth week visit is the low uptake, as women might skip this visit due to various structural, social and economic problems (10). Although the context of the postpartum visit covers postpartum contraception in some settings, a Cochrane review reported that two-thirds of postpartum women have unmet needs for contraception (11).

Immediate postplacental and early postpartum intrauterine device (IUD) insertion is a convenient and reliable contraceptive method but the expulsion rate is higher than the interval insertion and immediate postplacental IUD insertion requires a trained practitioner (12). Progestin-bearing hormonal contraceptives (PHC) are effective without any negative impact on lactogenesis, breastfeeding rates, and milk supply during the postpartum period (6,13). PHC implants can also be used during the early postpartum period but insertion and removal requires a visit to a qualified health center, similar to IUDs (14). Progestin-only contraceptive pills (POP) are safe and effective. POPs are currently under-utilized although they are a good choice for almost any women but especially for postpartum and breastfeeding women and women with a higher risk of thromboembolism, such as diabetic, obese and smoking women who choose to use a hormonal method (15). Post-abortion contraception is an essential component of comprehensive abortion care in women who do not want to get pregnant immediately after abortion as a return of fertility is much shorter after surgical abortion and POP can be started at the time of abortion (16).

While traditional POP provides contraception through thickening of the cervical mucus and endometrial atrophy and therefore must be taken within a three-hour window at the same time every day, the new generation desogestrel POP inhibits ovulation besides these effects and has a range of 12 hours delay within the same day without jeopardizing its contraceptive efficacy (17).

Desogestrel POP was licensed in 2011 in Turkey and it was procured for the first time by the Ministry of Health and distributed to study sites for evaluation of the efficacy, acceptability and safety of this method among Turkish post-abortive and early postpartum women. In this pioneering Turkish study, this contraceptive drug was distributed free of charge to all post-abortive/postpartum women who had consented for POP use for the first time as a part of the Ministry of Health Reproductive Health and Women's Health Programme.

The aim of this study was to evaluate the efficacy, side-effects and continuation of the new generation desogestrel POP initiated in the early postpartum and post-abortive period and its relation with breast-feeding.

Material and Methods

This multicenter, prospective study was conducted in three centers: Ministry of Health Etlik Zübeyde Hanım Women's Health Training and Research Hospital; Ministry of Health Zekai Tahir Burak Women's Health Research and Training Hospital; and Adıyaman University Hospital Department of Obstetrics and Gynecology, between March 2016 and March 2017, in collaboration with the Ministry of Health Reproductive and Women's Health Department after obtaining Ethical approval from the Ethics Committee (approval number: 57536863-231.02.01). IUDs, depot-medroxyprogesterone injections, oral contraceptives and desogestrel POP (Cerazette® 75 μg, Merck Sharp & Dohme Pharmaceuticals Co.Ltd.) were procurred and delivered, free of charge, to women by the MOH. All women who delivered vaginally or had a cesarean section or had a surgical abortion (manual vacuum aspiration) for termination of pregnancy on demand up to 10 weeks of pregnancy (legal in Turkey) were counselled for all methods of postpartum, post-abortive contraception before discharge, as part of routine practice. Women who wanted to receive desogestrel POP (Cerazette 75 μg) and gave a written informed consent were recruited to the study. All recruits received counselling promoting full-breast-feeding and about POP at each visit. Women started using POP immediately after abortion or at 21 days postpartum. Not wanting to receive a contraceptive method or prefering another contraceptive method or having a stillbirth or having a contraindication for POP use according to WHO medical eligibility criteria and unwillingness to take part in the study were the exclusion criteria for recruitment to the study (18).

The patient's demographic characteristics and obstetric histories were recorded. They were given three packs of POP, sufficient for three months, and the initial follow-up was scheduled for three months after their discharge. Three follow-up visits were scheduled, at the third, sixth and ninth months. Women attending follow-up visits had their vital signs and weight measured and were asked about contraceptive method continuation, method satisfaction, side-effects and breast-feeding via questionnaire. Among them, women who opted to continue the method were given another three months POP supply at each follow-up. The study flow-chart is shown

in Figure 1. Contraceptive method continuation, method satisfaction/side-effects and the incidence of full breast-feeding during each visit were recorded and analyzed.

Statistical Analysis

The Statistical Package for Social Science, version 21 was used for statistical analysis (IBM Corporation, Armonk, NY, USA). Paired samples t-test was used for continuous variables and the data are given as mean ± standard deviation. Categorical variables were evaluated using Pearson chi-square test. Statistical significance was accepted as $p<0.05$ and the confidence interval was taken as 95%.

Results

Out of the 21,924 women from three centers who were counselled about contraception during the study period, 7,468 women (34.1%) who met the inclusion criteria were recruited to the study. Out of 7,468 women, 66.5% were postpartum (n=4963), while the remaining 33.5% were post-abortive. The average age of the patients was 30.03±6.76 years, the median number of pregnancies and number of children were 3 (range: 0-18) and 2 (range: 0-10) respectively. The mean body mass index was 26.8±4.7 kg/m^2, the systolic blood pressure was 110.4±11.4 mmHg and diastolic pressure was 70.9±8.8 mmHg. The average hemoglobin (Hb) and hematocrit values were 12.08±1.58 g/dL and 36.58±4.65% respectively. The percentage of women with systemic disease was 4.8%, including 134 (1.8%) women with hypertension, 21 (0.3%) with diabetes mellitus, and 201 (2.7%) with gestational diabetes. When contraceptive use prior to the last pregnancy was investigated, 24.1% were on a modern contraceptive while 63.8% were not using a method. The demographic and medical features of the women recruited is shown in Table 1.

The percentage of women who came for a follow-up visit at the third-, sixth- and ninth-month follow-ups was 944 (12.6%),

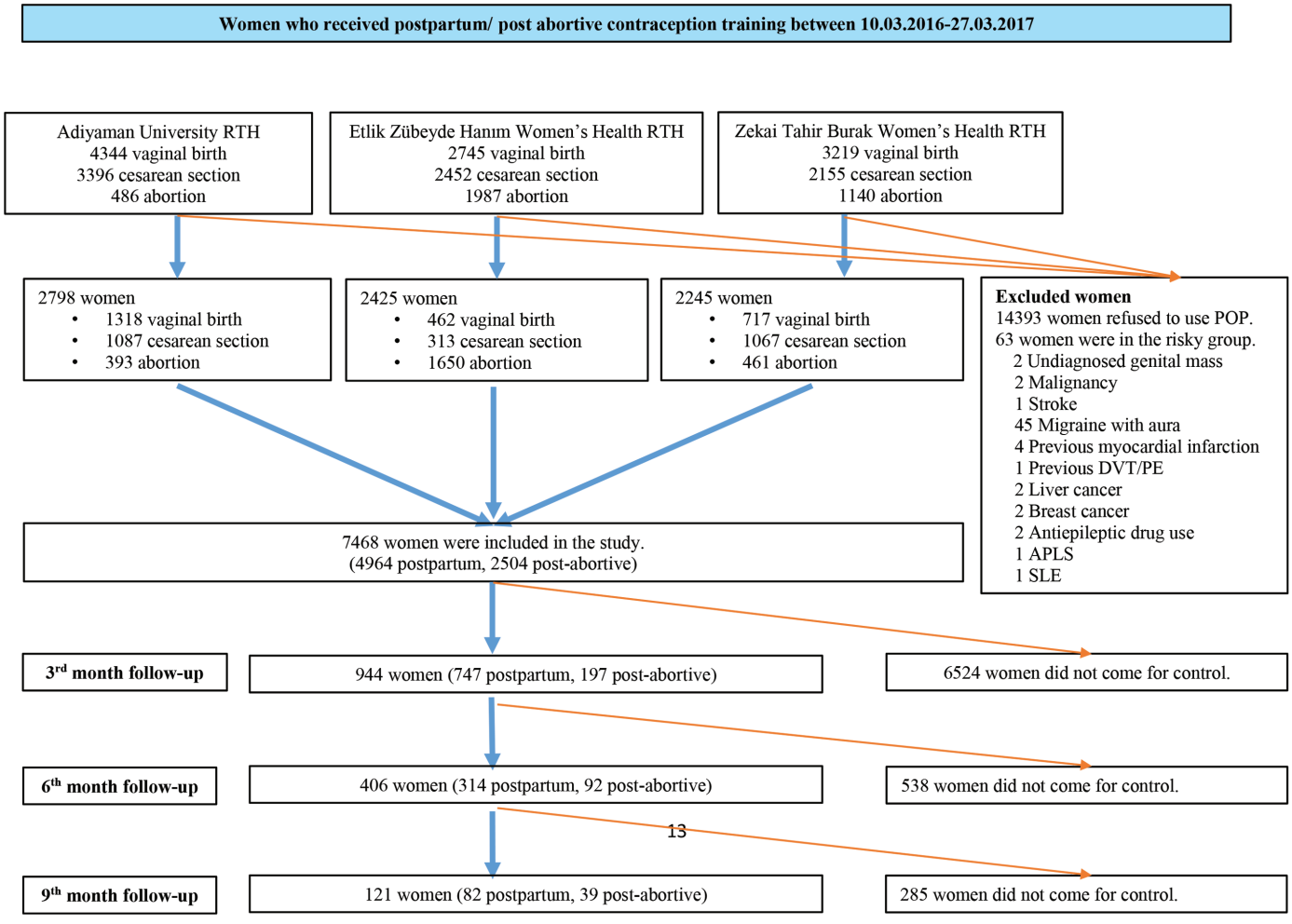

Figure 1. Study flow-chart

RTH: Research and Training Hospital, POP: Progestin-only contraceptive pills, DVT: Deep vein thrombosis, PE: Pulmonary embolism, APLS: Anti-phospholipid antibody syndrome, SLE: Systemic lupus erythematosus

406/944 (43%) and 121/406 (29.8%), respectively. Out of the 7,468 women recruited, only 6% continued with the method at the end of the ninth month (Table 2). Out of 944 women attending the initial third month visit, 37/944 (3.9%) wanted to discontinue, while this figure was 2/406 (0.5%) at sixth month and 16/121 (13.2%) at the ninth month.

The mean weight at the third month was significantly lower than the initial mean weight ($p<0.001$) but there was no difference between the third, sixth- and ninth-month follow-up mean weights and systolic and diastolic blood pressure measurements ($p>0.05$). The percentage of women who lost weight during POP use was high, most probably due to the expected postnatal weight loss. There was a significant increase in Hb level at the third month compared to the initial (postpartum/post-abortion) values (12.08±1.58 g/dL vs. 13.19±1.07 g/dL; $p<0.05$), with no significant change during subsequent follow-up visits. The incidence of breast-feeding during the three consecutive visits was 68.4%, 54.8% and 58.5%, respectively.

Although discontinuation rate was high, method satisfaction was also high among the women who continued to use the method. The main reasons for method discontinuation, based

Table 1. The demographic and medical features of the patient group

(n=7468)		
Name of the center, n (%)	ADYU	2798 (37.5)
	EZH	2425 (32.5)
	ZTB	2245 (30.0)
Age, (mean ± SD)		30.03±6.76
Age distribution, n (%)	<19 years	155 (2.1)
	20-34 years	5737 (76.8)
	35-39 years	1000 (13.4)
	>40 years	576 (7.7)
Method use prior to the last pregnancy,n (%)	No	4763 (63.8)
	CI	905 (12.1)
	Condom	553 (7.4)
	COC	319 (4.3)
	IUD	837 (11.2)
	Injection*	59 (0.8)
	POP	32 (0.4)
Height, cm (mean ± SD)		161.1±6.1
Weight, kg (mean ± SD)		69.5±12.5
BMI, (mean ± SD)		26.8±4.7
SBP, (mmHg) (mean ± SD)		110.4±11.4
DBP, (mmHg) (mean ± SD)		70.9±8.8
Hemoglobin, (mean ± SD)		12.08±1.58
Hematocrit, (mean ± SD)		36.58±4.65
Number of vaginal birth, (median, range)		1 (0-10)
Number of cesarean sections, [median (minimum-maximum)]		1 (0-6)
Gravidy, (median, range)		3 (0-13)
Parity, (median, range)		2 (0-18)
Number of living children, (median, range)		2 (0-10)
Number of abortions, (median, range)		0 (0-11)
Number of voluntary termination of pregnancies, (median, range)		0 (0-7)
Ectopic pregnancy, (median, range)		0 (0-3)
Disease history, n (%)	Hypertension	134 (1.8)
	Diabetes mellitus	21 (0.3)
	Gestational diabetes mellitus	201 (2.7)

SD: Standard deviation, ADYU: Adıyaman University Research and Training Hospital, EZH: Etlik Zübeyde Hanım Women's Health Research and Training Hospital, ZTB: Zekai Tahir Burak Women's Health Research and Training Hospital, CI: Coitus interruptus, COC: Combined oral contraceptive, IUD: Intrauterine device, POP: Progestin-only contraceptive pills, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index. *All injection types (progesterone Injections, depot injections and DMPA)

on responses of the limited number of patients (n=55) who had discontinued but attended follow-up visits and answered the questionnaire were side-effects and dissatisfaction. Oligomenorrhea, spotting and headache were the three leading side-effects and the incidence of these had decreased by the ninth month follow-up. Apart from vaginal discharge, the incidence of almost all side-effects reported subsided gradually (Figure 2). None of the patients had method failure during POP use or had an adverse event. The percentage of women who resumed normal menstruation increased from 7.2% at the third month to 14.9% at the ninth month. The incidence of amenorrhea increased from 46.4% to 57% at the ninth month, while the incidence of oligomenorrhea decreased from 43.2% to 24.8%.

Discussion

POP prevents pregnancy through causing cervical mucus to become impermeable to sperm, inducing endometrial changes that interfere with implantation, inhibiting ovulation and changing tubal motility. These contraceptive actions vary according to the dose and type of the progestin involved. Desogestrel is a third generation progestin that inhibits ovulation, in addition to thickening cervical mucus and reducing tubal motility, when taken continuously without a break at a dose of 75 µg. This contrasts with older oral formulations containing levonorgestrel and norethisterone that are not able to supress ovulation effectively (19,20). As these pills are estrogen-free, they can be used in various conditions when combined hormonal contraceptive use is contraindicated, such as early postpartum women, lactating women, women with cardiovascular risks (obesity, smoking), thromboembolic risks (family history, thrombophilia) and specific arterial risks

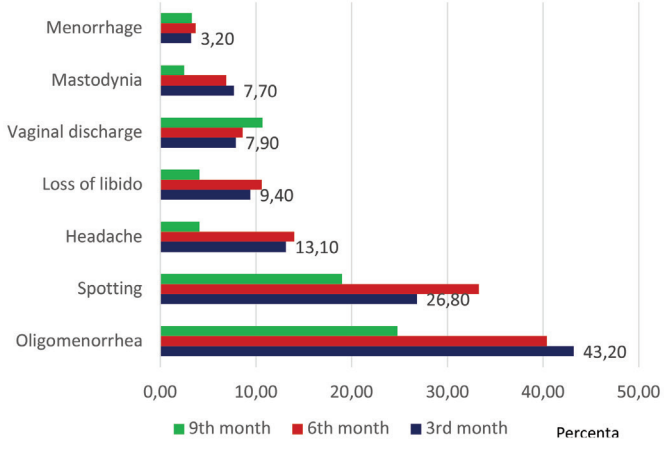

Figure 2. The incidence of major side-effects related to desogestrel-progestin-only-pill use in the third, sixth- and ninth months

POP: Progestin-only contraceptive pills

(valvular heart disease, past ischemic heart disease). They have a limited number of contraindications, the main ones being breast cancer, active liver disease, and benign and malignant liver tumors. Desogestrel POPs should be taken continuously. With a crude Pearl index of 0.41, its efficacy is similar to combined oral contraceptives and the incidence of ovulation inhibition is 97% when a 75 µg dose/day is used (21,22). None of the patients followed up in our study experienced pregnancy during the use of desogestrel POP.

Disturbance of menstrual bleeding patterns effects the compliance of women on progestin-only contraceptives. In natural ovulatory cycles, the estrogenic effect leads to endometrial proliferation in the first phase prior to ovulation and this is followed by a secretory transition of the estrogen-primed endometrium due to progestagenic activity (20). At the end of the menstrual cycle, mensturation is triggered by progesterone withdrawal. In women on progestin-only contraceptives, breakthrough bleeding is thought to arise from the fragile vascular structures, adjacent to the uterine lumen, that have lost their integrity and also a change in angiogenic factors (23,24). In a double-blind, randomized, multicenter trial comparing desogestrel-POP with levonorgestrel-POP, a higher incidence of amenorrhea and infrequent bleeding was encountered in the desogestrel-POP group but there was also a higher incidence of lessened bleeding over time in this group (22). In a study comparing desogestrel-POP with drospirenone-POP, women on desogestrel-POP experienced a higher proportion of different bleeding patterns, such as amenorrhea, infrequent bleeding, frequent bleeding and prolonged bleeding. However, from cycles 2 to 9 subjects who had no bleeding or spotting increased from 26.0 to 54.7% in the desogestrel group (25). In our study, the proportion of women who were amenorrheic increased as the duration of use of desogestrel POP increased. Zigler and McNicholas (26) suggested that the high incidence of discontinuation with the method might be related to the high incidence of unscheduled bleeding that occurs in 20% of the women using progestin-only contraceptive methods, even though method satisfaction is high. In our study group, the women who came for an initial follow-up visit and stated that they were satisfied with the method was relatively high, but the number coming for a second and third follow-up for continuation of the method decreased and this may have been due to the change in bleeding patterns.

There are few studies on the metabolic effects of desogestrel-POPs. In a systematic review and meta-analysis conducted by Glisic et al. (27), POPs were found to demonstrate no effect on blood pressure and, moreover, oral progestin-only contraceptives did not increase the risk of developing cardiometabolic syndrome, in contrast to injectable progestin-only contraceptives. In our series there was no significant

change in mean blood pressure measurements at any of the three follow-up points.

The most frequent side effects related to progestagens are acne, mild hirsutism, depressive mood, sexual pain, and weight gain (20). Vaginitis has also been reported to be a side-effect in a collaborative study (22). In our patient group, none of the women complained of acne, hirsutism, or depressive mood changes. Vaginal discharge was one of the side-effects reported and the incidence did not change through follow-up visits.

There are few studies on the effect of POPs on sexuality. In a double-blind, placebo-controlled study the effect of combined oral contraceptives on well-being and sexuality was compared with women on progestin-only pill and no adverse effect of POP on sexuality was found, while some improvement in well-being was noted (28). In our study the incidence of loss of libido was 9.4% but decreased to 4.1% at the ninth month. In a study from Germany, 403 women who experienced estrogen-related symptoms during combined oral contraceptive use and 403

Table 2. Findings of desogestrel progestin-only pill users at the third-, sixth- and ninth-month follow-ups

		Third month	Sixth month	Ninth month
		(n=944)	(n=406)	(n=121)
Weight, kg (mean ± SD)		67.83±12.47[β]	67.55±12.89	68.61±13.55
Systolic blood pressure, mmHg (mean ± SD)		112.53±10.89	113.54±10.59	112.89±12.68
Diastolic blood pressure, mmHg (mean ± SD)		71.35±8.19	72.43±8.08	70.23±8.39
Hemoglobin, g/dL (mean ± SD)		13.19±1.07*	13.31±1.40[Ω]	13.28±1.23
Cycle characteristics, n (%)	Amenorrhea	438 (46.4)	185 (45.6)	69 (57.0)
	Oligomenorrhea	408 (43.2)	164 (40.4)	30 (24.8)
	Normal mensturation	68 (7.2)	42 (10.4)	18 (14.9)
	Menorrhagia	30 (3.2)	15 (3.7)	4 (3.3)
Breast-feeding, n (%)		511 (68.4)	172 (54.8)	48 (58.5)
Method satisfaction, n (%)	Very satissfied	248 (26.3)	84 (20.7)	27 (22.3)
	Satisfied	677 (71.7)	313 (77.1)	84 (69.4)
	Not satisfied	19 (2.0)	9 (2.2)	10 (8.3)
Reason for method discontinuation, n (%)	Side-effects	10 (1.1)	1 (0.3)	4 (3.3)
	Not happy with the method	14 (1.5)	1 (0.3)	7 (5.8)
	Forgets taking pills	8 (0.9)	0 (0.0)	1 (0.8)
	Friends, -neighbours do not approve of the method	5 (0.5)	0 (0.0)	0 (0.0)
	Wants to get pregnant	0 (0.0)	0 (0.0)	4 (3.3)
Side-effects, n (%)	Mastodynia	73 (7.7)	28 (6.9)	3 (2.0)
	Headache	124 (13.1)	57 (14.0)	5 (4.1)
	Oligomenorrhea	408 (43.2)	164 (40.4)	30 (24.8)
	Spotting	253 (26.8)	135 (33.3)	23 (19.0)
	Menorrhage	30 (3.2)	15 (3.7)	4 (3.3)
	Vaginal discharge	75 (7.9)	35 (8.6)	13 (1.7)
	Loss of libido	89 (9.4)	43 (10.6)	5 (4.1)
	Difficulty in swallowing the pill	4 (0.4)	0 (0.0)	0 (0.0)
	Nausea	4 (0.4)	2 (0.5)	0 (0.0)
	Dizziness	3 (0.3)	1 (0.3)	0 (0.0)
	Hirsutism	1 (0.1)	0 (0.0)	0 (0.0)
	Itching, and rash	1 (0.1)	0 (0.0)	0 (0.0)
	Pelvic pain	3 (0.3)	0 (0.0)	0 (0.0)
Weight change, n (%)	Weight loss	481 (50.9)	263 (6.8)	84 (69.4)
	Weight gain	463 (49.1)	143 (35.2)	37 (30.6)

[β]The mean weight at the third month was significantly lower when compared to the initial mean weight ($p<0.001$). *There is a significant increase compared to the first hemoglobin ($p<0.001$). [Ω]Sixth month hemoglobin value was higher than at the third month ($p=0.008$), SD: Standard deviation

women with dysmenorrhea received 5 μg/d desogestrel-POP and remarkable resolution or improvement of the estrogen-related symtoms, such as nausea, breast-tenderness, estrogen-related headache and oedema, was noted in 70% (29). However, in the presented study group, 13.1% of the women experienced headache while this incidence decreased to 4.1% at the ninth month follow-up. Merki-Feld et al. (30) reported improvement in migraine frequency, migraine intensity and use of pain medication for migraine in women on desogestrel 75 μg/d POP. This finding was supported by the meta-analysis conducted by Warhurst et al. (31). None of the women in the presented group was diagnosed as having migraine nor were recieving any treatment for migraine.

POP is a good choice for lactating patients, as are the other progestin-only contraceptive methods. In a Cochrane review, analysis of published trials comparing combined oral contraceptives with POPs showed no difference in duration of breast-feeding, milk volume or composition (32). Goulding et al. (33) reported that women using POPs were most likely to breast-feed when compared to using combined hormonal contraceptives, even at the ninth month. In our patient group the incidence of breast-feeding did not change among the group who continued with the contraceptive method.

In our study, we found the follow-up rate at the first visit (third month) to be only 12.6%.

Study limitation

This high loss rate is the most important limitation of our study. As this was a hospital-based study, women's transportation to the hospital besides the difficulties in obtaining a suitable appointment from the hospital for a breast-feeding mother are obstacles that might have contributed to the lower follow-up rate. In the second phase of the project in order to improve the service delivery for the women, the reproductive health service providers working at the primary health care facilities were trained by the Ministry of Health Reproductive Health and Women's Health Division and the POPs were made available for use in the primary health services.

Conclusion

Progestin-only contraceptives are safe, effective methods of contraception and can be used by most women, as the contraindications for their use are very few. Progestin-only intrauterine systems and implants are long-acting contraceptive methods but their cost and the need for medical services for initiation and discontinuation is a burden for some women. New generation, POPs are very effective due to their inhibitory effect on ovulation. However, public awareness of the availability and advantages of this is method is still low. The menstrual changes related to progestin-only contraceptive methods might lead to a higher incidence of discontinuation. Therefore, pre-POP counselling sessions should address this and can include the information that the incidence of menstrual changes decreases with longer use of the contraceptive method. This sudy also demonstrated that POPs progestin-appear to be a good choice for breast-feeding women.

According to the latest Turkish Demographic Health Survey (TDHS 2018) (34), out of the 70% of currently married women using a method of contraception, 49% are using a modern method. The unmet need for family planning among currently married women has reached 12%. The percentage of women using the pill is only 5% and has not changed since 2013. The proportion of subjects still using the desogestrel-POP use at the end of the ninth month of the study was still higher than the overall rate of pill use reported by the TDHS 2018. Increasing awareness about POP will provide women with another choice, especially if they have contraindication, for combined hormonal contraceptives and are breast-feeding.

Ethics Committee Approval: *This study was carried out with the permission of the Ministry of Health, Reproductive and Women's Health Department (approval number: 57536863-231.02.01).*

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The etiology of adnexal masses in women with a history of non-gynaecological malignancy: recurrence, second, primary or none?

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Abstract

Objective: The occurrence of adnexal masses in patients with a history of non-gynaecological malignancy (NGM) raises concerns for malignancy, either primary or metastasis. Subsequent treatment and prognosis depends on the etiology. Our aim was to investigate the characteristics and results of the patients with suspicious adnexal masses, who had a history of NGM.

Material and Methods: The records of 61 patients with a history of NGM were analyzed, who were operated for an adnexal mass. Complex adnexal masses were included in the analysis while simple cysts were excluded.

Results: The most common NGM origins were gastrointestinal (gastric and colorectal) tract and breast. Of all adnexal masses, four were benign (6.5%), 22 were primary ovarian malignancy (36.1%) and 35 were metastasis (57.4%). Two of the 22 primary cases were borderline ovarian tumor. Among the characteristics of primary and metastatic groups, laterality in pathology results and serum CA125 levels were statistically different ($p<0.05$). Among the patients with history of gastrointestinal cancers, the percentage of ovarian metastasis was 81%. Primary ovarian malignancy was most frequently (64%) observed among the patients with history of breast cancers.

Conclusion: For patients with a history of gastrointestinal cancer, recurrence of the cancer in the form of ovarian metastasis was more likely, rather than a second primary cancer. The risk of primary ovarian cancer (POC) was remarkable in those with history of a breast cancer. A multidisciplinary strategy, including a gynaecological oncologist, plays an important role in managing these cases, regardless of whether or not it is a POC. (J Turk Ger Gynecol Assoc 2022; 23: 263-7)

Keywords: Ovarian neoplasms, metastasis, Krukenberg tumor

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Introduction

Adnexal masses are usually incidentally diagnosed during the follow-up of patients with a history of non-gynaecological malignancy (NGM). For these patients, the occurrence of an adnexal mass raises concerns for malignancy, either primary or metastasic, but the overall risk is not clearly defined. The prognosis and treatment depend on the etiology. Ovarian metastasis is usually associated with an advanced, incurable disease and needs only palliative systemic therapy. In contrast, primary ovarian cancer (POC) is a potentially curable disease and the standard treatment is surgery followed by systemic chemotherapy. The definitive diagnosis must be made by histopathology. If it is likely an ovarian metastasis of NGM, laparoscopy can be performed for the diagnosis, thereby avoiding more invasive routes. However, for early stage POC, this procedure carries the risk of POC cells spilling into the abdomen (1). Furthermore, surgical exploration and debulking cannot be performed at advanced stages by laparoscopy. The primary purpose of evaluating a suspected adnexal mass with a history of NGM is to clarify the most likely etiology of the mass and subsequent management. This specification does not have any clear rules. Ultrasonography (USG) remains the standard tool for preoperative assessment, and magnetic resonance

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imaging (MRI) should be used as a second imaging study if further information is needed for surgical decision making. Tumor markers are also helpful for identifying the underlying disease. Compared with POC, lower serum CA125 levels and higher levels of the other markers have been reported in metastatic cases (2). Ovarian metastases tend to be bilateral (3), and are mostly caused by gastrointestinal tract and breast carcinomas (4).

The characteristics of adnexal masses in patients with a history of NGM are investigated in this study, and our aim was to clarify the differential diagnosis of adnexal masses in these patients.

Material and Methods

The study protocol was approved by the Local Ethics Committee of the İstanbul University (approval number: 2019/539). It was not applicable for informed consent.

We analysed the files of patients with a history of NGM, who attended for investigation of an adnexal mass in the gynaecological oncology department between 2006-2020. Patients who were under 18 or above 85 years, had a pregnancy, or had a history of genital sourced malignancy were excluded from the study. All patients underwent transvaginal or transrectal and transabdominal 2D-USG by a consultant gynaecological oncologist. The presence of solid areas, multilocular cysts and bilateral lesions were noted. Simple cysts were not included. Tumour size was based on the largest diameter on USG. Serum CA125 levels and other NGM-related tumor markers, including CA19-9, CA15-3 and carcinoembryonic antigen (CEA), were measured preoperatively. Patients, in whom adnexal masses were suspected because of a combination of USG findings and/or CA125 level and/or menopausal status, underwent MRI and were evaluated at our tumor board meeting. For presumed malignancy, patients underwent laparotomy with midline incision and masses were sent for frozen-section. Surgical procedure was performed according to the results of perioperative frozen-section, considering age and fertility requirements. The final histopathological diagnosis was considered for statistical analysis. Tumors were classified and staged according to World Health Organization and International Federation of Gynaecology and Obstetrics classifications. A patient was accepted as postmenopausal, if she was amenorrhoeic for more than a year or had undergone hysterectomy and was 50 years or older. Borderline ovarian tumor (BOT) was accepted as a primary ovarian malignancy.

Statistical analysis

SPSS, version 21.0 was used for statistical analysis (IBM Inc., Armonk, NY, USA). Data were written as mean ± standard deviation or median and interquartile range. Categorical values were expressed as absolute numbers and percentages. Non-parametric tests included Mann-Whitney U and chi-square test and the parametric test was Independent-samples t-test, which were used as appropriate. A p-value <0.05 was considered statistically significant.

Results

Fifty-nine patients with an adnexal mass and a history of NGM were identified, of whom 48 (81.4%) had no symptoms and were diagnosed during their routine follow-up. The other patients had abdominal bloating and/or pain. The majority of patients had a history of gastrointestinal tract [colorectal (n=22) and gastric (n=9)] and breast cancer (n=25) while there were a small number with renal cancer (n=2) and pancreas cancer (n=1) (Table 1). Of all adnexal masses, three were benign (5%), 21 were primary ovarian malignancy (36%) and 35 were metastatic disease (59%). Ovarian metastasis was most frequently (81%) observed among the patients with a history of a gastrointestinal cancer, while primary ovarian malignancy was most frequently (64%) observed among the patients with a history of breast cancer.

Ten (16.9%) of all patients with an adnexal mass had a recent diagnosis of NGM within the preceding six months, nine of these masses were metastases to ovaries and one was diagnosed with a primary ovarian malignancy. Of the 35 metastatic cases, two had relapsed before without ovarian metastasis, while 33 patients first relapsed with ovarian metastasis.

Forty (67.8%) had a history of undergoing chemotherapy. Only one patient had received pelvic radiotherapy (due to colorectal cancer), and no second primary cancer was diagnosed, but she had ovarian metastasis of colorectal cancer.

One patient with ovarian carcinoma underwent second surgery for re-staging, because frozen-section diagnosis was consistent with breast cancer metastasis to ovary, but final diagnosis confirmed a primary ovarian malignancy. Strikingly, the frozen-section accuracy rate was 96.6%.

All of the POCs were epithelial and histological subtypes were either serous (n=17) or endometrioid (n=3) adenocarcinoma. Eight of the 20 (40%) POCs were at early stage (stage 1-2) and the remaining twelve were at stage 3. One of the 21 primary cases was BOT which was serous type at stage 1.

Table 2 shows a comparison of the characteristics of patients who had primary ovarian malignancy or metastatic carcinoma to the adnexa. Among these features, the laterality in pathology specimens and serum CA125 levels exhibited significant differences.

High CA125 levels (>35 IU/mL) were present in 14 (40%) of the metastatic cases. Eleven (78.6%) of these 14 patients also had high levels of the NGM-related tumor marker, such as CA19-9, CA15-3 and CEA. Of three remaining cases whose CA125 levels were high but NGM-related markers were misleadingly normal,

one had breast and two had gastric cancer. Twenty-one (60%) of the metastatic cases had normal CA125 levels. Seven (4 colorectal, 1 gastric, 1 breast, 1 renal cell cancer) had normal levels of other tumor markers while twelve had high levels of CA19-9 and/or CEA with gastrointestinal cancer metastasis to adnexa; the other two patients with breast cancer had high level of CA15-3.

Five (24%) of the primary cases had normal CA125 levels. The levels of NGM-related markers of the other five cases (3 gastrointestinal and 2 breast cancer) were also normal. High CA125 levels were present in 16 (76%) of the primary cases and half of them also had high levels of other NGM-related markers.

The rate of bilaterality observed with preoperative USG did not differ significantly between metastatic cases (37%) and primary ovarian malignancies (29%) (p=0.7). In contrast, histopathologically, the percentage of microscopic bilaterality in metastatic (83%) and primary cases (52%) was significantly different (p=0.019).

Discussion

Metastasis comprises 5-20% of all ovarian neoplasms and the most common non-gynecological source is gastrointestinal tract cancer (57%), followed by breast cancer (30%) (5). Although the ovaries are frequently the site of metastasis from

Table 1. Histopathologic results of patients

Prior cancer history	Primary ovarian malignancy, n (%)	Metastatic carcinoma to the adnexa, n (%)	Benign, n (%)
Breast (n=25)	16 (1 BOT) (64)	8 (32)	1 (4)
Colorectal (n=22)	3 (13.6)	18 (81.8)	1 (4.6)
Gastric (n=9)	2 (22.2)	7 (77.8)	0
Renal (n=2)	0	1 (50)	1 (50)
Pancreas (n=1)	0	1 (100)	0
BOT: Borderline ovarian tumor			

Table 2. Characteristics of patients

Prognostic factors	Primary ovarian malignancy (n=21, 1 borderline)	Metastatic carcinoma to the adnexa (n=35)	p
Age (years)	56.2±9.2	52.4±12.0	0.216
Interval time (month)	48 (24-156)	24 (12-54)	0.184
BMI, kg/m²	30.0±5.8	27.4±6.2	0.15
Active treatment/recent diagnosis, n (%)	1 (4.8)	9 (25.7)	0.072
Chemotherapy history, n (%)	12 (57.1)	29 (82.9)	0.073
Menopause status, n (%)			
Premenopausal	4 (19.0)	13 (37.1)	0.231
Postmenopausal	17 (81.0)	22 (62.9)	
Tumor diameter, cm	8.1±5.8	9.6±4.5	0.264
USG findings, n (%)			
Solid	10 (47.6)	21 (60)	0.251
Multiloculate	3 (14.3)	1 (2.9)	
Solid + multiloculate	8 (38.1)	13 (37.1)	
Laterality (USG), n (%)			
Unilaterally	15 (71.4)	22 (62.9)	0.716
Bilaterally	6 (28.6)	13 (37.1)	
Laterality (microscopic), n (%)			
Unilaterally	10 (47.6)	6 (17.1)	0.019
Bilaterally	11 (52.4)	29 (82.9)	
Ascites, n (%)	3 (14.3)	3 (8.6)	0.661
CA125, U/mL	205 (33-262)	27 (14-70.5)	0.001
BMI: Body mass index, USG: Ultrasonography			

NGM, women with a history of NGM may also be at increased risk of developing a POC. In Europe, it was estimated that 66,693 new ovarian cancers would be diagnosed in 2020 (6). This risk is doubled after a diagnosis of breast cancer (7). Although there are many studies on ovarian metastasis rates in other types of cancer, there is no precise data on the rate of POCs and their discrimination. In the present study, colorectal cancer was the most common NGM resulting in metastasis to the ovaries and the rate of POC was extremely low (13.6%). Despite the low overall rate of POCs, in those with a history of breast cancer presenting with a suspicious adnexal mass this was as high as 64%. A recent study that included one hundred and seventy-seven patients with ovarian metastasis from non-gynecological primary sites found that the colorectum (n=68) and stomach (n=61) were the two most common non-gynecological primary sites of ovarian metastasis (8). These authors also reported that more than 70% of synchronous ovarian metastases were misdiagnosed as POC prior to surgery. Juretzka et al. (9) operated on two hundred and sixty-two patients with an adnexal mass and a history of NGM and 202 (77.1%) had a history of breast cancer. In all, 49 patients (18.7%) had malignancy, including 19 (38.8%) patients with a new POC and 30 (60.2%) patients with a metastatic malignancy to the ovary. Of the 202 patients with a history of breast cancer, thirty-seven had adnexal malignancy and 18 (48.6%) had POC. Of the twelve patients with a history of gastrointestinal tract cancer, seven had adnexal malignancy and 6 (85.7%) of them had metastasis to adnexa (9). In contrast to the study of Juretzka et al. (9), the overall malignancy rate in our series was 95%, which was higher, possibly because we did not include probable benign cysts. The second major difference was that we found the POC/metastasis ratio approximately twice as high in patients with breast cancer.

Serum tumor markers may aid as part of the evaluation of these patients. We found CA125 useful in identifying the type of ovarian malignancy, primary or metastasis. The other NGM-related markers were also useful, but a statistical comparison could not be made in the present study because there were different markers regarding different NGM with a small number of samples. These NGM-related markers, including CEA, CA19-9 and CA15-3, might be useful in identifying the etiology of adnexal mass, but they might also be elevated at a POC. In a series of 284 metastatic breast cancer cases, elevated serum levels of CA15-3 and CEA were found, significantly associated with breast cancer subtypes. While elevated CEA levels did not differ between patients with a single and those with multiple metastatic sites, increased CA15-3 tend to correlate with a larger number of metastatic sites and might also be more commonly associated with hormone receptor-positive disease (10). CA19-9 is a useful marker for tumors of gastrointestinal origin, including the pancreas. A study which analyzed preoperative findings in NGM metastasizing to the ovaries, reported that CEA was a useful marker to distinguish NGM from POC and the CEA levels were significantly higher in colorectal cancer than in gastric cancer (11). A ratio of CA125: CEA >25 was an effective and convenient method to distinguish POC from metastatic colorectal cancer. Thus it is apparent that one marker is not sufficient for an accurate prediction and it would be wise to combine markers. Human epididymis protein 4 (HE4), which is a relatively new marker, rises in POC. However, NGM, including invasive ductal carcinoma of breast, endometrial, pancreaticobiliary, and renal cell carcinoma, can also express HE4 proteins or genes (12). Further research is needed to investigate the utility of HE4 in discriminating NGM from POC.

In the literature, bilaterality and lesser ovarian enlargement were found to be helpful to discriminate metastatic tumors to the ovary (3). In 2004, Moore et al. (4) reported bilateral ovarian metastasis was demonstrated in 39 (66%) patients and unilateral ovarian metastasis in 20 (34%) patients (4). In our analysis, both tumor size and laterality, monitored by USG, were not different. However, bilaterality by microscopic evaluation was found significantly different. These results suggest that USG findings did not help preoperatively and were deceptive for laterality.

In our 59 patients, the frozen-section and final histopathological results had >95% correlation, which was similar to previous reports. We performed laparotomy in all cases, but laparoscopy is recommended by most authors. However, if the frozen-section diagnosis suggests a POC at advanced stage or if an ovarian mass cannot be dissected safely, laparotomy should be performed (9,13).

Study Limitations

In terms of limitations, although the number of cases appears low, it should be remembered that we only included complex adnexal masses.

Conclusion

Recurrence of prior malignancy is more likely than POC, but especially in patients with a history of breast cancer the risk of POC should not be disregarded. Given the high rates of metastasis, it would be reasonable to start with laparoscopy in patients with a history of a gastrointestinal cancer presenting with an adnexal mass. A multidisciplinary team with the involvement of a gynaecological oncologist is necessary, in our opinion, to evaluate these challenging cases.

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Ethics Committee Approval: *The study protocol was approved by the Local Ethics Committee of the İstanbul University (approval number: 2019/539).*

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Fetal intracranial hemorrhage: prenatal sonographic diagnosis criteria and postnatal outcomes

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Abstract

Objective: The aim of this study was to improve knowledge of prenatally diagnosed fetal intracranial hemorrhage (ICH), defining the ultrasound (US) examination results, the contribution of fetal magnetic resonance imagination (MRI) to the diagnosis, and the pregnancy outcomes, from a series of fetal ICH cases.

Material and Methods: This retrospective, observational study included eleven fetuses diagnosed with ICH from April 2016 to August 2020. The data regarding the medical records, prenatal US and MRI findings, treatment, and prognosis of fetal ICH cases were collected from the hospital database and analyzed.

Results: Fetal ICHs were grade 3 in six cases, and grade 4 in the remaining five cases. The mean gestational age at diagnosis was 30.2 weeks. Nine (81.8%) of the cases were diagnosed in the third trimester and two (18.2%) in the second trimester. Fetal cranial MRI was performed in 7/11 (63.6%) following ultrasonographic diagnosis. MRI confirmed fetal ICH diagnosis and previous US findings regarding location and grade in all cases. Five patients (45.5%) diagnosed with grade 3 (n=1) and grade 4 (n=4) ICH underwent pregnancy termination. Of the remaining six cases, one (9.1%) diagnosed with grade 3 fetal ICH resulted in an intrauterine fetal demise. Four cases classified as grade 3 fetal ICH and one case with grade 4 fetal ICH were born alive at term.

Conclusion: The clinical manifestations of fetal ICH are diverse and have a wide spectrum of severity and prognostic implications. Fetal ICH cases were mainly detected in the third trimester, with a minority detected in the second trimester. These cases can be safely diagnosed and graded by US examination, but the underlying etiology frequently cannot be determined. Fetal cranial MRI may aid in diagnosis confirmation if this is unclear from US in order to provide appropriate counseling to the parents. (J Turk Ger Gynecol Assoc 2022; 23: 268-74)

Keywords: Fetal intracranial hemorrhage, prenatal diagnosis, ultrasound

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Introduction

Neonatal intracranial hemorrhage (ICH) is a common postnatal complication in low birth weight and/or premature infants in the postnatal period. However, it rarely occurs in the prenatal period, affecting approximately 0.5-0.9 per 1000 pregnancies (1). Fetal ICH is mostly diagnosed in the later stages of gestation as an incidental ultrasound (US) finding following a normal US examination in the second trimester (2). Prenatal diagnosis of fetal ICH has been increasingly reported in recent years because of the advances in both US examination and magnetic

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resonance imaging (MRI) technologies (3). However, the exact incidence of fetal ICH is still unclear, due to difficulties with ultrasonographic diagnosis in some cases and some fetal ICHs are still missed (4).

In most cases, the cause of fetal ICH cannot be identified. Possible predisposing factors for this complication include maternal trauma, thrombocytopenia, maternal use of anti-coagulants that can cross the placenta, fetal coagulation disorders, non-immune hydrops fetalis, twin to twin transfusion syndrome (TTTS), fetal infections, and severe fetal hypoxia (5-7).

There is a wide variation in the US appearance of fetal ICH as it is difficult to identify and differentiate from other intracranial lesions (5). The prognosis of fetal ICH is closely associated with the grade of hemorrhage and the severity of associated brain injury (3). Previous studies reported that prenatally diagnosed ICHs experience a poor outcome; approximately 40% of fetuses die either during the course of gestation or within the first month following birth and less than half of the survivors exhibit healthy neurological development (8). Therefore, diagnosis in the early stages is crucial.

In recent years, with the advancement of US technologies, and the utilization of fetal MRI as a diagnostic tool for fetal cerebral pathologies, the number of diagnosed patients has increased and the predictive ability of the prognosis of this complication has improved. Knowledge of diagnostic criteria, early identification, clinical importance, and the prognosis of fetal ICH is essential to provide accurate prenatal parental counseling and pregnancy management (7,9).

The aim of this study was to improve knowledge of prenatally diagnosed fetal ICH, defining the US examination results, the contribution of fetal MRI to the diagnosis, and the pregnancy outcomes from a series of 11 fetuses with ICH.

Material and Methods

This retrospective, observational study was performed with patients admitted to the Perinatology Unit of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, from April 2016 to August 2020. Eleven fetuses diagnosed as having ICH were included. The study protocol was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Institutional Ethics Committee (approval number: 2020.12.226). A written informed consent form was obtained from all parents.

Data from the medical records, prenatal two-dimensional (2D) US and MRI findings, treatments used, and prognosis of these 11 fetal ICH cases were collected from the hospital database and analyzed. All ultrasonographic fetal cranial examinations were performed and analyzed by expert sonographers with advanced training in prenatal diagnosis. US examinations were conducted transabdominally and also transvaginally when the fetus was in cephalic presentation, using high-resolution US devices (Voluson 730 Expert and Voluson E6) with a convex probe (3.5-5 MHz for transabdominal examinations, 5-6.5 MHz for transvaginal examinations).

The central nervous system (CNS) examination was performed according to the ISUOG practice guidelines (10). This examination included evaluation of the cisterna magna, lateral ventricles, choroid plexus, thalamus, and cavum septum pellucidum in the transcerebellar, transventricular, and transthalamic planes. In addition, the umbilical cord and its insertion, all four extremities, intra-abdominal organs, heart and great vessels, spine, and face were evaluated to determine any associated abnormalities. Serial 2D US examinations were performed every 2-4 weeks to investigate lesion progression, fetal biometry, and fetal wellbeing. In cases where fetal intrauterine growth restriction (IUGR) was suspected, a Doppler US examination of the fetal umbilical arteries was performed (11).

The diagnosis of fetal ICH was based on the presence of one or more of the following characteristics: intraventricular hyperechogenic foci suggesting clots; hyperechogenic and intended ventricular walls; ventriculomegaly with irregular bulky choroid plexus; parenchymal hyperechogenic avascular mass; increased echogenicity in periventricular white matter; and/or porencephalic cyst formation. The location, size, and appearance of all the lesions were assessed. Intraventricular hemorrhage was classified as grade 1 when the hemorrhage was limited to the subependymal germinal matrix, grade 2, when the blood clots were inside the lateral ventricle without ventriculomegaly or with ventriculomegaly but the clots were <15 mm at the level of lateral ventricular atria, grade 3, when the clots affected one or two lateral ventricles with ventriculomegaly >15 mm at the level of the lateral ventricular atria, and grade 4, when grade 1 to 3 hemorrhages were accompanied with hemorrhage in a large part of the periventricular parenchyma (3,9).

Antenatal work-up to determine the underlying cause of fetal ICH included a history of previous pregnancy characteristics, maternal trauma, history of drug exposure (especially acetylsalicylic acid and anticoagulant therapy), assays for alloimmune and isoimmune thrombocytopenia, coagulation tests (platelet count, prothrombin time, activated partial thromboplastin time), and maternal serological testing for parvovirus B19, toxoplasmosis, rubella, and cytomegalovirus infections (6).

Fetal cranial MRI was offered to all patients to confirm the ICH diagnosis and to evaluate the hydrocephaly, irrespective of the degree of ventriculomegaly (2). Standard MRI scanning

procedures were conducted using a 1.5 T MRI scanner. The mothers underwent MRI scanning after a four hour fast, with an empty bladder, and in the supine position without sedation. Pediatric neurologists performed postnatal evaluation and cranial brain imaging in all living neonates. Pediatric hematologists evaluated all living neonates regarding congenital bleeding diseases. Pregnancy outcomes, fetal and postnatal morbidity, and mortality were analyzed.

Statistical analysis

IBM SPSS, version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical program was used for statistical evaluation of the research data. A descriptive analysis was performed following completion of the audit. Continuous variables are presented as mean ± standard deviation or median (minimum-maximum). Categorical variables are presented as frequencies and percentages.

Results

During the study period, a total of 11 cases with fetal ICH were identified in a single tertiary referral hospital. The demographic characteristics, US and MRI findings, and outcomes of the cases are summarized in Table 1. Fetal ICHs were grade 3 in six cases, and grade 4 in the remaining five cases. No cases of grade 1 or 2 hemorrhage were detected. ICH was observed as bilateral in all cases (n=11, 100%). The mean gestational age at diagnosis was 30.2 weeks (ranging from 22 weeks to 36 weeks). Nine (81.8%) of the cases were diagnosed in the third trimester and two (18.2%) were diagnosed in the second trimester. One of the cases diagnosed in the second trimester was grade 3 fetal ICH and the other was grade 4. Maternal serological testing was performed in eight cases, while hematological and coagulation tests were performed in all cases. All of these tests were normal and underlying etiology could not be identified in any case.

A selection of US findings of the cases included is presented in Figure 1a-d. Figure 1a demonstrates echogenic, irregular and nodular lateral ventricular borders. Figure 1b shows intraventricular hyperechogenic foci, suggesting clots with unilateral and bilateral ventriculomegaly. Figure 1c represents periventricular hypoechoic nodules. Figure 1d illustrates periventricular leukomalacia.

The outcomes of the six grade 3 fetal ICH cases included one pregnancy termination and one intrauterine fetal demise (IUFD) at 25 weeks of gestation. In one further case, ventricular width showed progression at follow-up. This case underwent a ventriculoperitoneal shunt (VPS) placement after the birth but died at six months of age. In two more grade 3 fetal ICH cases, ventriculomegaly showed regression during the postnatal follow-up. However, epilepsy and hemiparesis were observed in both these cases. A VPS placement was performed in one case in the postnatal period. In this case, whose follow-up continued, no complications or neurological handicaps were observed regarding the fetal ICH and shunt placement.

Similarly, when the five cases with initial diagnosis of grade 4 fetal ICH were investigated, periventricular leukomalacia was observed in three, and both periventricular leukomalacia and porencephalic cysts were observed in the remaining two (Figure 2). Four of these pregnancies were terminated. One live birth infant was lost to follow-up during the postnatal period.

Fetal cranial MRI was performed in 7/11 (63.6%) following ultrasonographic diagnosis. The fetal MRI confirmed the fetal ICH diagnosis and previous US findings regarding location and grade in all cases.

In this series of 11 cases, 5 cases (45.5%) diagnosed with grade 3 (n=1) and grade 4 (n=4) fetal ICH underwent pregnancy termination. Of the remaining six, one case (9.1%) diagnosed with grade 3 fetal ICH resulted in an IUFD. Four cases classified as grade 3 fetal ICH and one case with grade 4 fetal ICH were born alive at term. Live born infants were followed-up for a median duration of 18 months (ranging from 7 months to 36 months).

Discussion

In this series of fetal ICH cases, similar to the previous reports, a range of US findings were seen across various clinical presentations, from hyperechogenic and intended ventricular walls to complete liquefaction with a cystic hypoechoic mass. Different US signs of fetal ICH have been identified. These signs differ because of variation in extension, location and amount of bleeding, and internal echo pattern which also varies depending on the blood clot formation and clot lysis status. Thus, prenatal diagnosis is frequently challenging. Furthermore, the ultrasonographic characteristics of fetal ICH will changes over time in a relatively predictable manner (12). The US appearance of a recent hemorrhage, irrespective of location, is a brightly echogenic mass without dorsal shadowing. Initially, a fetal ICH appears as a homogeneous, echogenic zone within the brain parenchyma or ventricles, separated from the choroid plexus. Over time, as the blood clot dissolves, the US presentation becomes more heterogeneous, and an internal sonolucent core becomes evident with an external echogenic rim (2). Fetal ICH is commonly related to ventricular dilatation as a consequence of cerebral aqueduct obstruction by the blood clot. In addition, the blood within the ventricles terminates in an echogenic border lining the ventricle or nodular structures (5). Involvement of the brain cortex can be identified by demonstration of the echogenic collection extension to the surrounding periventricular parenchyma in the early stages (8). Retraction, lysis, and resorption of the surrounding parenchyma and blood clot will conclude with the formation of a porencephalic cyst, a solid mass-like structure

Table 1. Demographic characteristics, US and MRI findings, and outcomes of the cases

Case	Age	Gestational week at diagnosis (weeks + days)	Grade of ICH	Ultrasonographic findings	MRI findings	Outcome	Gestational week at delivery (weeks + days)	Type of delivery
1	20	36	Gr 3	- Ventriculomegaly (39/33 mm) - Intraventricular hyperechogenic foci suggesting clots	- Ventriculomegaly (32/35 mm) - Bilateral intraventricular hyperechogenic foci suggesting clots	- Pregnancy termination	37	Vaginal delivery
2	20	25	Gr3	- Ventriculomegaly (15/22 mm)	-	- IUFD	25	Vaginal delivery
3	25	31+2	Gr3	- Ventriculomegaly (19/21 mm) - Echogenic and irregular lateral ventricle borders - Intraventricular hyperechogenic foci suggesting clots	-	- Died at postnatal 6th months	38	Vaginal delivery
4	26	32+5	Gr 3	- Ventriculomegaly (33/20 mm) - Intraventricular hyperechogenic foci suggesting clots	- Ventriculomegaly (37/25 mm) - Intraventricular hyperechogenic foci suggesting clots (More prominent in the left ventricle)	- Hemiparesis and epilepsy	37	Cesarean Delivery
5	19	30+1	Gr4	- Ventriculomegaly (12/22 mm) - Porencephalic cyst	- Ventriculomegaly (11/21 mm) - Intraventricular hyperechogenic foci suggesting clots - Porencephalic and encephalomalastic cysts in periventricular white matter	- Pregnancy termination	32	Vaginal delivery
6	29	32+6	Gr 4	- Ventriculomegaly (19/14 mm) - Echogenic and irregular lateral ventricle borders - Ventricular leukomalacia	-	- Lost to follow-up	36	Vaginal delivery
7	19	22+1	Gr 4	- Ventriculomegaly (19/20 mm) - Diffuse liquefication in the parenchyma	-	- Pregnancy termination	23	Vaginal delivery
8	30	28+6	Gr 4	- Ventriculomegaly (13/15 mm) - Echogenic and irregular lateral ventricle borders - Parenchymal hemorrhage	- Ventriculomegaly (16/14 mm) - Parenchymal hemorrhage - Cystic-encephalomalastic changes	- Pregnancy termination	30+5	Vaginal delivery

Table 1. Continued

Case	Age	Gestational week at diagnosis	Grade of ICH	Ultrasonographic findings	MRI findings	Outcome	Gestational week at delivery	Type of delivery
9	20	35	Gr 3	- Ventriculomegaly (28/28 mm) - Echogenic and irregular lateral ventricle borders	- Ventriculomegaly (32/35 mm) - Intraventricular hyperechogenic foci suggesting clots	- Ventriculoperitoneal shunt placement	38+2	Cesarean delivery
10	21	28	Gr 3	- Ventriculomegaly (14/13 mm) - Echogenic and irregular lateral ventricle borders	- Ventriculomegaly (17/17 mm) - Irregular lateral ventricle borders - Intraventricular hyperechogenic foci suggesting clots	- Hemiparesis and epilepsy	36+3	Vaginal delivery
11	18	32	Gr4	- Ventriculomegaly (26/35 mm) - Echogenic lateral ventricle borders - Parenchyma is liquefied	- Ventriculomegaly (26/35 mm) - Parenchyma is liquefied	- Pregnancy termination	32+3	Vaginal delivery

US: Ultrasound, MRI: Magnetic resonance imagination, ICH: Intracranial hemorrhage, Gr: Grade, IUFD: Intrauterine fetal demise

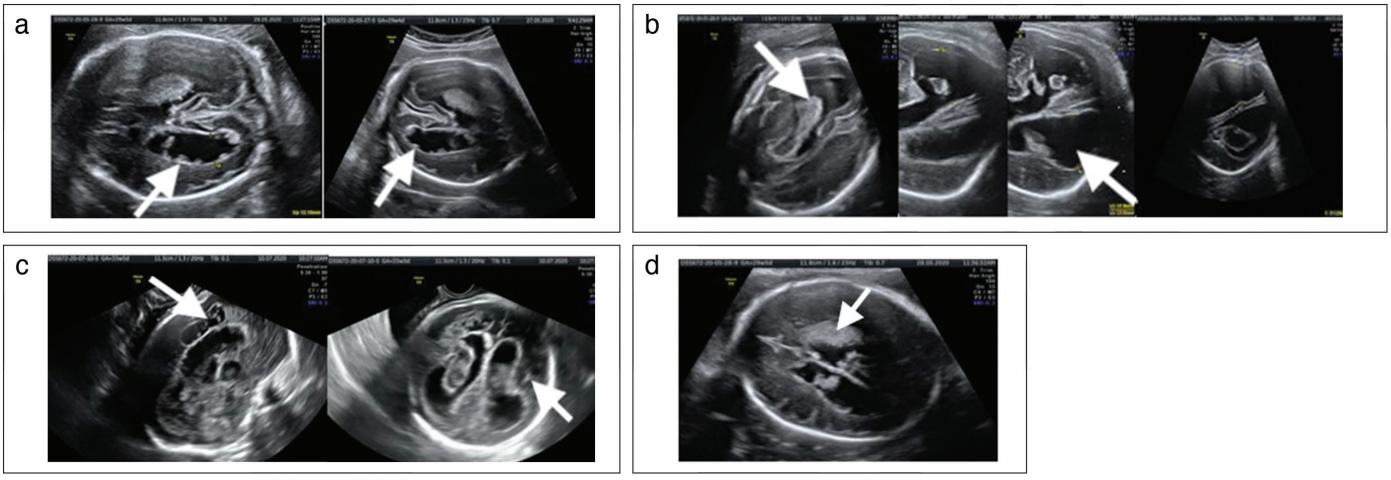

Figure 1. (a) Echogenic, irregular and nodular lateral ventricle borders. (b) Intraventricular hyperechogenic foci suggesting clots with unilateral and bilateral ventriculomegaly (arrow). (c) Periventricular hypoechoic nodules (arrow). (d) Periventricular leukomalacia (arrow)

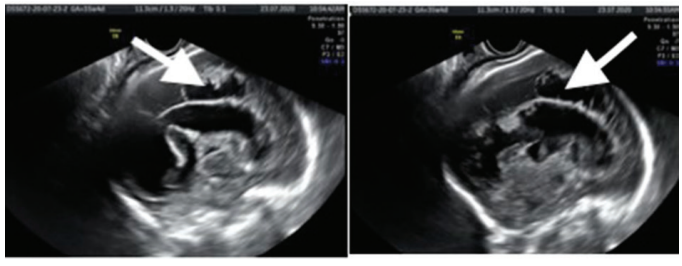

Figure 2. Porencephalic cyst (arrow)

composed of the infarcted brain and blood clot (3). This cyst commonly becomes evident about two weeks after the initiation of hemorrhage (8).

Fetal and maternal risk factors have been associated with fetal ICH. Predisposing fetal risk factors include fetal alloimmune thrombocytopenia, umbilical cord entanglement, umbilical cord thrombosis, fetal thrombophilia, the demise of a co-twin in monochorionic placentation, TTTS, severe hypoxia, and severe IUGR. Maternal risk factors include vitamin K deficiency, pregnancy complications (placental abruption, preeclampsia), infections, immune thrombocytopenia, coagulation disorders,

seizures, trauma, medications (warfarin), and drugs (3,7,13). However, previous studies reported that in the majority of cases no identifiable risk factor was found and identified fetal and maternal pathologies that may have caused the fetal ICH are only present in 20-45% of cases (6,8,13,14). In this study, no identifiable etiologic factor was detected in any of the cases. However, maternal serological testing was performed in 8/11 cases with no abnormalities found.

The mean gestational age at the time of diagnosis in this study cohort was 30.2 weeks. This finding was consistent with previous studies (6-8,13,14). All cases suffered from bilateral fetal ICH, similar to previous reports (7,13). All cases were grade 3 and 4, and consistent with those of previous studies, where incidence of these grades ranged from 70% to 100% (7,12,13). Grade 1 fetal ICH was rarely reported since the findings are subtle and are easily missed in the standard axial planes used on US examination.

The neurodevelopmental outcomes of the fetuses affected by ICH are still unclear due to the paucity of data in the literature. Also, differing pregnancy termination rates and the heterogeneity of the etiology in fetal ICH or concomitant co-morbidities make it difficult to evaluate the results. Previous studies reported that there was a significant association between the grade and location of the hemorrhage and the occurrence of severe neurologic complications (15,16). Cases with grade 2 ICH are reported to have good outcomes, with a survival rate of 100% and only 10% suffer from mild neurologic sequelae. Also, in lower grades of hemorrhage, complete disappearance of abnormal US findings may be observed with better postnatal neurologic consequences (3,8,13). However, evidence concerning outcome in grade 1 and 2 fetal ICHs is limited and these grades were absent from the present study. Grade 3 and 4 hemorrhages are associated with poorer neonatal outcomes than the lower grade fetal ICHs. Ghi et al. (8) reported that no losses were reported in fetuses with grade 1 and 2 hemorrhages and 72% of these infants showed healthy neurologic development. However, only 41% of infants staged as grade 3 and 4 were considered neurodevelopmentally normal (8). A recent study reported that 2/3 of infants with grade 3 fetal ICH suffered from adverse neurologic outcomes (3). In our study cohort, 45.5% (5/11) were born alive at term, with no postnatal deaths. Of these, two cases suffered from epilepsy and hemiparesis while the other three (60%) were reported to exhibit healthy neurologic development.

In most fetal ICH cases, the sonographic signs were detected between 28 and 33 weeks of pregnancy. However, Anderson and McGahan (17) stated that fetal ICH may be identified between 18-20 weeks of gestation. Previous studies demonstrated that US examination provided an accurate diagnosis with no false-positive results (6,8,13). However, blood clots may undergo complete resolution and disappear, ventriculomegaly resolves and thus may be observed as a healthy brain appearance in later US examination. These US features make the prenatal diagnosis challenging (12). Therefore, fetal ICH should be considered in the differential diagnosis of ventriculomegaly cases in the prenatal period.

The role of fetal MRI in the diagnosis, grading, and evaluation of fetal ICH is still controversial and dependent on clinician experience (6,8). Previous studies postulated that fetal MRI is a beneficial adjunct to US examination in the examination of fetal ICH or ischemic lesions and provides information differing from other imaging techniques (3,6,8). Ghi et al. (8) reported that US examination was always diagnostic in fetal ICH cases, and MRI, when performed, proved accurate but did not add further information about the case. They stated that MRI has a role at least in those patients where the US examination is inconclusive (8). Kutuk et al. (6) demonstrated that MRI confirmed the diagnosis made by the US and defined the hematoma dimension, bleeding zone, and eliminated other intracranial abnormalities, particularly in fetuses with grade 3 and 4 ICHs. In the case series of Adiego et al. (3), MRI accurately detect the location and grade of the ICH, and provided additional information concerning the etiology of ICH in one case. In this cohort, fetal cranial MRI was performed in seven (63.6%). In these cases, MRI confirmed the diagnosis, bleeding region and grade of the hemorrhage detected by US examination. However, fetal MRI did not provide additional information. This may be because the study cohort consisted only of fetuses with grade 3 and 4 hemorrhage. It should be noted that we performed fetal MRI within seven days of US evaluation, eliminating the probability of up-grading of the fetal ICH between US and MRI investigations. It seems reasonable to combine MRI with US in the evaluation of the fetuses with lower grade ICH. This may help in identifying the predisposing factors of the hemorrhage.

Study Limitations

There are some limitations of this study, including its retrospective design, an absence of autopsy information and the small sample size. Also, the lack of grade 1 and 2 fetal ICH cases may lead to biased outcomes due to the high termination rate in grade 4 ICH. The absence of serologic testing in three cases may be considered another limitation of this study. Moreover, we did not perform three-dimensional (3D) sonography in the assessment of ICH. Pooh and Kurjak (18) demonstrated that a 3D US scan was superior to an MRI in the evaluation of normal and abnormal CNS findings. Further studies with larger cohorts, including all grades of ICH, are needed to compare 3D US scan findings with those of MRI.

Conclusion

The clinical manifestations of fetal ICH are diverse and have a wide spectrum of severity and prognostic implications. Fetal ICH cases were mainly detected in the third trimester, with a minority detected in the second trimester. These cases can be safely diagnosed and graded using US examination, but the underlying etiology is often not determined. Fetal cranial MRI appears to add little additional information but may provide some information as to the etiology of fetal ICH. Further studies are required, with larger cohorts should be performed to compare 3D US and MRI in affected fetuses. Combined use of US and MRI may also enable appropriate counseling to the parents.

Ethics Committee Approval: *The study protocol was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Institutional Ethics Committee (approval number: 2020.12.226).*

Informed Consent: *A written informed consent form was obtained from all parents.*

Peer-review: *Externally peer-reviewed.*

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Awareness, knowledge and attitude toward the relationship between periodontal health and pregnancy outcomes among obstetrician-gynecologist healthcare professionals in Turkey: Results of 11th Turkish-German Gynecological Association Congress based survey

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Abstract

Objective: The aim of this study was to evaluate the knowledge and practice behavior of Turkish obstetrician-gynecologists regarding oral healthcare during pregnancy and the association between periodontal disease and adverse pregnancy outcomes.

Material and Methods: A cross-sectional study was conducted on randomly selected Turkish obstetrician-gynecologists using a questionnaire consisting of 26 questions during 11th Turkish-German Gynecological Association Congress. Participation in the survey was voluntary.

Results: Out of 435 attendees approached, 382 (88%) of the gynecologists at the Congress participated in the written questionnaire. Most of the participants (96.1%) acknowledged a connection between oral health and pregnancy, and 77.5% agreed that periodontal disease may affect the outcome of pregnancy. Moreover, a high proportion of participants were aware of the clinical signs of periodontal diseases, mainly gingival bleeding (92.1%). However, almost 20% of participants thought that dental treatment could be performed safely in the first or last trimester of pregnancy. Only 36.9% of participants recommended guidance on dental examination for their patients during prenatal care.

Conclusion: This study demonstrated that Turkish obstetrician-gynecologists have a relatively high degree of knowledge with respect to the relationship between periodontal disease and pregnancy outcomes, but practice behavior was poorly correlated with their knowledge. (J Turk Ger Gynecol Assoc 2022; 23: 275-86)

Keywords: Attitude, awareness, knowledge, periodontal diseases, pregnancy

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Introduction

Periodontium is a structure consisting of gingiva, cementum, periodontal ligament and alveolar bone that surrounds and supports the teeth. The main task of the periodontium is to meet functional requirements and to keep the teeth in the mouth (1). Periodontal diseases are infectious and/or inflammatory diseases affecting the hard and soft tissues around the teeth (2). Microbial dental plaque (MDP) is the primary etiological factor for periodontal diseases, which are generally divided into gingivitis and periodontitis. Gingivitis is an inflammatory and reversible disease of the gum without loss of attachment and alveolar bone (3). In periodontitis, there is an advanced destruction of tooth-supporting alveolar bone (4). Periodontal

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disease is initiated by oral microorganisms, but the amount of periodontal destruction has been associated with the host's inflammatory response (5). Systemic diseases and conditions can change the severity of periodontal diseases by affecting the microbiota and host response (6). Thus, MDP is a prerequisite but not the sole factor for the onset of periodontal diseases (7). The severity of the disease, how it affects the person, and how fast it will progress, depends on the immune and inflammatory response of the host which is regulated by systemic factors (8). Moreover, periodontal diseases are increasingly accepted as a risk factor for many systemic diseases and may affect systemic health (9). The association between systemic conditions, such as diabetes or pregnancy, and periodontal diseases have been reported (10). Furthermore, several studies have been conducted on the negative effects of periodontal disease on systemic health and conditions such as cardiovascular diseases, diabetes, preterm birth and aspiration pneumonia (11-15). Especially in recent years, the biological mechanism of systemic infection caused by periodontal disease has been investigated and oral pathogens causing bacteremia have been detected in amniotic fluid (12). Therefore, the two-way relationship between pregnancy and periodontal diseases has recently become more prominent.

The negative effects of periodontal disease, such as preterm birth, low birth weight, miscarriage, preeclampsia and lower genital area infection have been widely investigated (16-30). It has been shown that the treatment of periodontal diseases is important for the health of both pregnant individuals and babies, and it has been shown in many studies that successful treatment causes a significant decrease in negative pregnancy outcomes (25-27,31-35). These results clearly demonstrate the importance of periodontal health during or before pregnancy.

Hormonal changes during pregnancy cause modification of the immune response, increasing the response to irritation accordingly. This state may affect the biological and clinical features of periodontal infections (36). However, without dental plaque, hormonal imbalances do not cause gingivitis (37,38). It has been reported that the distribution and severity of gingivitis increases during pregnancy (36,39-43). As a steroid sex hormone, estrogen, has various effects on periodontium. These include reducing epithelial keratinization, weakening the epithelial barrier, increasing proliferation of blood vessels, stimulating polymorphonuclear leukocyte (PMNL) phagocytosis, inhibiting PMNL chemotaxis, suppression of bone marrow induced leukocytes, inhibition of bone marrow secretion of proinflammatory cytokines, reduction in T-cell inflammation, stimulating gingival fibroblast proliferation and possibly initiating an increase in gingival inflammation without the existence of MDP (44). Another important steroid sex hormone, progesterone, also effects the periodontium by increasing vascular permeability and dilatation, increasing prostaglandin production, decreasing PMNL count and prostaglandin-E_2 levels in gingival crevicular fluid, inhibition of glucocorticoids, reduction of gingival fibroblast proliferation, loss of organization of collagen structure and decrease in its production rate (44). Sex hormones also produce changes in the subgingival flora. Notably, anaerobic microorganisms, which have important roles in the initiation and progress of periodontal disease, become more prominent (36).

Obstetrician-gynecologists, as the most common physicians to see pregnancy candidates and pregnant women, are obliged to provide a wide range of guidance for the mother and baby to complete this period in a healthy way. These include evaluating the oral care of pregnant women and providing precautionary guidance against negative birth results. For this reason, it is expected that obstetrician-gynecologists should have sufficient knowledge about the relationship between periodontal health and pregnancy outcomes, in order to appropriately guide their patients (45).

Studies conducted in the United States, France, India and Brazil have investigated the knowledge and behavior of obstetrician-gynecologists relating to the relationship between periodontal disease and pregnancy (46-50). These studies demonstrated that, even though obstetricians-gynecologists had a remarkably high awareness of this association, their practice was not as effective as expected in the guidance (46,50-52). The studies state that increasing obstetrician-gynecologists' levels of behavior, as well as the knowledge, in terms of periodontal disease and pregnancy outcomes is an important factor in preventing negative outcomes. However, to the best of our knowledge, there is very little evidence in this field regarding obstetrician-gynecologists in Turkey. Therefore, the aim of the study was to evaluate the knowledge and behaviors of Turkish obstetrician-gynecologists relating to the relationship between periodontal disease and pregnancy.

Material and Methods

The study protocol was approved by the Marmara University Faculty of Medicine Local Ethics Committee (approval number: 09.2016.264, date: 03.2016). The study participants were obstetrician-gynecologists who participated in the 11th Turkish-German Gynecology Congress held in Belek-Antalya on 11-15.05.2016. The Congress secretariat was contacted on 08.05.2016. It was established that around 1300 Turkish obstetrician-gynecologists would attend the Congress. By taking the error rate as 5% and power as 95%, it was calculated that 297 contributors should be reached.

Survey content

The survey questions used in our study were taken from previous studies (46,48,49). The survey consisted of 26 single and multiple-choice questions. There were multiple-choice questions in which a single answer was correct or multiple answers were correct. The survey contained three parts. The first part included questions about the participants' personal and sociodemographic characteristics, such as gender, age, experience, type of practice, practice zone, last visit to the dentist and history of periodontal disease. The second part included questions about the etiology of periodontal disease, its systemic effect on pregnancy and their negative consequences, and questions about the attitude and behavior of the participants.

Study plan

The surveys were distributed to 435 Turkish obstetrician-gynecologists randomly selected from the first day of the Congress to its last day. Verbal information was given about the purpose of the study. It was stated that participating in the questionnaire was voluntary. After participants had given written informed consent form they subsequently filled out the questionnaire form.

Inclusion criteria

The inclusion criteria were: willingness to participate in the study; being a citizen of the Republic of Turkey; having a specialty degree in the related discipline; practicing his/her profession in Turkey; and answering all of the survey questions.

Statistical analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS for Windows), Release 25.0 (IBM Inc., Armonk, NY, USA). Univariate and multivariate analyzes were performed according to age, gender, professional experience, type of application, way of working, periodontal disease history to assess whether demographic characteristics of the participants affect their attitudes and behaviors in their knowledge and clinical practice. In the presentation of the data, chi-square or Fisher's exact tests were used in the analysis of categorical variables with frequency, percentage, arithmetic mean and standard deviation. A $p<0.05$ value was considered statistically significant.

Results

In the present study, 382 (87.8%) of the 435 questionnaires distributed to obstetrician-gynecologists were completed and the responses were included in the study.

Socio-demographic characteristics, level of knowledge about oral health and self-assessment of periodontal disease histories

Table 1 shows participant self-assessments and information, including gender, age, experience in their expertise, regional location and type of practice, dental examination history, whether they have been diagnosed with periodontal disease before, whether they have been treated for periodontal disease and their level of knowledge about oral health. Sex distribution was 43.5% male and 56.5% female. The average age of the participants was 39.9±7.9 years. When the participants were stratified by age, 58.6% were 40 years old and below, while 41.4% were over 40 years old. The average experience of the participants was 10.3±7.9 years. Therefore, the participants were grouped based on having 10 years of experience or not. While 60.7% of obstetrician-gynecologists were in the group with 10 years and less experience, 39.3% were in the group with more than 10 years. In terms of the type of practice, 92.1% stated that they worked in a hospital, 4.7% in private practice and 3.6% in both hospital and private practice. Regional distribution was: 7.9% Black Sea region; 11.5% Aegean region; 13.4% Mediterranean region; 37.4% Marmara region; and 29.8% in inner Anatolia or other regions. Most (81.9%) reported a personal dental visit at least every year. Only 35.1% of the participants were previously diagnosed with periodontal disease, of which only 82.1% were treated. Nearly two fifths (39.8%) stated that they found their own knowledge about oral health sufficient.

Knowledge levels of obstetrician-gynecologists about the relationship between periodontal disease and pregnancy

Data relating to the knowledge levels of participants on the relationship between periodontal disease and pregnancy are shown in Table 2. In the question "Definition of periodontal diseases", 92.7% of participants knew that it is a disease in which inflammation is seen and more than one microorganism is effective. However, over 30% thought that periodontal disease was always characterized by degenerative process and smaller proportions thought there was a relationship with osteoporosis (8.1%), that it is an infection caused by a single type of microorganism (1.8%) and one respondent (0.3%) believed that a tumoral process was at work. In the question "Clinical findings that can be seen in periodontal disease", the correct options from the multiple choice answers were selected by a proportion of respondents as follows: gingival bleeding (92.1%); tooth mobility (67.8%); alveolar bone destruction (43.2%); and tooth loss (66.5%). However, the wrong tooth decay option was marked by a large percentage (40.8%). Notably, 95.5% of participants considered periodontal disease an important disease that needed to be treated. The intraoral findings that pregnant women frequently complain

of were selected as: 78% gingival bleeding; 53.9% dental caries; 38.7% gingival enlargement; and 26.7% tooth loss. The majority of respondents (96.9%) thought that oral care is always important during pregnancy, whereas 3.1% of the participants stated that oral care is important in cases when any risks are present. Most (85.3%) believed that pregnancy influences periodontal disease. A larger proportion (97.4%) reported that tooth/gum treatment could be done during pregnancy, but only 79.3% felt that treatment should be done in the second trimester, while 4.6% and 16.1% of participants stated that treatment should be done in the first and third trimesters, respectively. Nearly all (96.1%) agreed that pregnant women should pay more attention to oral health in order to prevent possible pregnancy problems. The proportion of participants who knew the effect of periodontal disease on pregnancy was 77.5%. When asked about what these effects might be, 92.6% of participants believed preterm delivery, 45.2% low-weight delivery, 33.4% abortion, 10.1% lower genital area infection and 3.4% preeclampsia.

The behavior of the obstetrician-gynecologists on the relationship between periodontal disease and pregnancy

Data relating to participant's behavior towards the relationship between periodontal disease and pregnancy is shown in Table 3. The proportion of participants who clinically observed the effect of periodontal disease on pregnant women was 37.2%. The rate of those who asked questions about oral health to women who would become pregnant was 38.5% and the rate of those who visually examined the mouth was 12.3%. Only 36.6% of the participants stated that they referred their patients who considered becoming pregnant to the dentist. Worryingly, only 15.2% of participants informed their patients about oral health.

When participants' behavior regarding the relationship between periodontal disease and pregnancy were evaluated according to participant demographic characteristics, there was no difference between the groups, with the exception of age grouping and experience (Table 4). In answer to the question "Do you perform visual oral examination?", those in the age group >40 said "yes" significantly more often than those in the ≤40 group (p=0.017). Similarly, referral rate of the patients who considered becoming pregnant to the dentist was more reported often by older respondents (p=0.049). Furthermore, there was a difference detected between the age groups in the frequency of giving information about oral health to pregnant patients (p=0.037) with respondents aged >40 years significantly more likely to report always providing this information (p=0.042).

Comparative evaluation of participants' behavior towards the relationship between periodontal disease and pregnancy by respondent clinical experience is shown in Table 5. In the question "Do you perform visual oral examination", those who

Table 1. Socio-demographic characteristics, knowledge and self-assessment levels of obstetrician-gynecologists (n=382) regarding their periodontal disease histories

		n (%)
Sex	Males	166 (43.5)
	Females	216 (56.5)
Mean ± SD age (years)	39.9±7.9	-
Mean ± SD professional experience (years)	10.3±7.9	-
Type of practice	Hospital	352 (92.1)
	Private practice	16 (4.7)
	Hospital and private practice	14 (3.6)
Practice region	Mediterranean	51 (13.4)
	Black sea	30 (7.9)
	Aegean	44 (11.5)
	Marmara	143 (37.4)
	Central Anatolia and others	114 (29.8)
Last dental visit (years)	≤1	313 (81.9)
	>1	69 (18.1)
Diagnosed with periodontal disease		134 (35.1)*
Diagnosed with periodontal disease and treated (n=134)		110 (82.1)*
Evaluate your knowledge about oral health	Good	152 (39.8)
	Middle/poor	230 (60.2)

*M: Mean, SD: Standard deviation, p<0.001, *Yes responders

Table 2. Knowledge levels of obstetrician-gynecologists (n=382) regarding the relationship between periodontal disease and pregnancy

		n (%)
Definition of periodontal diseases	*The disease in which inflammation is seen and multiple microorganisms are effective*	354 (92.7)
	It is always characterized by a degenerative process	116 (30.4)
	It is an autoimmune disease	15 (3.9)
	It is a disease related to osteoporosis	31 (8.1)
	It is an infection caused by a single type of microorganism	7 (1.8)
	Tumoral process always accompanied	1 (0.3)
Clinical findings that can be seen in periodontal disease	*Gingival bleeding*	352 (92.1)
	Tooth mobility	259 (67.8)
	Alveolar bone destruction	165 (43.2)
	Tooth loss	254 (66.5)
	Dental caries	156 (40.8)
Are periodontal diseases important diseases to be treated?	*Yes*	365 (95.5)
	No/I don't know	17 (4.5)
Oral symptoms often described in pregnant women	*Gingival enlargement*	148 (38.7)
	Gingival bleeding	298 (78.0)
	Dental caries	206 (53.9)
	Tooth loss	102 (26.7)
How important is oral care during pregnancy?	*Always*	370 (96.9)
	At risk	12 (3.1)
	Never	0 (0)
Does pregnancy influence periodontal disease?	*Yes*	326 (85.3)
	No/I don't know	56 (14.7)
Can dental/ periodontal treatment be performed during pregnancy?	*Yes*	372 (97.4)
	No/I don't know	10 (2.6)
If yes, what is the safest trimester for tooth/periodontal treatment? (n=372)	First	17 (4.6)[a]
	Second	29 (79.3)[a]
	Third	60 (16.1)[a]
Is it necessary for pregnant women to pay more attention to oral health to prevent possible pregnancy problems?	*Yes*	367 (96.1)
	No/I don't know	15 (3.9)
Does periodontal disease influence pregnancy?	*Yes*	296 (77.5)
	No	86 (22.5)
If yes, what situation/ situations affected? (n=296)	*Preterm birth*	274 (92.6)[b]
	Low-weight newborn	134 (45.2)[b]
	Abortion	99 (33.4)[b]
	Low genital-tract infection	30 (10.1)[b]
	Pre-eclampsia	10 (3.4)[b]

[a]n=372, [b]n=296, Correct answers are shown in italics

Table 3. The behavior of obstetrician-gynecologists (n=382) on the relationship between periodontal disease and pregnancy

		n (%)
Have you clinically observed the effect of periodontal disease on pregnant women?	Yes	142 (37.2)
	No	240 (62.8)
During the examination, do you ask questions about oral health to pregnant women or women who will become pregnant?	Yes	147 (38.5)
	No	235 (61.5)
Do you perform visual oral examination?	Yes	47 (12.3)
	No	355 (87.7)
Do you refer your patients who want to get pregnant to the dentist?	Yes	140 (36.6)
	No	242 (63.4)
How often do you inform your pregnant patients about oral health?	Always	58 (15.2)
	At risk	256 (67.0)
	Never	68 (17.8)

had >10 years experience were significantly more likely to than those in the ≤10 group (p=0.006). Participants in the >10 year experience group also referred their patients who decided for pregnancy to the dentist significantly more often (p=0.017). Moreover, there was a significant difference between the experience groups in the frequency of giving information about oral health to pregnant patients (p=0.003), with those who never provided information about oral health to pregnant patients significantly more likely to be less experienced (p=0.01).

Referral frequency of pregnant individuals to the different health specialities by obstetrician-gynecologists

Data including the referral frequency of pregnant individuals by participants to different health specialities is shown in Table 6. The frequency participants recommended birth courses to pregnant patients was: 0.2% always; 30.1% usually; 22% occasionally; 16.2% rarely; and 11.5% never. The frequency participants provided nutritional counseling advice to pregnant

patients was 39% always, 38.2% generally, 16% occasionally, 4.5% rarely and 2.4% never. However, the frequency participants recommended that pregnant patients seek a dental examination was 14.4% always, 22.5% generally, 31.4% occasionally, 20.9% rarely and 10.7% never. Conversely, the frequency participants provided genetic screening advice to pregnant patients was 36.6% always, 23% generally, 18.3% occasionally, 19.1% rarely and 3.9% never time responses.

Discussion

Studies conducted around the world suggest that pregnant women have inadequate oral care and mostly do not apply for dental examination (53). Pregnant women have been shown to have a higher incidence of periodontal disease compared to those are non-pregnant (42). The negative relationship between periodontal disease and pregnancy have been investigated and demonstrated in various studies (20,23-25,28,38,54). Moreover, the high rate of periodontitis (20%) seen in pregnant women suggests the importance of identification and treatment of the population in this risk group (55). Obstetrician-gynecologists are in an ideal position to improve the oral health of mothers and to avoid any problems during pregnancy, as they often see pregnant women or women who are about to become pregnant. Various studies have been conducted to measure the knowledge and attitudes of obstetrician-gynecologists regarding the relationship between periodontal disease and pregnancy in different countries, including the USA, Brazil, France, India, Iran, the United Arab Emirates and Saudi Arabia (46-50,52,56-59). The aim of this study was to investigate the level of this knowledge and attitudes towards this relationship among Turkish experts.

Since we wished to make comparisons with existing studies, a questionnaire was prepared which included questions from previously published studies (46,48,49). In previous studies, the questionnaires were either e-mailed (45,47,48,60,61), mailed (50) or forms distributed by hand (46). We decided to apply the method of distributing questionnaires by hand, with the aim of increasing the return rate, despite the higher cost. The questionnaires were distributed to 435 obstetrician-gynecologists at Turkish-German Gynecology Congress, which had a high number of contributors and 398 questionnaires were collected at the end of the Congress, with a 91% return rate. Researchers in existing studies achieved a return

Table 4. Comparative evaluation of the behaviors of the obstetrician-gynecologists (n=382) regarding the relationship between periodontal disease and pregnancy in different age groups

		Age	n (%)	P[a]	P[b]
Have you clinically observed the effect of periodontal disease on pregnant women?	Yes	≤40	79 (35.3)	0.359	-
		>40	63 (39.9)		
	No	≤40	145 (64.7)		
		>40	95 (60.1)		
During the examination, do you ask questions about oral health to pregnant women or women who will become pregnant?	Yes	≤40	78 (34.8)	0.080	-
		>40	69 (43.7)		
	No	≤40	146 (65.2)		
		>40	89 (56.3)		
Do you perform visual oral examination?	Yes	≤40	20 (8.9)	**0.017**	-
		>40	27 (17.1)		
	No	≤40	204 (91.1)		
		>40	131 (82.9)		
Do you refer your patients who want to get pregnant to the dentist?	Yes	≤40	73 (32.6)	**0.049**	-
		>40	67 (42.4)		
	No	≤40	151 (67.4)		
		>40	91 (57.6)		
How often do you inform your pregnant patients about oral health?	Always	≤40	27 (12.1)	**0.037**	**0.042**
		>40	31 (19.6)		
	At risk	≤40	150 (67)		0.980
		>40	106 (67.1)		
	Never	≤40	47 (21)		0.053
		>40	21 (13.3)		

[a]Chi-square test, $p<0.05$. [b]Fisher's exact test $p<0.05$.

rate between 25% and 88% (45-47,49,50,61). Of them, 382 questionnaires (88%) that met the inclusion criteria were evaluated. Notably, the existing studies, which come from a range of countries, have differing numbers of participants. In the study conducted in Brazil, 875 participants were included (48). Since the number of participants in other existing studies varies between 55 and 349 (45-47,49,50,60,61) the present study has a relatively high rate of participants. Women constituted 56.5% of participants of our study. In a study conducted in India, all participants were women (60). This was unusual, as in other studies the rate of female participants was between 40% and 60% (45-48,50). In the present study 58.6% of participants were 40 years old or younger. Similar to our study, it was shown in studies conducted in India (49) and the United States of America (45,50) that the mean age was between 40 and 50 years. In other studies conducted in India (60) and France (46), 51% to 74% of the participants were ≤45 years old.

In the present study, participants' average years of experience was 10.3±7.9. Moreover, 60.7% of participants had 10 years or less experience. Similarly, 67.8% of participants in the Indian study had 10 years or less experience (60). In another study conducted in France, 39.5% of the participants had 10 years or less experience (46).

When the type of practice was evaluated in the present study, 92.1% of participants worked only in hospital. In contrast, in studies conducted in India (60) and France (46), between 35% and 49% of the experts worked only in hospital.

In the present study, it was observed that 81.9% of participants applied to a dentist and had an examination in the preceding year. Similarly, in studies conducted in France (46) and Brazil (48), 71.6% and 83.9% of the participants, respectively, stated that they were examined by a dentist in the previous year. In the study conducted in India, 42% of the participants stated that they had not been examined by a dentist in the last year (60). This suggests that Turkish obstetrician-gynecologists who responded to this questionnaire were at least as concerned about their own dental health as French and Brazilian peers.

More than a third of respondents had been formerly diagnosed with periodontal disease. Studies conducted in India (60) and France (46) showed that, respectively, only 62% to 75.4% of the participants with a history of periodontal disease received treatment, respectively. This suggests that obstetrician-gynecologists pay attention to their own oral hygiene, but they

Table 5. Comparative evaluation of the behaviors of the obstetrician-gynecologists (n=382) regarding the relationship between periodontal disease and pregnancy by experience

		Experience	n (%)	P[a]	P[b]
Have you clinically observed the effect of periodontal disease on pregnant women?	Yes	≤10	78 (33.6)	0.074	-
		>10	64 (42.7)		
	No	≤10	154 (66.4)		
		>10	86 (57.3)		
During the examination, do you ask questions about oral health to pregnant women or women who will become pregnant?	Yes	≤10	83 (35.8)	0.176	-
		>10	64 (42.7)		
	No	≤10	149 (64.2)		
		>10	86 (57.3)		
Do you perform visual oral examination?	Yes	≤10	20 (8.6)	**0.006**	-
		>10	27 (18)		
	No	≤10	212 (91.4)		
		>10	123 (82)		
Do you refer your patients who want to get pregnant to the dentist?	Yes	≤10	74 (31.9)	**0.017**	-
		>10	66 (44)		
	No	≤10	158 (68.1)		
		>10	84 (56)		
How often do you inform your pregnant patients about oral health?	Always	≤10	29 (12.5)		0.069
		>10	29 (19.3)		
	At risk	≤10	150 (64.7)	**0.003**	0.222
		>10	106 (70.7)		
	Never	≤10	53 (22.8)		**0.001**
		>10	15 (10)		

[a]Chi square test, p<0.05. [b]Fisher's exact test p<0.05.

cannot be protected from periodontal diseases and they care about the treatment.

Only 39.8% of participants in the present study found themselves capable of assessing the oral health of their patients. This rate was approximately 85% in studies from India (60) and France (46). This suggests that Turkish obstetrician-gynecologists find themselves inadequate in this regard. In the present study, 92.7% of participants were aware that periodontal disease is a disease in which inflammation is present and more than one microorganism may be effective. Similarly, in France (46), Brazil (48) and the United States (50) the rate of awareness of a relationship between periodontal disease and pregnancy was between 85% and 94%. On the other hand, in India, around 48% of obstetrician-gynecologists were unaware of this relationship (60).

The majority of participants accurately marked gingival bleeding as an earliest clinical finding of periodontal diseases. Similarly, in a study conducted in France, 87.4% of the participants correctly identified gingival bleeding (46). In a study conducted in India, gingival bleeding was identified by only 45.5% (60). Regarding the question 'Clinical findings that can be seen in periodontal disease', 67.8% of participants accurately marked tooth mobility, which gives an idea about the existence or loss of the tooth supporting structures. Likewise, tooth mobility was similarly identified by 59.4% in France (46). Again, the proportion with this knowledge was lower in India (30.3%) (60). Regarding the question "Clinical findings that can be seen in periodontal disease", alveolar bone destruction was identified by around 43% in the present study and 46.8% in France (46). In the study conducted in India, only 4.4% of participants identified this sign as being of importance (60). Regarding the question "Clinical findings that can be seen in periodontal disease", 66.5% of participants accurately identified tooth loss while this was less in the Indian (60) and French (46) studies, at 5.3% and 21.1%, respectively. In an American study only 5% and 32% identified gingivitis and periodontitis as causes of tooth loss (50). These findings suggest that obstetrician-gynecologists' knowledge about late signs of periodontal disease is lower than that of early signs. Regarding the question "Clinical findings that can be seen in periodontal disease", dental caries was incorrectly identified by 40.8%. This incorrect option was selected by only 9.5% in India (60) and 14.2% in France (46). Reassuringly, 95.5% of participants thought that periodontal diseases are important diseases that should be treated which compares favorably with rates reported of 42.8% in India (60) and 53.5% in France (46).

Table 6. The referral frequencies of the pregnant individuals to different specialities by obstetrician-gynecologists (n=382)

		n (%)
How often would you recommend childbirth classes to your pregnant patient?	Always	77 (20.2)
	Occasionally	115 (30.1)
	Usually	84 (22.0)
	Rarely	62 (16.2)
	Never	44 (11.5)
How often would you recommend nutrition consultation to your pregnant patient?	Always	149 (39.0)
	Occasionally	146 (38.2)
	Usually	61 (16.0)
	Rarely	17 (4.5)
	Never	9 (2.4)
How often would you recommend dental examination to your pregnant patient?	Always	55 (14.4)
	Occasionally	86 (22.5)
	Usually	120 (31.4)
	Rarely	80 (20.9)
	Never	41 (10.7)
How often would you recommend genetic screening to your pregnant patient?	Always	136 (35.6)
	Occasionally	88 (23.0)
	Usually	70 (18.3)
	Rarely	73 (19.1)
	Never	15 (3.9)

This study also investigated obstetrician-gynecologists' knowledge of oral symptoms often described by pregnant women. Participants selected gingival bleeding (78%) most often from intraoral signs. Gingival bleeding was similarly identified by 65% in France (46), 68% in Brazil (48) and 81% in India. In the United States, gingival bleeding was selected by 52% (50). Gingival enlargement, one of the intraoral findings that pregnant women often complain about, was selected by 38.7% of the participants in the present study. Response rates to the same finding were 81% in India (49), 80.4% in France (46), 68.5% in Brazil (48) and 52% in the United States (50). Tooth loss was identified by 26.7% of participants in the present study. These rates were 42.4% in Brazil (48) and 25% in the United States (50). In France (46), tooth loss was identified by only 4.2%. Dental caries was marked by 53.9% of participants in the present study. Tooth decay was similarly incorrectly selected by 42% and 58% in studies conducted in Brazil (48) and the United States (50).

Regarding the importance of oral care during pregnancy, 96.9% of participants in the present study stated that it is always important, and 3.1% stated that it is important in the presence of any risk. Studies conducted in the United States (47) and France (46) similarly indicated that oral care is always important during pregnancy, 71.5% and 85%, respectively. In the study conducted in India (60), this rate was 39.2%. Only 13.1% of the obstetrician-gynecologists in France (46) and 33%

in India stated that oral care is important in the presence of any risk (60).

In the present study 85.3% of participants stated that pregnancy has impacts on periodontal disease. Studies have shown that the rate of those who think that pregnancy influences periodontal disease is between 64% and 81% (46,47,50,60). The slightly higher rate detected in our study suggests that gynecologists in Turkey can make evaluations by giving more importance to the relationship between periodontal disease and pregnancy.

In the present study, 97.4% of participants stated that dental/periodontal treatment can safely be performed during pregnancy. Obstetrician-gynecologists stated the same in the studies from France (46) and India (49,60), with rates between 84.8% and 97.4% respectively. However, only 79.3% of participants in the present study stated that the second trimester would be the most appropriate period for proper dental/periodontal treatment. Higher rates of this recognition were reported from Brazil at 94% (61) and between 84% and 92% in two studies (49,60) conducted in India. This data reveals that a substantial percentage of obstetrician-gynecologists in Turkey do not know that the second trimester is the most appropriate period for dental treatment of periodontal disease. This knowledge should be reinforced amongst Turkish obstetrician-gynecologists.

In this study, the rate of participants who knew that periodontal disease effected pregnancy was 77.5%. This was similar to results from the USA and France, at 84% and 74.7%, respectively (46,47). In a study conducted in India, this rate was only 47.3% (60).

In terms of the effect of a preterm birth, 92.6% in the present study selected this. Similarly, preterm birth was marked by between 80% and 85% in studies conducted in the United States and France (45-47). However, in studies from Brazil and India, lower rates were reported, with rates between 57% and 65% (49,60,61). In the present study, 45.2% of participants identified low birth weight as one of the possible effects of periodontal disease in pregnancy, which falls in the middle of the range reported from elsewhere of between 32.1% and 66.9% (45-47,60,61). In the present study, only 10.1% of participants marked lower genital tract infection as one of the effects of periodontal disease on pregnancy. Even fewer respondents identified this in studies conducted in France and India (46,60). In the present study, only 3.4% selected preeclampsia as one of the effects of periodontal disease in pregnancy. In contrast, preeclampsia was identified by 33% of respondents in a study from India (49), but this response rate was, at most, 11% in other similar studies conducted in France and the United States (45-47). In the present study, only 37.2% of participants had personal clinical experience of the effect of periodontal disease on pregnant women. Similarly, this rate was 23% in a French study (46). However, in India, 62.5% of gynecologists reported that they observed this effect (60). Given that experts' knowledge about the effects of periodontal disease has yielded such different results in terms of observed symptoms, this may be due to behavioral and cognitive differences specific to different regions and cultures of both physicians and patients.

In the present study, only 38.5% of the participants asked questions about oral health of women who would become pregnant. This rate was 26.3% in France (46) and 49% in the United States (47). However, in India, the majority of the participants stated that they asked questions about oral health to their patients who were about to become pregnant (60).

The proportion who actually examined the mouth of the women planning a pregnancy was only 12.3% in the present study. This rate is much lower than in other reports where the proportion varied from 25% to 80% (46,47,60). The majority of those who visually performed oral examinations were in the >40 age group ($p=0.017$). Moreover, the majority of respondents who would perform an oral exam were also in the more experienced group ($p=0.006$). The cause of these discrepancies may be due to poorer emphasis on the importance of this aspect of health care during more recent medical training as, with increasing age and experience, obstetrician-gynecologists were more likely to perform oral examinations.

In the present study, the proportion of participants who referred their patients who were considering pregnancy to a dentist was just over a third. Similarly, the referral rates were 33.2% in France (46) and 36.7% in Brazil (61). We suggest that the reasons behind these low referral rates should be investigated globally. In the present study, increasing age and experience of the respondent was positively correlated with referral to a dentist.

In the present study, only 15.2% of participants always informed their patients about oral health regardless of risk factors, whereas 67% informed their patients only in case of risk. Similarly, the proportion who always gave information was 10.5% in France and 33.9% in India (46,60). The rate of obstetrician-gynecologists who provided information in the presence of any risk was 55.8% in France and 38.3% in India, but in India a higher proportion always informed their patients regardless of risk (46,60). Again in the present study, most of the respondents who always informed their patients were in the older age group ($p=0.042$). Furthermore, most of the participants who never gave information about oral health were less experienced ($p=0.042$). Once again, older, more experienced respondents were more likely inform patients about the importance of oral health in pregnancy.

Finally, the reported intention of advising patients about consulting with other specialists was investigated. Recommendation to

attend childbirth courses was at the forefront with just over half reporting that they would recommend this to their patients. In a study conducted in Brazil, this rate was 87.3% for obstetricians to "always or generally" refer to childbirth courses (48). In the present study, 77.2% of the participants always or generally referred pregnant patients for nutritional counseling, while in a study from Brazil, this rate was 88.9% (48). However, in the present study, 36.9% of participants always or usually referred for dental examination which is less than in a study conducted in Brazil (48). Conversely, in this study, 58.6% of the participants always or usually referred for genetic screening. Fewer participants (28.6%) always or generally refer pregnant individuals for genetic screening in Brazil (48), possibly due to the lower consanguinity rates in Brazil. These results suggest that Turkish obstetrician-gynecologists give the greatest importance to nutritional counseling but least to dentist referral.

Conclusion

Given the limited nature of the study, we conclude that Turkish obstetrician-gynecologists have enough knowledge about periodontal diseases and their effects. However, the clinical practice and advice given by Turkish obstetrician-gynecologists in this field of pregnancy health care are inadequate. Older and more experienced Turkish obstetrician-gynecologists tend to be better at dealing with this aspect of health care and also more frequently refer pregnant patients to a dentist. Considering the frequency with which Turkish obstetrician-gynecologists refer pregnant patients to different health branches, it is striking that referrals to a dentist is in the last place. It would be beneficial to create common clinical and educational environments where dentists/periodontologists and obstetrician-gynecologists can share their knowledge about the relationship between periodontal disease and pregnancy. We believe that it may be useful to make presentations on this subject in joint workshops and gynecology congresses.

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A systematic review of the reproductive and oncologic outcomes of fertility-sparing surgery for early-stage cervical cancer

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Abstract

In this review, we aim to evaluate the current literature on reproductive and oncologic outcomes after fertility-sparing surgery for early-stage cervical cancer (stage IA1-IB1). This is a systematic review of the existing literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to report on fertility-sparing surgery and its outcomes in early-stage cervical cancer. Outcomes of interest were subsequent clinical pregnancy rate, reproductive outcomes, and cancer recurrence outcomes. Included in this systematic review were 68 studies encompassing 3,592 patients who underwent fertility-sparing surgery. Of these, reproductive outcomes were reported in 1096 pregnancies. The mean clinical pregnancy rate was 53.2%. Those who underwent vaginal radical trachelectomy had the highest clinical pregnancy rate (67.5%). The mean live birth rate was 67.8% in our study. Twenty-one percent of pregnancies after fertility-sparing surgery required assisted reproductive technology. The mean cancer recurrence rate was 3.2%, and the cancer death rate was 0.6% after a median follow-up period of 40.1 months with no statistically significant difference across surgical approaches. Offering fertility-sparing surgery in early-stage cervical cancer is reasonable. Highest clinical pregnancy rate is associated with vaginal radical trachelectomy. Moreover oncologic outcomes of minimally invasive approaches were comparable with abdominal approaches. We encourage detailed preoperative counseling and multidisciplinary approach to achieve best outcomes. (J Turk Ger Gynecol Assoc 2022; 23: 287-313)

Keywords: Cervical cancer, fertility-sparing surgery, pregnancy outcomes

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Introduction

Cervical cancer is the fourth most common malignancy in women worldwide (1). The incidence of cervical cancer is reported to be highest between 35 and 49 years of age and decreases after that. In women between 20 to 45 years of age, this incidence has been reported as as 47.3 per 100,000 (2). Based on the International Federation of Gynecology and Obstetrics 2019 classification system, imaging data and pathology information are used to supplement clinical findings to stage cervical cancer. Details of this staging system is included in Table 1 (3,4). Global Papanicolaou screening and human papillomavirus vaccination have resulted a significant decline in the rate of cervical cancer. Currently the National Cancer Institute reports 90% 5-year survival rate in patients with localized cervical cancer (2). Traditionally total hysterectomy, radical hysterectomy with or without lymphadenectomy, or chemoradiation have been considered the only treatment

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options for cervical cancer. Given the fact that approximately 40% of patients diagnosed with cervical cancer are in the reproductive age, attention to alternative treatment methods for surgical and/or functional preservation of the reproductive system and lead to uterine, tubal, or ovarian factor infertility is of importance (5). Fertility-sparing surgery for early-stage cervical cancer (stage IA1-IB1) is now a viable option that can be offered per the National Comprehensive Cancer Network guidelines. Current fertility sparing options are cervical conization, simple and radical trachelectomy. Trachelectomy can be done abdominally, vaginally, and laparoscopic with or without robot assistance.

The invention and development of video-assisted laparoscopy by Dr. Camran Nezhat has impacted and improved the minimally invasive options as the standard of care in many surgical disciplines including gynecologic oncology (6-10). Reports of the first video-assisted laparoscopic radical hysterectomy, paraaortic and pelvic lymphadenectomy which was performed the Nezhats in 1989 have been previously published (11,12). The early work of surgeons Dargent, Salvat, Querleu, Nezhat, and Childers later on proved the feasibility and safety of retroperitoneal lymphadenectomy (13-16). Roboticassisted radical trachelectomy and pelvic lymphadenectomy have also been reported for the first time by Chuang and Nezhat in 2008, after which other's experiences have been published (17-19).

It is recommended that fertility-sparing surgery be offered to patients after extensive and detailed disclosure of risks, benefits and alternatives. Multidisciplinary meetings by gynecologic oncologists, infertility specialists and other appropriate services are strongly encouraged. Existing evidence offers fertility-sparing surgery in the setting of early-stage cervical cancer (IA1-IB1). In a prospective cohort study, 88 patients underwent laparoscopic radical trachelectomy for early-stage cervical cancer. Based on this study a tumor size of >2 cm was found to be associated with increased risk of cancer recurrence in the setting of fertility sparing surgery (as high as 20%) (20,21).

In patients with more advanced stage disease, those with more aggressive tumor histology like adenoma malignum, gastric adenocarcinoma, clear cell adenocarcinoma, embryonal rhabdomyosarcoma or small cell cancer, and those with no future fertility planning, fertility sparing options are contraindicated and definitive management should be offered. Even in those who undergo fertility sparing treatments radical hysterectomy should be offered when the fertility is no longer desired or when there is persistent HPV abnormality (3).

Based on retrospective and non-randomized research minimally invasive approach to radical hysterectomy for early-stage cancer is being considered safe and is associated with less short-term and long-term morbidity including shorter hospital stay, decreased blood loss (22-30). In a research that was done by Wang et al. (31) it was concluded that both 5-year recurrence free survival and overall survival rates are similar in laparoscopic versus abdominal radical hysterectomies. Another study in 2008 also concluded that the 3-year recurrence free survival and overall survival rates are similar in laparoscopic versus robotic radical hysterectomies for early-stage cervical cancer (32). After the the Laparoscopic Approach to Cervical Cancer (LACC) trial by Ramirez et al. (33), definitive management of early-stage cervical cancer in being considered via laparotomy route in many institutions. This study concluded that radical hysterectomy via minimally invasive routes are associated with lower rates of disease-free and overall survival rates as compared to open surgery. This is the only randomized trial to date that reports the comparison of outcomes of open approach versus minimally invasive options. This study was statistically powered as a noninferiority study with primary endpoint of disease-free survival at 4.5 years. Subjects were randomized to radical hysterectomy by either an abdominal or minimally invasive (laparoscopic or robotic-assisted) approach. The data and safety monitoring committee ended the study in June 2017 due to a safety issue with one of the blinded surgical treatment arms in one of

Table 1. Cervical cancer stages and fertility-sparing surgical treatment

Cervical cancer stage	Staging criteria	Treatment
IA1	Invasive carcinoma diagnosed on microscopy with stromal invasion <3 mm	No LVSI: Cone biopsy with negative margins. LVSI: Cone biopsy with negative margins and pelvic lymphadenectomy OR radical trachelectomy with pelvic lymphadenectomy. Consider sentinel lymph node mapping.
IA2	Invasive carcinoma diagnosed on microscopy with stromal invasion ≥3 mm and <5 mm in depth.	Cone biopsy with negative margins and pelvic lymphadenectomy OR radical trachelectomy with pelvic lymphadenectomy. Consider sentinel lymph node mapping.
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion and lesion <2 cm in greatest dimension, limited to the cervix.	Radical trachelectomy with pelvic lymphadenectomy and possible para-aortic lymph node dissection. Consider sentinel lymph node mapping.

Adapted from 2019 FIGO staging for cervical cancer and National Comprehensive Cancer Network treatment guidelines (3,4). LVSI: Lymphovascular space invasion

the interim analyses. The authors reported the outcomes on 312 subjects in the abdominal hysterectomy arm versus 319 subjects under the minimally invasive arm (83% laparoscopy, 16% robotic surgery). The disease-free survival rate was 96.5% in the abdominal hysterectomy arm as compared to 86% in the minimally invasive surgery arm based on the intention to treat analysis; this corresponds to 13% difference decrease in hazard of death in open surgery arm. Moreover, the number of total disease recurrences in the minimally invasive arm was about four times higher than the number of recurrences after open surgery (27 vs. 7). In this research a significantly lower overall survival was reported in the minimally invasive arm (3 of 312 vs. 19 of 319; HR: 6.00; 95% confidence interval: 1.48-20.3; p=0.004). Based on this finding, the open approach was presented as the preferred route of radical hysterectomy for early-stage cervical cancer. There are some significant limitations associated with the LACC trial. 1) The minimally invasive arm was significantly skewed towards laparoscopic approach over robotic approach, which might not be an appropriate reflection of current practices. 2) In this study the majority of subjects were stage IB1. 3) There was a significant lack of detailed histopathologic data in the final study report. 4) The specific preoperative imaging strategy, and adequate follow up was lacking. 5) Additionally, as a multinational multicenter study in 33 surgical cneters around the world different surgical skills are not unexpected. All the recurrences had happened in 14 out of 33 recruiting centers however no additional informal is provided in the publication regarding details of surgical methodology and perioperative management in any of the other recurrence free institutes. Therefore, the surgical practices and techniques may have contributed significantly as confounding variables. The authors of this paper believe that the conclusion of of the LACC trial should be inetpreted with caution (34). We are in agreement with Donnez (35) who hypothesized that survival differences between minimally invasive and open surgeries will diminish with more surgical experience in minimally invasive approaches. In 2020, an international European cohort observational study compared minimally invasive surgery versus open abdominal radical hysterectomy in a patient with stage IB1 cervical cancer (36). They concluded that minimally invasive surgery in cervical cancer is associated with an increased risk of relapse and death as compared to open surgery. However, it is worth mentioning that in that study, by avoiding uterine manipulators and by using maneuvers to avoid tumor spread at the time of colpotomy in minimally invasive surgeries, outcomes were similar to open surgery.

At a time when open approach is recommended for management of early cervical cancer there is lack of evidence on the route of radical trachelectomy specifically. It is also unclear if the surgical approach (open versus minimally invasive) will affect the final cancer related outcomes.

In this study, we aim to report the result of systematic evaluation of current literature on fertility sparing interventions for early-stage cervical cancer and their associated cancer related, reproductive and obstetric outcomes.

Material and Methods

This paper is a systematic review of the current literature on fertility-sparing surgery for early-stage cervical cancer and the associated reproductive, obstetrics and oncologic outcomes. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was utilized. Medline database used to review the literature. The screening query was “uterine cervical neoplasms” AND “gynecoogic surgical procedures” AND “infertility.” We then performed a Medline search for the query “fertility-sparing surgery” and “cervical cancer.” Two independent authors reviewed the results. This study was exempt from institutional review board approval since there is no human subject research involved.

Included fertility sparing procedures were conization, vaginal radical trachelectomy, open radical trachelectomy, simple trachelectomy with and without lymphadenectomy, or minimally invasive radical trachelectomy (laparoscopic with or without robotic assistance). Literature were included if they specified pregnancy and/or reproductive outcomes per surgical approach. Only papers written in English language between May 1980 and August 2021 were included. Figure 1 depicts the details of the identification process. We excluded the studies that addressed subjects with greater than stage IB1, or those

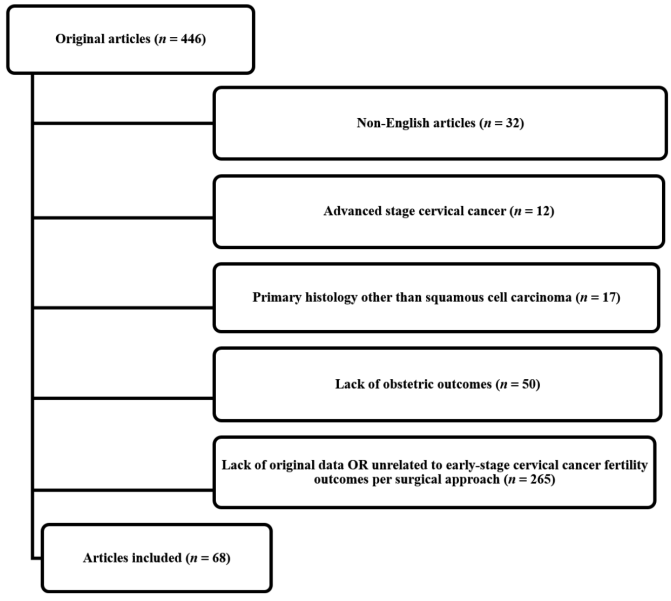

Figure 1. Identification process for studies included in the systematic review

with tumor size >2 cm or those who underwent experimental procedures. Unusual pathologies other than squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma were excluded too. Table 1 shows cervical cancer stages and associated fertility-sparing surgical treatments. D Any review article without any new patient data or any case reports or case series that addressed fewer than 2 subjects were also excluded. PubMed was last screened on 5 August 2021.

Our outcome variables were: live birth rate, clinical pregnancy rate, as well as rates for preterm delivery, cancer related death and cancer recurrence. We divided the number of subjects with minimum of one pregnancy to the number of those who were trying to conceive and defined the clinical pregnancy rate. When the number of patients who were conceiving was not reported; the absolute number of patients with at least one pregnancy was included instead. Preterm delivery was defined as delivery between 24- and 36-weeks' gestation. Per different surgical protocols some of the subjects had intact superior branches of the uterine artery versus in some the arteries were ligated at the origin; this rate was reported as percentage. Recommendation on delay in conception postoperatively was also addressed and reported.

Statistical Analysis

Analysis of variance (one tailed) with post-hoc Tukey tests were used for comparison. The p-value was calculated by the software as a function of F statistic and degrees of freedom for study numerator and denominators. Statistical analysis was performed using SPSS version 23.0. $P<0.05$ was considered statistically significant.

Results

A total of 68 studies were included in this study. Tables 2-6 show the data on 3592 patients based on surgical treatment (37-99, 110-112).

Of the total of 3,592 subjects who underwent fertility-sparing surgery, 1,391 (39%) attempted to conceive, resulting in 1,097 pregnancies. The subjects were followed up for a median of 41 months after their fertility sparing procedure. In 20 studies trying for conception was delayed between 3 to 48 months to monitor for cancer related symptoms prior to conception. The rate for cervical stenosis was 4.7% (169 patients). Analysis of mode of conceptions revealed the rates of 79%, and 29% for spontaneous conception versus assisted reproductive technology (ART) [including in-vitro fertilization, intrauterine insemination (IUI) with or without ovulation induction or cervical dilation with IUI], respectively.

Number of patients who were trying to conceive was reported in 49 studies; the mean clinical pregnancy rate after cancer treatment was 53.2% in this population. Further statistical evaluation of association of surgical approach and clinical pregnancy rate revealed higher rate in vaginal as compared with abdominal radical trachelectomy (67.5±20.0% versus 39.8±15.1%; $p<0.01$). No statistically significant association was found for other surgical routes.

The rate of live birth was reported in 62 studies revealing the mean rate of 67.8%. Further statistical evaluation of association of surgical approach and live birth rate revealed a higher live birth rate in subjects who underwent simple trachelectomy or conization (86.4±16.8%) as compared to vaginal radical trachelectomy (63.4±23.3%; $p=0.04$) and laparoscopic radical trachelectomy with or without robotic assistance (57.3±17.1%; $p=0.03$). No difference in this rate was found among other surgical approaches.

The rate of preterm delivery was reported in 51 studies revealing the mean rate of 29% after all fertility sparing surgical approaches. There was no association between this rate and the various surgical approaches ($F=0.22$; $p=0.8$). No association between various surgical approaches and the second trimester loss rate (8.2%) was found either ($F=0.385$; $p=0.764$).

Table 2. Reproductive and cancer outcomes in different fertility-preserving procedures

Procedure	Patients		Pregnancies		Obstetric Outcomes				Cancer Rates	
	Total (n)	TTC (n)	Total (n)	ART (n)	CPR (%)	LBR (%)	PDR (%)	Median follow-up (mo.)	Recurrence (%)	Death (%)
CKC/ST	283	83	131	8	65.0±20.0	86.4±16.8	25.1±33.4	47.5	1.4±2.1	0.2±0.8
VRT	1387	608	606	78	67.5±17.6	63.4±23.3	34.6±26.4	51.5	3.7±3.7	1.1±1.8
AbRT	1427	608	264	122	42.1±19.2	66.4±23.0	30.5±28.9	33	3.5±7.2	0.7±1.8
LART	335 (88 with RA)	81	96	21	53.2±29.1	57.3±17.1	31.5±22.9	27	3.4±7.0	0.1±0.4
Overall	3592	1391	1097	229	56.1±23.5	67.8±22.9	31.6±27.2	40.1	3.2±5.0	0.6±1.9

CKC: Cold knife conization, VRT: Vaginal radical trachelectomy, AbRT: Abdominal radical trachelectomy, LART: Laparoscopic-assisted radical trachelectomy, TTC: Trying to conceive, ART: Assisted reproductive technology, CPR: Clinical pregnancy rate, LBR: Live birth rate, PDR: Preterm delivery rate

The superior branches of the uterine artery remained intact in 100% of patient who underwent simple trachelectomy or conization, 88.9% of those who underwent vaginal radical trachelectomy, 44.6% of those who underwent abdominal radical trachelectomy, and 58.8% of those who underwent laparoscopic radical trachelectomy. The postoperative infections reported as follows: pelvic lymphocyst in 9 patients, pelvic inflammatory disease in 6 patients, pelvic abscess in 6 patients, pelvic peritonitis in 2 patients, and "pelvic infection" in one patient.

The cancer recurrence rate and cancer death rate after fertility-sparing procedure was reported in 65 studies. The overall mean cancer recurrence rate was 3.2%; no statistically significant association was found between this rate and the surgical approach ($F=0.536$; $p=0.659$). The overall mean cancer death rate was 0.7% with no significant association with surgical approach either ($F=1.759$, $p=0.163$).

Discussion

Our study shows that among all fertility-sparing treatments, vaginal radical trachelectomy has the highest clinical pregnancy rate (67%). Vaginal radical trachelectomy is a minimally invasive technique that can be associated with decreased rate of intraabdominal and pelvic adhesions. This approach is also associated with spared superior branches of uterine artery by the end of procedure. On the other hand, there is a higher potential to develop tuboovarian adhesion (as a known tubal factor for infertility) in the setting of abdominal procedure. Moreover, uterine arteries are ligated most of the times in the setting of abdominal radical trachelectomy; which may theoretically be associated with fertility rate (100). In a study by Tang et al. (101) patients with open procedure underwent computed tomography (CT) angiograms. Assessment of those with spared versus ligated uterine artery and the association with infertility was done. Interestingly, their study revealed that 87.5% of anatomically preserved uterine arteries occluded after surgery and overall 65.4% of subjects developed appropriate collateral circulation to perfuse their uteri (101). In another study by Muraji et al. (102), 18 subjects who underwent open radical trachelectomy with only inferior uterine artery branch ligation were studied and AMH level compared with control group; this study found no statistically significant difference in AMH as an index of ovarian reserve between cases and controls (102). This implies that ovarian reserve is likely unaffected by the ligation of inferior branches of uterine artery.

Obstetric outcomes

Per our systematic review revealed that the live birth rate was highest to lowest in simple trachelectomy/conization, followed by abdominal and then vaginal and then laparoscopic radical trachelectomy. Although those who underwent simple trachelectomy/cervical conization had the highest live birth rate as compared to all the other approaches, this can be attributed to selection bias with more advanced cancers are more likely to be treated via other routes. None of the reviewed studies mentioned cervical insufficiency as a potential complication of the fertility sparing procedures. We used second trimester pregnancy loss as a proxy for this variable and found to statistically significant difference across various surgical approaches.

We reported a 31% risk of preterm delivery after fertility sparing procedures. This rate seems to be significantly more than the 10.6% baseline risk in the general population (103). As a result of surgeon preference, some patients undergo a cervical cerclage placement at the time of trachelectomy routinely. To the best of our knowledge, there are no high-level evidence is available to date to support this intervention and its efficacy in preventing preterm delivery in the setting of fertility sparing surgery (17,40,54,73,104,105). We believe that all patients after fertility sparing procedures should be referred to maternal fetal medicine specialists for antepartum management.

Sufficient data and protocols to decrease the rate of preterm delivery in this population is lacking. One study found that magnetic resonance imaging (MRI) measurement of residual cervical length after radical trachelectomy might be a reliable predictor of preterm delivery or PPROM with significantly increased risk for cervical lengths <10 mm (105). Another study reported that a cervical length of less than 13 mm after abdominal radical trachelectomy was associated with increased risk of preterm delivery; they concluded that a routine second-trimester ultrasound screening can be used as a reliable screening measure (105).

Cervical stenosis

Our study revealed that about 5% of patients were diagnosed with cervical stenosis during their postoperative course. Based on the available data from the existing literature, it is unclear which exact types of fertility treatments were required in the setting of post procedure cervical stenosis. Only 40% of patients were trying to conceive during the study period after their fertility sparing surgery; although the reasons are unclear but potential associated factors can be planned delayed childbearing, postoperative dyspareunia or decreased libido. This topic deserves a further studies in future.

Cancer related outcomes

Based on our review, there was no association between in the different surgical approaches and the cancer recurrence or cancer death rate. Moreover, the authors believe that similar benefits to laparoscopic radical hysterectomy can be achieve

Table 3. Reproductive outcomes of conization or simple trachelectomy in the literature (21,36-47)

Study	Design	Patient		FIGO stage	UAP (%)	Cerclage (%)	Follow-up Interval (median, range mo.)	Conception	
		n	Age (median, range)					Delay (mo.)	TTC (n)
Bogani et al. (37)	**Prospective**	**26 (with LPL)**	**32 (26-40)**	**IA2-IB2**	**100**	12 (during pregnancy)	75 (12-184)	-	16
Okugawa et al. (38)	Retrospective	14 (with LPL)	33 (21-43)	AIS-IA1	100	100	61 (8-31)	3-6	4
Plante et al. (39)	Retrospective	35 (with LPL)	29 (22-44)	IA1-IB1	100	- 68.6 (prophylactic) - 2.9 (during pregnancy)	42 (1-100)	-	24
Andikyan et al. (40)	Prospective	9 (with LPL)	28 (18-36)	IA1-IB1	100	0	17 (1-83)	-	-
Fanfani et al. (41)	Retrospective	23 (with LPL)	30 (24-43)	IA2-IB1	100	16.7 (during pregnancy)	40 (32-125)	3-48	10
Lindsay et al. (42)	Retrospective	40 (with LPL)	29 (22-38)	IA2-IB1	100	15 (during pregnancy)	44 (0-91)	-	-
Biliatis et al. (43)	Prospective	35 (88.6% with LPL)	32 (26-43)	IB1	100	0	56 (16-132)	-	-
Palaia et al. (44)	Prospective	14 (with LPL)	32 (28-37)	IA2-IB1	100	0	38 (18-96)	-	-
Raju et al. (45)	Prospective	15 (with LPL)	28 (20-40)	IA2-IB1	100	100 (prophylactic)	96 (12-120)	12	5
Maneo et al. (46)	Prospective	36 (with LPL)	31 (24-40)	IB1	100	-	66 (6-168)	-	-
Rob et al. (21,47)	Prospective	- 32 - 10 cone (with LPL) 22 simple trachelectomy	28.3 (24-35)	IA2 (CKC)-1B1 (simple trachelectomy)	100	-	47 (12-102)	-	24
McHale et al. (48)	Retrospective	4 (without LPL)	30.75	IA1	100	-	48 (25-108)	-	-

FIGO: International federation of gynecology and obstetrics, UAP: Uterine artery preservation, TTC: Traying to conceive, ART: Assisted reproductive technology, CPR: Clinical pregnancy rate, PTD: Preterm delivery, LBR: Live birth rate, SAB: Spontaneous abortion, TAB: Therapeutic abortion, POI: Primary ovarian insufficiency

Obstetric Outcomes				Fertility complications	Cancer rates	
Total pregnancies (n)	**ART pregnancies**	**CPR**	**Details**		**Recurrence (%)**	**Death (%)**
11	-	69%	PTD (9.1%) Term delivery (72.7%) LBR (82%)2nd-trimester SAB (9.1%) Ongoing pregnancy (9.1%)	POI (3.8%)	0	0
1	100% (1 IVF)	25%	PTD (100%) LBR (100%) 2nd-trimester SAB (0) Hemorrhage during pregnancy (100%)	-	0	0
25	8% (1 IVF, 1 IUI)	75%	PTD (8%) Term delivery (72%) LBR (80%)1st-trimester SAB (20%) 2nd-trimester SAB (0)	Cervical stenosis (11.4%)	2.9	0
3	0	3 patients conceived	-	-	0	0
7	14% (1 IVF)	70%	PTD (14.2%) LBR (100%) Placenta previa (14.2%) 2nd-trimester SAB (0)	Cervical stenosis (4.4%)	0	0
18	-	18 patients conceived	PTD (22.2%) LBR (83.3%)1st-trimester SAB (5.6%) TAB (5.6%)	Infected pelvic lymphocyst (2.5%)	5	0
7	-	7 patients conceived	LBR (100%) 2nd-trimester SAB (0)	-	0	0
8	-	8 patients conceived	Term delivery (37.5%)	Cervical stenosis (14.3%)	0	0
4	0	80%	LBR (100%) 2nd-trimester SAB (0)	-	0	0
21	-	17 patients conceived	PTD (9.5%) LBR (66.7%)1st-trimester SAB (14.3%) 2nd-trimester SAB (4.8%) Tubal ectopic pregnancy (4.8%) TAB (4.8%) Ongoing pregnancy (4.8%)	-	5.5	2.8
23	17.4% (2 IUI, 2 IVF)	#######	PTD (13%) LBR (52.2%)1st-trimester SAB (8.7%) 2nd-trimester SAB (13%) Tubal ectopic pregnancy (4.3%) TAB (4.3%) Ongoing pregnancy (13%)	-	3.1	0
3	-	3 patients conceived	LBR (100%) 2nd-trimester SAB (0)	-	0	0

Table 4. Reproductive outcomes of vaginal radical trachelectomy in the literature (44,48-70)

Study	Design	Patients		FIGO Stage	UAP (%)	Cerclage (%)	Follow-up Interval (Median, Range mo.)	Conception	
		n	Age (Median, Range)					Delay (mo.)	TTC (n)
Malmsten et al. (49)	Retrospective	28	(24-37)	IA1-IB1	-	- 96.4 (prophylactic) - 3.6 (subsequently had cerclage outside of pregnancy)	(26.5-182.4)	-	-
Wang et al. (50)	Prospective	83	-	IA1-IB1	100	100 (prophylactic)	36.2 (24-96)	-	69
Wu et al. (51)	Retrospective	7	33 (29-39)	IB1	-	100 (prophylactic)	5 (3-13)	-	-
Zusterzeel et al. (52)	Retrospective	132	31 (24-43)	IA1-IB1	-	100 (prophylactic)	51 (2-153.2)	6	70
Hauerberg et al. (53)	Prospective	120	30 (22-42)	CIS-IB1	-	100 (prophylactic)	55.7 (5.5-147)	-	72
Kim et al. (54)	Prospective	35	33 (24-39)	IA2-IB1	100	- 88.9 (prophylactic) - 11.1 (during pregnancy)	-	6	-
Cao et al. (55)	Prospective	77	29 (18-38)	IA1-IB1	-	-	-	6	43
Speiser et al. (56,57)	Prospective	212	31.9 (21-48)	IA1-IB1	-	100 (prophylactic)	-	-	76
Kim et al. (58)	Retrospective	42	25-38	IA1-IB1	-	100 (prophylactic)	-	6	23

Obstetric outcomes				Fertility Complications	Cancer Rates	
Total Pregnancies (n)	**ART Pregnancies**	**CPR**	**Details**		**Recurrence (%)**	**Death (%)**
22	#######	14 patients	LBR (72.7%) PPROM (22.7%) 1st-trimester SAB (9.1%) 2nd-trimester SAB (4.5%)	- Cervical stenosis (14.3%) - Cerclage erosion (10.7%)	7.1	0
58	0	#######	PTD (13.8%) LBR (86.2%) PPROM (8%) 1st-trimester SAB (6.9%) 2nd-trimester SAB (0) TAB (6.9%)	Amenorrhea (2.4%)	1.2	0
3	-	3 patients conceived	PTD (0) LBR (0) 1st-trimester SAB (100%) 2nd-trimester SAB (0)	Cervical stenosis (14.3%)	14.3	0
47	#######	#######	PTD (25.5%) LBR (78.7%) 1st-trimester SAB (19.1%) 2nd-trimester SAB (0) TAB (2.1%)	- Cerclage erosion (6.1%)	6.8	3
77	#######	#######	PTD (42.9%) LBR (68.8%) PPROM (18.2%) 1st-trimester SAB (20.8%) 2nd-trimester SAB (2.6%) TAB (3.9%)	- Cervical stenosis (23.3%) - Postoperative sepsis (0.8%)	5.1	1.7
9	-	8 patients	PTD (66.7%) LBR (66.7%) PPROM (66.7%) Chorioamnionitis (66.7%) 2nd-trimester SAB (33.3%)	- Cerclage erosion (12.5%)	0	0
21	-	#######	PTD (19%) LBR (40.7%) TAB (23.8%) 1st-trimester SAB (9.5%) 2nd-trimester SAB (9.5%) Tubal ectopic pregnancy (4.8%)	-	9.1	2.6
60	-	#######	PTD (30%) LBR (75%) 1st-trimester SAB (8.4%) 2nd-trimester SAB (5%) Tubal ectopic pregnancy (1.7%) TAB (3.3%)	- Cervical stenosis (12.7%)	3.8	1.9
19	-	#######	PTD (26%) LBR (78.9%) Tubal ectopic pregnancy (18.8%) 1st-trimester SAB (4.3%) 2nd-trimester SAB (0) TAB (13%)	-	0	0

Table 4. Continued

Study	Design	Patients		FIGO Stage	UAP (%)	Cerclage (%)	Follow-up Interval (Median, Range mo.)	Conception	
		n	Age (Median, Range)					Delay (mo.)	TTC (n)
Persson et al. (59)	Retrospective	10	30 (24-38)	IA1-IB1	100	100 (prophylactic)	(48-115)	-	8
Raju et al. (45)	Prospective	49	28 (20-40)	IA2-IB1	100	100 (prophylactic)	96 (12-120)	12	19
Uzan et al. (60)	Retrospective	28	32 (28-40)	IA2-IB1	-	-	59 (3-132)	-	15
Plante et al. (61)	Prospective	125	31 (20-42)	IA1-IIA	-	-	93 (4-225)	6-12 months	61
Knight et al. (62)	Retrospective	3	30.5 (29-45)	IB1	-	100 (prophylactic)	-	-	3
Chen et al. (63)	Prospective	16	24-31	IA1-IB1	100	100 (prophylactic)	(8-50)	-	-
Pahisa et al. (64)	Retrospective	13	-	IB1	-	-	(2-95)	-	4
Sonoda et al. (65)	Retrospective	36	31 (20-40)	IA1-IB1	-	-	21 (3-60)	-	14
Hertel et al. (66)	Prospective	108	32 (21-41)	IA1-IB1	100	100 (prophylactic)	29 (1-128)	-	-
Shepherd et al. (67)	Retrospective	112	(21-45)	IA2-IB1	-	100 (prophylactic)	(1-120)	6	63

Obstetric outcomes				Fertility Complications	Cancer Rates	
Total Pregnancies (n)	**ART Pregnancies**	**CPR**	**Details**		**Recurrence (%)**	**Death (%)**
10	-	#######	PTD (100%) LBR (100%) 2nd-trimester SAB (0)	- Cervical stenosis (30%) - Cerclage erosion (30%) - Pelvic infection (10%)	0	0
17	17.6% (3 IVF)	#######	LBR (82.4%) 1st-trimester SAB (5.9%) 2nd-trimester SAB (5.9%) Tubal ectopic pregnancy (5.9%)	- Amenorrhea (4.1%) - Cervical stenosis (4.1%)	4.1	2
10	10%	60%	PTD (20%) LBR (80%) 1st-trimester SAB (20%) 2nd-trimester SAB (0)	-	7.1	0
106	7.50%	#######	PTD (18%) LBR (73%) 1st-trimester SAB (20%) 2nd-trimester SAB (3%) TAB (4.7%)	- Cervical stenosis (10%) - Pelvic abscess (2%)	4.8	1.6
4	25% (1 IVF)	100%	PTD (75%) LBR (75%) PPROM (25%) 1st-trimester SAB (25%) 2nd-trimester SAB (0)	Cervical stenosis (33.3%)	0	0
5	20% (1 IVF)	5 patients	LBR (40%) 2nd-trimester SAB (40%) Ongoing pregnancy (10%)	Cervical stenosis, hematometra (6.3%)	0	0
3	-	75%	LBR (33%) Ongoing pregnancies (66%) 2nd-trimester SAB (40%)	-	7.6	7.6
14	36%	#######	PTD (21.4%) LBR (28.6%) PTD (21.4%) TAB (11.8%) 1st-trimester SAB (7.1%) Ongoing pregnancy (28.6%)	Infected pelvic lymphocyst (5%)	2.3	0
18	-	-	LBR (66%) 1st-trimester SAB (5.5%) 2nd-trimester SAB (0) TAB (11.1%) Ongoing pregnancies (16.7%)	Cervical stenosis (7.4%)	4	2
55	#######	#######	LBR (50.9%) 2nd-trimester SAB (3.6%) 1st-trimester SAB (25.5%) TAB (3.6%) Tubal ectopic pregnancy (1.8%) Ongoing pregnancy (5.5%)	Uterine perforation (0.89%) Cervical stenosis (3.6%) Cerclage erosion (2.7%) Amenorrhea (2.7%)	3.3	1.8

Table 4. Continued

Study	Design	Patients		FIGO Stage	UAP (%)	Cerclage (%)	Follow-up Interval (Median, Range mo.)	Conception	
		n	Age (Median, Range)					Delay (mo.)	TTC (n)
Bernardini et al. (68)	Prospective	80	30 (25-36)	-	100	100 (prophylactic)	-	-	39
Burnett et al. (69)	Prospective	18	30 (23-41)	IA2-IB1	0	100 (prophylactic)	(8-81)	-	4
Schlaerth et al. (70)	Prospective	6	34 (25-44)	IA2-IB	100	100 (prophylactic)	(28-84)	-	-
Dargent et al. (71)	Prospective	47	(20-40)	IA1-IIB	-	-	52 (7-123)	-	25

FIGO: International federation of gynecology and obstetrics, UAP: Uterine artery preservation, TTC: Traying to conceive, ART: Assisted reproductive technology, CPR: Clinical pregnancy rate, PTD: Preterm delivery, LBR: Live birth rate, SAB: Spontaneous abortion, TAB: Therapeutic abortion, PPROM: Preterm prelabor rupture of membranes

Obstetric outcomes				Fertility Complications	Cancer Rates	
Total Pregnancies (n)	**ART Pregnancies**	**CPR**	**Details**		**Recurrence (%)**	**Death (%)**
22	27% (3 IVF, 3 IUI)	#######	PTD (27.3%) LBR (81.8%) PPROM (22.7%) Placenta previa (4.5%)	-	1.3	0
3	#######	75%	PTD (33.3%) LBR (66.7%) 2nd-trimester SAB (33.3%)	-	0	0
3	-	50%	-	Pelvic hematoma (16.7%)	0	0
20	15%	52%	LBR (50%)	POI (2.1%) Cervical stenosis (4.3%)	4.3	2.1

Table 5. Reproductive outcomes of abdominal radical trachelectomy in the literature (37,50,54,71-91,110)

Study	Design	Patients		FIGO stage	UAP (%)	Cerclage (%)	Follow-up interval (median, range mo.)	Conception	
		n	Age (median, range)					Delay (mo.)	TTC (n)
Li et al. (111)	Retrospective	360	31 (11-42)	IA1-IB1	-	64 (prophylactic)	65 (7-183)	-	149
Ayhan et al. (72)	Retrospective	22	33 (28-39)	IA1-IB1	100	0	47 (22-175)	-	9
Okugawa et al. (38)	Retrospective	- 137 - 89 radical trachelectomy- 48 modified radical trachelectomy	33 (21-43)	IA2-IIA1	0	100 (prophylactic)	61 (8-131)	3-6	57
Wu et al. (51)	Retrospective	3	31 (29-37)	IB1	-	100 (prophylactic)	3 (1-4)	-	-
Kasuga et al. (73)	Prospective	172	-	IA1–IB1	-	100 (prophylactic)	-	6	109
Tamauchi et al. (74)	Retrospective	28	31 (27-37)	IA2-IB1	100	100 (prophylactic)	43 (13-63)	-	12
Tokunaga et al. (75)	Prospective	42	32 (22-39)	IA1-IB1	-	-	29.9 (1-122)	-	18
Vieira et al. (76)	Retrospective	58	29.3 (21-40.3)	IA1-IB1	34.4	-	66 (11-147)	-	27

Obstetric outcomes					Cancer rates	
Total pregnancies (n)	**ART pregnancies**	**CPR**	**Details**	**Fertility complications**	**Recurrence (%)**	**Death (%)**
30	16	17.4	PTD (16.7%) Term delivery (46.6%) elective termination (6.7%) 1st trimester SAB (10%) 2nd trimester SAB (20%)	Cervical stenosis (27%), fallopian tube obstruction (23%), Infertility before surgery (12.6)	-	-
5	60%	-	PTD (40%) LBR (20%) Term delivery (20%) PPROM (20%) 1st-trimester SAB (20%) 2nd-trimester SAB (20%)	Cervical stenosis (4.5%)	4.5	0
20	71.4% (3 IUI, 13 IVF)	-	- PTD (40%) LBR (70%) 1st-trimester SAB (30%) PPROM (30%) Term delivery (30%) 2nd-trimester SAB (0) Hemorrhage during pregnancy (14.3%)	-	0.7	0
0	-	0 patients conceived	-	-	33.3	0
61	69% (3 IUI, 39 IVF)	44%	LBR (70.5%) PPROM (23%) Chorioamnionitis (14.8%) 1st-trimester SAB (16.4%) 2nd-trimester SAB (4.9%) Ongoing pregnancy (8.2%) Placenta previa (3.3%) Massive bleeding during pregnancy (9.8%)	-	0	0
8	87.5% (2 IUI, 5 IVF)	-	PTD (50%) LBR (62.5%) PPROM (37.5%) 1st-trimester SAB (37.5%) 2nd-trimester SAB (0) Term delivery (12.5%)	Cervical stenosis (28%) Amenorrhea (10.7%)	0	0
5	100%	-	LBR (60%) 1st-trimester SAB (20%) TAB (20%) PTD (40%) Term delivery (20%) 2nd-trimester SAB (40%)	-	7.1	4.8
16	-	-	PTD (50%) LBR (56.3%) Term delivery (6.3%) 1st-trimester SAB (18.8%) 2nd-trimester SAB (6.3%) Ongoing pregnancies (18.8%)	Cervical stenosis (8.6%) Cervical erosion (10.3%) Uterine avulsion (1.7%) Pelvic abscess (1.7%)	1.7	1.7

Table 5. Continued

Study	Design	Patients		FIGO stage	UAP (%)	Cerclage (%)	Follow-up interval (median, range mo.)	Conception	
		n	Age (median, range)					Delay (mo.)	TTC (n)
Capilna et al. (77)	Retrospective	26	32 (24-40)	IA2-IB2	0	0	20 (4-43)	-	7
Kucukmetin et al. (78)	Prospective	16	26 (24-36)	IB1	6.3	100 (prophylactic)	43 (8-110)	-	-
Van Gent et al. (79)	Retrospective	28	31 (21-37)	IA2-IB2	100	100	47 (6-122)	-	17
Cao et al. (55)	Prospective	73	31 (22-39)	IA1-IB1	-	-	20.6 (6-42)	6	34
Nishio et al. (80)	Retrospective	114	33 (25-40)	IA1-IB1	100	- 98.2 (prophylactic) - 1.8 (during pregnancy)	33 (25-40)	-	69
Testa et al. (81)	Retrospective	25	31 (22-40)	IA2-IB1	24	- 24 (prophylactic) - 8 (during pregnancy)	29.6 (6-68)	6	6
Muraji et al. (82)	Retrospective	20	25-42	IA1-IB1	60	-	(2-45)	12	10
Nick et al. (83); Pareja et al. (84)	Retrospective	24	29 (21-37)	IA1-IB1	0	100 (prophylactic)	26 (0-65)	6	-
Saso et al. (85)	Retrospective	30 (3 laparoscopic-assisted)	32.5 (23-41)	IA2-IIA	0	80 (prophylactic)	24 (7-113)	-	10
Wethington et al. (86)	Retrospective	70	31 (19-43)	IA1-IIA	0	47 (prophylactic)	(1-124)	-	38
Du et al. (87)	Prospective	60	33 (18-41)	IA2-IB1	-	- 48.3 (prophylactic) - 5 (during pregnancy)	38 (3-84)	6	15

Obstetric outcomes					Cancer rates	
Total pregnancies (n)	**ART pregnancies**	**CPR**	**Details**	**Fertility complications**	**Recurrence (%)**	**Death (%)**
3	-	-	PTD (0) LBR (33%) Term delivery (33%) 1st-trimester SAB (66%) 2nd-trimester SAB (0)	Amenorrhea (11.54%) Pelvic peritonitis (3.85%) Cervical stenosis (3.85%) POI (3.8%)	3.85	0
1	-	1 patient	PTD (0) LBR (100%) Term delivery (100%) 2nd-trimester SAB (0)	Vaginal erosion (6.3%) Cervical stenosis/ hematometra (6.3%)	6.25	0
14	14.3% (2 IVF)	-	PTD (0) LBR (100%) Term delivery (100%) 2nd-trimester SAB (0)	-	7.1	3.6
3	-	8.80%	PTD (0%) LBR (100%) Term delivery (100%) 2nd-trimester SAB (0)	-	0	0
31	71% (2 IUI, 20 IVF)	-	PTD (54.8%) LBR (67.7%) 1st-trimester SAB (12.9%) 2nd-trimester SAB (3.2%) Term pregnancy (12.9%) Ongoing pregnancy (16.1%) Placenta previa with accreta (3.2%)	Cervical stenosis (3.5%) PID (5.2%)	0	0
3	0	50%	PTD (66.7%) LBR (100%) Term delivery (33.3%) 2nd-trimester SAB (0)	Cervical stenosis (8%) Asherman syndrome (4%)	0	0
1	0	10%	PTD (100%) LBR (100%) 2nd-trimester SAB (0)	Cervical stenosis (10%) Amenorrhea (10%) Infected pelvic lymphocyst (5%)	0	0
4	25% (1 IVF)	3 patients conceived	PTD (25%) LBR (25%) 1st-trimester SAB (50%) 2nd-trimester SAB (25%)	Cerclage erosion (16.7%) Cervical stenosis (12.5%) Amenorrhea (29.2%) Pelvic abscess (4.2%)	0	0
3	33% (1 IVF)	30%	PTD (0) LBR (66.7%) PPROM (33%) 2nd-trimester SAB (33%) Term delivery (66.7%)	Uterine avulsion (3%) Cervical stenosis/ hematocolpos (3%)	10	6.7
31	-	74%	LBR (51.6%) 1st-trimester SAB (9.7%) 2nd-trimester SAB (19.5%)	Cervical stenosis (12%) Cerclage erosion (2%)	4	0
8	-	33%	PTD (25%) LBR (62.5%) PPROM (25%) 1st-trimester SAB (12.5%) 2nd-trimester SAB (0) Ongoing pregnancy (25%)	Cervical stenosis (28.3%) Infected pelvic lymphocyst (8.3%) Amenorrhea (5%)	3.3	0

Table 5. Continued

Study	Design	Patients		FIGO stage	UAP (%)	Cerclage (%)	Follow-up interval (median, range mo.)	Conception	
		n	Age (median, range)					Delay (mo.)	TTC (n)
Li et al. (88)	Retrospective	59	29.5 (11-41)	IA1-IB1	100	100 (prophylactic)	23 (1-78)	6	10
Yao et al. (89)	Retrospective	10	29 (28-30)	IA2-IB1	100	100 prophylactic (using mesh)	(4-68)	-	-
Olawaiye et al. (90)	Retrospective	10	32 (24-38)	IA1-2A	-	100 prophylactic	(1-74)	-	3
Ungar et al. (91)	Prospective	30	30.5 (23-37)	IA2-IB2	0	0	47 (14-75)	24	5
Rodriguez et al. (92)	Retrospective	3	26 (24-30)	IA2	33	100 (prophylactic)	(9-31)	-	-

FIGO: International federation of gynecology and obstetrics, UAP: Uterine artery preservation, TTC: Traying to conceive, ART: Assisted reproductive technology, CPR: Clinical pregnancy rate, PTD: Preterm delivery, LBR: Live birth rate, SAB: Spontaneous abortion, TAB: Therapeutic abortion, PPROM: Preterm prelabor rupture of membranes

Obstetric outcomes					**Cancer rates**	
Total pregnancies (n)	**ART pregnancies**	**CPR**	**Details**	**Fertility complications**	**Recurrence (%)**	**Death (%)**
2	50% (1 IVF)	20%	PTD (0%) LBR (50%) Term delivery (50%) Ongoing pregnancy (50%) 2nd-trimester SAB (0)	Cervical stenosis (8.5%) Infected pelvic lymphocyst (3.4%) - 5.1% POI	0	0
2	50% (1 IVF)	2 patients conceived	PTD (50%) LBR (100%) Term delivery (50%) 2nd-trimester SAB (0)	-	0	0
3	66.7% (1 IUI, 1 IVF)	-	PTD (33%) LBR (66.7%) Term pregnancy (33%) Ongoing pregnancy (33%) 2nd-trimester SAB (0)	Cervical stenosis (20%) Cerclage expulsion (20%)	0	0
3	33% (1 IVF)	60%	PTD (0) LBR (66.7%) 1st-trimester SAB (33.3%) Term delivery (66.7%) 2nd-trimester SAB (0)	Asherman syndrome (6.7%) Cervical stenosis (3.3%)	0	0
2	0	1 patient conceived	PTD (0) LBR (50%) Term delivery (50%) Ongoing pregnancy (50%) 2nd-trimester SAB (0)	Cervical stenosis (33%) Pelvic abscess (33%)	0	0

Table 6. Reproductive outcomes of laparoscopic radical trachelectomy with or without robotic assistance in the literature (20,57,62,69,75,77,82,92-98)

Study	Design	Patients		FIGO stage	UAP (%)	Cerclage (%)	Follow-up interval (median, range mo.)	Conception	
		n	Age (median, range)					Delay (mo.)	TTC (n)
Johansen et al. (93)	Prospective	48 (with RA)	29 (23-41)	IA1-IB1	95.8	100 (prophylactic)	24 (1-89)	-	21
Vieira et al. (76)	Retrospective	42 (22 with RA)	30.1 (25.4-40.6)	IA1-IB1	4.8	-	25 (10-69)	-	7
Kucukmetin et al. (78)	Prospective	11	28 (25-40)	IB1	9.1	100 (prophylactic)	9 (1-20)	-	-
Park et al. (20)	Prospective	79	31 (20-40)	IA2-IB1	-	-	29 (5-90)	-	-
Ebisawa et al. (94)	Retrospective	56	(22-42)	IA2-IB1	100	100 (prophylactic)	60 (4-138)	6	25
Lu et al. (95)	Retrospective	25	29 (22-34)	IA2-IB1	100	100 (prophylactic)	66 (1-82)	6	12
Kim et al. (58)	Retrospective	4 (with RA)	(25-38)	IA1-IB1	-	100 (prophylactic)	-	6	0
Nick et al. (83)	Retrospective	8 (with RA)	29 (21-37)	IA1-IB1	0	100 (prophylactic)	11 (0-65)	6	-
Martin et al. (96)	Retrospective	9	-	IA2-IB1	77.8	100 (prophylactic)	(6-32)	6	4
Burnett et al. (97)	Retrospective	6 (with RA)	27 (25-30)	IB1	100	100 (prophylactic)	(9-13)	-	-
Park et al. (98)	Retrospective	4	29.5 (25-33)	IA2-IB1	0	100 (prophylactic)	(27-37)	-	-

Obstetric outcomes				Fertility complications	Cancer rates	
Total pregnancies (n)	**ART pregnancies (%)**	**CPR**	**Details**		**Recurrence (%)**	**Death (%)**
20	5	81%	- LBR (80%) - 2nd-trimester SAB (5%) - 1st-trimester SAB (5%) - 2nd-trimester SAB (0) - Ongoing pregnancy (10%)	- Cerclage erosion (8.3%) - Cervical stenosis (2%)	4.2	0
3	-	-	- LBR (33%) - PTD (33%) - 1st-trimester SAB (33%) - 2nd-trimester SAB (0) - Ongoing pregnancy (33%)	- Cerclage erosion (11.9%) - Cervical stenosis (7.1%) - Uterine necrosis requiring hysterectomy (2.4%) - Peritonitis (2.4%)	0	0
0	-	0 patients conceived	-	-	0	0
17	-	13 patients conceived	- LBR (76.5%) - PTD (41.2%) - Term delivery (35.3%) - 1st-trimester SAB (23.5%) - 2nd-trimester SAB (0)	-	3.8	0
21	47.6	52%	- LBR (61.9%) - PTD (47.6%) - PPROM (38.1%) - 2nd-trimester SAB (9.5%) - 1st-trimester SAB (23.8%) - Ongoing pregnancy (4.8%)	Cervical stenosis (8.9%)	1.8	1.8
9	33.3	75%	- LBR (44%) - PTD (11.1%) - PPROM (11.1%) - Chorioamnionitis (11.1%) - 1st-trimester SAB (33.3%) - 2nd-trimester SAB (0) - Term delivery (33.3%) - Ongoing pregnancy (22.2%)	-	0	0
0	-	0	-	-	0	0
0	-	0 patients conceived	-	-	0	0
2	50	50%	- LBR (50%) - Term delivery (50%) - Ongoing pregnancy (50%) - PTD (0) - 2nd-trimester SAB (0)	-	11.1	0
0	0	0 patients conceived	-	Extrusion of cerclage (28%)	0	0
0	-	0 patients conceived	-	-	25	0

Table 6. Continued

Study	Design	Patients		FIGO stage	UAP (%)	Cerclage (%)	Follow-up interval (median, range mo.)	Conception	
		n	Age (median, range)					Delay (mo.)	TTC (n)
Chen et al. (63)	Prospective	16	27.6 (24-31)	IA1-IB1	100	100 (prophylactic)	28.2 (8-50)	-	-
Jolley et al. (99)	Retrospective	2	30.5 (29-32)	IB1	-	•50 (prophylactic)•50 (during pregnancy)	-	-	2
Schlaerth et al. (70)	Retrospective	4	28.5 (24-34)	IA2-IB	0	100 (prophylactic)	(28-84)	-	-

ART: Assisted reproduction technology, CPR: Clinical pregnancy rate, FIGO: International Federation of Gynecology and Obstetrics, LBR: Live birth rate, POI: Primary ovarian insufficiency, PPROM: Preterm prelabor rupture of membranes, PTD: Preterm delivery, RA: Robotic assistance, SAB: Spontaneous abortion, TTC: Trying to conceive, UAP: Uterine artery preservation

by performing laparoscopic radical trachelectomy with or without robotic assistance. These benefits include and are not limited to lower short- and long term moribidity, decreased blood loss and shorter hospital stay.

Since this is a relatively new procedure, we recommend that patients should be referred to centers of excellence in gynecologic oncology with extensive experience in the evaluation and surgical management of early-stage cervical cancer. In brief, our recommendation is to perform a thorough histopathologic and preoperative evaluation. Performing a pelvic MRI, contrast axial CT, and positron emission tomography for proper assessment of the parametrium and possible lymphadenopathy is encouraged.

The LACC trial recently provided the notion that use of uterine manipulator might be associated with cancer recurrence and decreased survival rate. For that reason, our recommendation is to avoid uterine manipulators especially in the setting of a visible cervical lesion. At times and if no visible cervical lesion is present, after the cervix and parametrium are completely mobilized and resected the uterine manipulator to assist with making colpotomy can be used. We recommend removing the specimen immediately after transected from the vagina and maybe in a specimen retrieval bag. Appropriate radicality of the procedure should be assessed by confirming cancer free margins. Anastomosis of the vagina to uterine corpus and possible cerclage placement can be done either laparoscopically or vaginally per surgeon's preference. In the setting that there is visible disease on cervix, laparoscopic approach can be used to mobilize the cervix and dissect the parametrium and then the procedure can be converted to vaginal route. Colpotomy can be done vaginally with adequate margins. We recommend to bring the vaginal mucosa over the cervix at this point and clamp with appropriate instruments to cover the diseased cervix. The cervix should be amputated with negative margins and then the reanastomosis procedure can be continued vaginally. We believe that the role of surgeon's learning curve in the outcomes of these minimally invasive procedures is significant; this will make designing a randomized controlled trials comparing laparoscopic radical trachelectomy, with and without robotic assistance, and other surgical approaches hard.

Conclusion

Our study has several strengths. To the best of our knowledge, this is the largest and most comprehensive review of obstetrics, reproductive and fertility outcomes of fertility sparing methods in the setting of early-stage cervical cancer. To calculate the clinical pregnancy rate, we included only those who were trying to conceive as opposed to all the patients who undergone fertility sparing procedure.

Potential limitations of our study were limitations of data presented in the literature, with a lack of control over confounders that may affect oncologic or reproductive outcomes. This includes previous infertility or potential comorbid diagnosis. Also there were limited information

Obstetric outcomes				Fertility complications	Cancer rates	
Total pregnancies (n)	ART pregnancies (%)	CPR	Details		Recurrence (%)	Death (%)
5	20	5 patients	- LBR (40%) - PTD (20%) - Term delivery (20%) - 2nd-trimester SAB (40%) - PPROM (20%) - Ongoing pregnancy (20%)	Cervical stenosis, hematometra (6.25%)	0	0
3	0	100%	- LBR (66.6%) - PTD (66.6%) -1st-trimester SAB (33.3%) - 2nd-trimester SAB (0)	Cerclage erosion (50%)	0	0
1	-	25%	-	Cervical stenosis (50%)	0	0

regarding the details of the ART methods and protocols in primary literature.

Although no statistically significant difference was found in the preterm delivery rate across different fertility sparing approaches, the data for iatrogenic preterm deliveries was not available in the primary literature. Initially obstetricians tend to iatrogenically deliver their patient at 34 weeks, after fertility sparing procedures (62,104). Since the use of cerclage to prevent preterm delivery is not supported by high level evidence-based literature patients recently have been scheduled for delivery closer to term (108). For this reason there is an iatrogenic component in higher rate of preterm delivery in older and compared to more recent literature.

Attention to multiple factors is required to determine the optimal approach to fer-tility sparing procedure in early-stage cervical cancer. Patient's preference, disease's stage, surgeon's experience and available surgical instrumentation are some of these important factors. In this review, we provided the most updated relevant data that can be used in preoperative counseling. Further research in high volume surgical centers are encouraged to address the outcomes of minimally invasive radical trachelectomy in more details. We encourage multidisciplinary patient counseling, with gynecologic oncologists, reproductive endocrinologists, and maternal fetal medicine specialists present to set reasonable expectations regarding treatment and outcomes.

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Different perspectives on translational genomics in personalized medicine

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Abstract

Personalized medicine is a relatively new and interesting concept in the medical and healthcare industries. New approaches in current research have supported the search for biomarkers, based on the genomic, epigenomic and proteomic profile of individuals, using new technological tools. This perspective involves the potential to determine optimal medical interventions and provide the optimal benefit-risk balance for treatment, whilst it also takes a patient's personal situation into consideration. Translational genomics, a subfield of personalized medicine, is changing medical practice, by facilitating clinical or non-clinical screening tests, informing diagnoses and therapeutics, and routinely offering personalized health-risk assessments and personalized treatments. Further research into translational genomics will play a critical role in creating a new approach to cancer, pharmacogenomics, and women's health. Our current knowledge may be used to develop new solutions that can be used to minimize, improve, manage, and delay the symptoms of diseases in real-time and maintain a healthy lifestyle. In this review, we define and discuss the current status of translational genomics in some special areas including integration into research and health care. (J Turk Ger Gynecol Assoc 2022; 23: 314-21)

Keywords: Personalized medicine, translational genomics, women's healthcare, pharmacogenetics, cancer

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Introduction

Multiomics-integrated techniques, particularly genomic data acquired from new sequencing technologies, have made a significant contribution to expanding and deepening understanding of the molecular mechanisms of diseases. Translational genomics plays a crucial role in creating an informational bridge between diseases and health conditions (1-4). The goal of translational genomics is to improve human health by taking discoveries in genetic research and applying them to the clinic. The evolution of translational genomics for the management and treatment of various disorders is offering new perspectives for clinicians in managing medical conditions (3,5-6).

The terminology of the genomic sequence, which was released by the Human Genome Project in 2001, does not fully reflect the genome of individuals. This term is accepted as a reference DNA sequence, consisting of all human DNA landmarks without being based on any individual-specific information (7). As a result, the requirement for personalized genomic data to explain particular risk factors for genetic disorders stimulated researchers to develop new DNA sequencing technologies. Due to the developments in advanced technologies, both the cost and time of personal genome sequencing have decreased significantly (4,8). Genomic sequencing is now widely accepted as an essential tool for evaluating gene-linked diseases and is used in a variety of routine tests. As a result,

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personal genomic sequencing data, combined with medical records, provide medical professionals with important insights into the factors linked with genetic disorders and aids in the detection, diagnosis, and treatment of a wide range of complex diseases. It also enables medical professionals to administer targeted therapy (4,8,9).

In this review, we discuss different perspectives of translational genomics in human health. First, its general relation with personalized medicine with descriptions and explanations of terms and studies. We also discuss the impact of translational genomics on cancer research and women's diseases. In relation to this, the connection between translational genomics and pharmaceutical industries is considered.

Translational genomics in personalized healthcare

Personalized medicine (also known as personalized genomics, or genomic medicine) describes the approach for preventing and treating diseases that consider the genome, lifestyle, and environment on an individual basis. In contrast to the "one-size-fits-all" concept, this patient-specific approach also supports the assessment of individual risks, and the personalization of disease prevention and disease-management strategies in healthcare (1).

Next-generation sequencing (NGS) techniques have recently made significant progress in the detection of genetic diseases and pioneered personalized treatments by enabling the analysis of patient-specific genomic variations (10). New sequencing techniques enable massively parallel sequencing of millions of DNA/RNA molecules at a relatively small cost. In recent years, there has been an increasing interest in different NGS technologies because of their capacity to sequence rapidly and efficiently. Different sequencing options, such as exome sequencing (11,12), RNA-seq (13,14), ChIP-seq (15,16) and whole-genome sequencing (WGS) (17,18), are available depending on the type of sample being sequenced and the region of interest in the genome. The term "genome sequencing" refers to both genome and exome sequencing options. However, it should be pointed out that there are regions of the genome that are not mapped in "whole genome" or "whole exome" technologies. The genetic basis of a disease may be related to either small- or large-scale modifications of DNA sequences, such as single nucleotide variants, insertions and deletions (indels), copy number variations, and structural variants (19).

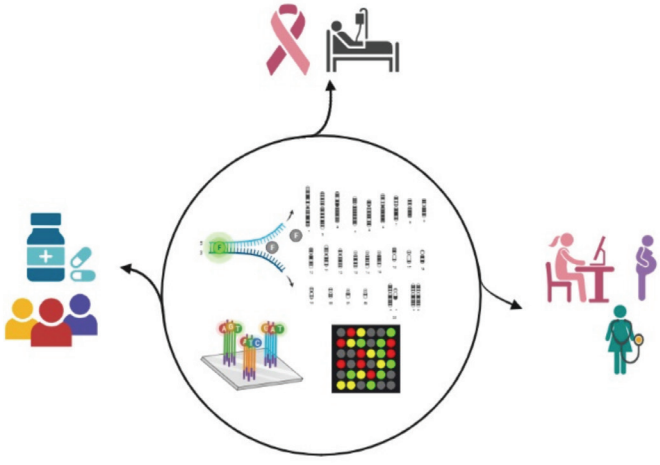

Figure 1. Graphical abstract

Clinical genome sequencing is not only a technology. Due to the clinical considerations, it requires extra components in addition to the technology. Since the Human Genome Project was completed, studies to integrate genetic information into clinical practice in health services have accelerated (8,9,19). However, this integration brings many challenges, including social, ethical, legal, educational, economic, and technical problems. The integration process also requires answering questions about how to produce, analyze, store, and use this information together with other medical data. Since the interpretation of genomic data needs the abilities of a specialist besides the general medical expertise of many clinicians, the integration process should be supported by a variety of experts, including genomic laboratory specialists, geneticists, and genetic consultants (8,20). Extensive research has been carried out into integration of genomic data into clinical practice (20,21).

The analytical process for a novel genetic variant includes several processes. Besides in silico analysis of the variant, biological characterization of the variant which includes the type, the location, and the frequency is also performed (22). Additionally, variant-related case studies, case controls and also functional studies should be considered. Clinical characteristics include the relation of the variant with disease or phenotype, as well as functional analyses of the mutation's effect in vitro or in vivo. The location of the variant is also be considered. The location mostly indicates the regions of genes (specific exons) or certain types of mutations (for example, activating) that are known to be related to a specific disease (19). Similarly, if known disease-causing mutations are all gain-of-function, other mutation types (e.g., stop or silent mutation) is less likely to be regarded as pathogenic (19). Additionally, specifics of the mode of inheritance, the prevalence of disease, and onset age are all essential variables with regard to the disease. Lastly, the clinical features and pedigree must be evaluated when reporting results—is this a diagnostic assessment or screening? How many other tests have been completed? It should also be considered whether there are other phenotypic data that may be useful in the interpretation of the results and how phenotypic

data should be interpreted. Is there any other phenotypic data that might be useful in interpreting the results and how should they be interpreted? Thus, this interpretation needs practical and clinical genetic knowledge (19,23).

Many clinical conditions can benefit from the use of translational genomics. However, interaction and collaboration between physicians and patients will occur in the light of a quality laboratory procedure, analytical validation, ongoing proficiency testing, bioinformatics analysis, and appropriate interpretation and reporting of data. This field is a fast-growing area, and it will surely lead to the emergence of new bioinformatics and genetic analysis professions (3,10,24).

Impact of translational genomic on cancer

Over the last few decades, genomic data has been used in many different fields, such as cardiovascular diseases, infectious illnesses, endocrinology, metabolic medicine, and hematology, to personalize health care. Oncology is another area that has seen a huge increase in the use of genomic data for diagnostic, prognostic and therapeutic assessment (25). Since cancer is partly a genetic-based disease, understanding the genetic structure of cancer improved our diagnostic, prognostic and therapeutic strategies (26). The rapid developments of high-throughput sequencing and bioinformatics tools have led to considerable success with the current massive effort (27). In the last decades, the identification of mutations in patient tumors has expanded our knowledge of many cancers due to remarkable advances in NGS technology (28). However, numerous questions about the clinical application of NGS for therapeutic decision-making remain unanswered. Questions range from how extensively the cancer genome should be characterized to how to explain altered genes that may result in a drug's response, to more social concerns like medical education and data sharing (3,29).

Currently, most cancer treatments have systemic effects on patients. While its efficiency is high in reducing cancer lesions, it is not as effective as targeted therapies. As a result of this systemic approach, some patients having more aggressive cancer types which may be undertreated, and conversely, patients with less aggressive types can be overtreated. Therefore, it is important to determine and treat the tumor of each patient on an individual basis. To reach this stage of cancer treatment, there has been a huge amount of research into many of the types of cancer, especially the more prevalent cancers. As a result of genetic approaches to cancer types, many candidate biomarkers for detection and prognosis have been discovered, but only a few have been validated in clinical practice. Some important challenges, such as tumor heterogeneity, cancer progression, the origin of cancer, and biomarker performance, have hindered biomarker identification. The development of cancer biomarkers will be driven by technological breakthroughs. As ultra-high-throughput sequencing technologies, such as WGS, improve and become more cost-effective, they can be used to identify rare, highly penetrant, high-risk alleles for many cancers and to determine cancer screening protocols for individuals at high risk. The challenges of carcinogenesis, cancer heterogeneity, and the tumor microenvironment mean that a unidirectional diagnostic approach is unlikely to be useful. Rather, the diagnosis will be a multi-step procedure that begins with the identification of at-risk patients, then followed by a sampling step, ideally involving a minimally invasive biosample such as blood or urine, and finally by molecular imaging to identify the lesions (24,25).

For risk assessment, screening, diagnosis, prognosis, and treatment of cancer, several cancer-specific genetic tests are performed. *MLH1, MSH2* (including *EPCAM*), *MSH6, PMS2* genes are screened for Lynch syndrome (hereditary nonpolyposis colorectal cancer), whereas *BRCA1* or *BRCA2* genes are screened for assessing risk-reducing surgery for breast and ovarian malignancies (24,30-32). Cervical cancer screening includes human papillomavirus (HPV) genotyping (24,33). *BCR-ABL, E2A-PBX1, TEL-AML1,* and *MLL* fusions and rearrangements are used to personalized leukemia treatment (24,34). Breast, colon, and prostate malignancies, and lymphoma-specific gene expression patterns can also be utilized to diagnose and for prognosis of the disease (25).

Targeted therapy strategies have been well characterized and are one of the treatment approaches applied by oncology. Cancer biomarkers and targeted therapeutics are key elements for the pharmaceutical industry. Those currently available pharmaceutical products are derived from the combination of molecular and clinical research, known as translational research (35). Many genes with mutations in a small number of hotspots are currently targetable by specific therapeutics. While Herceptin (trastuzumab) was developed to treat HER2-positive breast cancer, gefitinib and erlotinib were developed to target therapy for EGFR mutations in lung cancer and glioblastoma. Additionally, RAF inhibitors are also used in the treatment of melanoma. Many types of research are now being conducted that can be used to improve the success of personalized medicine via targeted therapy (3,25,32).

Numerous studies into cancer have led to many novel discoveries potentially translatable to the clinic for diagnostic and therapeutic applications. These have identified new treatment options that can be applied to other tumor types and expanded our knowledge of cancer pathways (36-38). Thus, a deeper understanding of cancer mechanisms will be realized

to target it with much greater therapeutic precision.

Personalized medicine in women's healthcare

Determining risk susceptibility considering women's age, health status and ability to respond to treatments, provides optimal care for women. Personalized medicine provides significant health and economic benefits for women, health services, and society, in order of enhanced medical decision-making, administration of suitable therapies, optimized disease preventive approaches, and reduced exposure to or avoidance of drugs with a lower efficacy. Additionally, it includes reduced exposure to potentially harmful pharmaceuticals, lower healthcare costs, improved approval of the treatment process, and lastly improved therapeutic tolerance and compliance in a variety of conditions (3,5,39). Multidisciplinary management with different specialists, including gynecologists and obstetricians, oncologists, pathologists, molecular biologists, and geneticists, has had an indisputable positive role like the traditional diagnosis and treatment process (40).

Women differ from men because of hormonal changes which are associated with several diseases and health status changes throughout their life. Sex and gender have been considered when planning the strategies for the management of diseases in precision medicine because biological gender has a range of genetic, epigenetic, and hormonal implications regarding disease mechanisms, development, and course (41).

Although personalized medicine is most widely used in the field of oncology, problems during the pregestational and gestational periods can be evaluated and overcome using precision medicine. With cell-free fetal DNA (cffDNA) obtained from maternal circulation as a minimally-invasive approach, it is possible to obtain genomic and molecular information from a fetus. Although it is a screening test, the list of disorders that can be detected by cffDNA is gradually growing. Increased usage of this test has provided more specific and accurate decisions with improved outcomes. Prenatal testing is preferred by many couples since it allows them to be aware of disease risk and implementation strategies to optimize newborn health. (42).

Preterm birth, described as delivery before 37 completed weeks of gestation, occurs in approximately 10% of all pregnancies and is the primary reason for neonatal morbidity, mortality, and lifelong health issues. Preterm birth can be caused by a variety of factors, including genetics, infection, inflammation, intrauterine bleeding, maternal stress, uterine overdistention, and nutrition, despite the fact that the pathophysiology is unknown. On the other hand, some molecular processes, such as changes in chemokines and cytokines resulting in reduced progesterone receptor function, play a role in the development of preterm delivery (43). Thus, understanding the predisposition of a woman for preterm delivery and personalized management provides optimal care for both the mother and fetus (44).

Preeclampsia is the most prevalent hypertensive disorder in pregnancy, affecting 2% to 8% of all pregnancies. It is a syndrome characterized by new-onset hypertension and proteinuria that appears after 20 weeks of pregnancy (45). Poor placentation is the main theory explaining the development of preeclampsia. However, multifactorial mechanisms, including oxidative stress, inflammation, immune maladaptation and angiogenic imbalance, have contributed to preeclampsia development (46). The determination of an individual's risk and the management of disease based on a personalized approach may prevent some preeclampsia-associated poor outcomes (47). Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is a potentially lethal pregnancy condition and is a subtype of preeclampsia (48). Both disorders are most common in the third trimester of pregnancy or shortly after childbirth. Personalized medicine is promising in HELLP syndrome, as in preeclampsia (49). Drugs should be prescribed by a personalized approach to pregnant women considering this change because during pregnancy, the woman's body also undergoes many changes which can affect drug pharmacokinetics (50).

Recurrent pregnancy loss is characterized by the loss of two or more pregnancies at any gestational age. Recurrent implantation failure refers to the failure of in-vitro fertilization attempts with good quality embryos three times. Both unfavourable conditions may be associated with several risk factors and causes (51). Management approaches should be determined based on an individual's set of characteristics. There are many treatment options depending on the underlying etiologic reason of the conditions (52). These two conditions are stressful, both for couples and their clinicians who seek to find an effective treatment option. Therefore, personalized medicine is a promising approach in this disease group too (53). In future, human genetics-inspired fertility regulators promise both understanding the underlying etiopathogenetic mechanisms of the disease and determining treatment approaches (54).

Throughout the last decade, large-scale genomic research using NGS technology has led to a better understanding of molecular pathways in relation to the genetic features of gynecological malignancies. As a result, cancer classification strategies, new diagnostic tools, and treatment methods have been developed. Early diagnosis and targeted treatment options for these gynecological malignancies have become possible, based on the identification of several mutations using tumor molecular profiling. Subsequently, personalized medicine is becoming more common with increasing patient demand (55). These new generation therapeutic options differ from chemotherapeutic agents in terms of their mechanism

of action. While chemotherapeutics target inhibition of DNA replication and mitosis, these recent agents act through signalling pathways, stroma, immune microenvironment, and vasculature in tumor tissues (56).

Endometrial cancer is the most prevalent type of cancer of the female reproductive tract. New insights into the pathophysiology and genetic risks of endometrial cancer have been gained due to advances in molecular methods and genome-wide analysis (57).

Cervical cancer is the fourth most common malignancy among women worldwide. When the molecular mechanisms underlying HPV persistence and related cervical cancer is clarified, the prognosis of women with HPV infections can be predicted at an earlier stage. Thus, clinicians can apply a personalized approach to these women greatly reducing the psychological and economic burdens of cervical cancer screening and HPV vaccination programs (58).

Ovarian cancer is the gynecological cancer with the highest mortality rate and there is currently no effective ovarian cancer screening method. Ovarian cancer is currently treated with extensive cytoreductive surgeries and systemic chemotherapy strategies. Despite these treatment approaches being generally efficient in treating ovarian cancer, chemoresistance and the recurrence of the disease are frequently seen after treatment. Due to its high heterogeneity, ovarian cancer has a high rate of recurrence. These days, to reduce the rate, precision medicine strategies are considered as life-saving approaches for ovarian cancer. With the widespread use of personalized medicine, ovarian tumors can be detected at an earlier stage with the greatest chance for optimum care (59). Hereditary breast and ovarian cancer, Peutz-Jeghers and Lynch syndromes are types of hereditary gynecologic cancers (60). A person's risk of these diseases increases if the person has a family history of these diseases. Genetic testing and counselling through personalized medicine has provided a chance for women with these family histories for the detection and management of the disease (61). As with other cancer types, ovarian cancer-related biomarkers will elevate the survival ratio in the future and will be used routinely in the clinic (36,62). Genomic-based therapy, such as PARP inhibitors in ovarian cancer, like other gynecologic malignancies, will provide modern standard-of-care strategies in the future (63).

Another area of personalized medicine in women's life is menopausal hormone treatment. The age, length, duration of menopause, and genetic variants in sex steroid metabolism can shape hormone therapy individually (64). Personalized medicine will provide a more natural approach to overcome undesirable symptoms, such as urogenital tract atrophy, menstruation abnormalities, vasomotor symptoms, sleep problems, and mood disturbances during the menopausal transition, as opposed to hormone treatments (65).

Pharmacogenetics and translational genomics

In determining drug doses in the classical pharmacological approach, individual factors such as age, body weight or body mass index, or markers indicating organ functions, such as creatinine and bilirubin levels, are considered (66). However, it is well known that there are significant differences in treatment response and side effect profile when standard doses are used in healthy adults, even of the same age and body structure. Adverse drug reactions or insufficient therapeutic responses are some of the most important concerns for modern medicine because it causes serious morbidity and mortality as well as increased health costs. In the last 50 years, it has become understood that personal genetic characteristics are the most important factors determining the pharmacokinetics, maximal effectiveness, and adverse event profiles of the drugs (67).

Pharmacogenetics is a combination of pharmacology and genetics. It examines the genetic variations underlying different clinical and laboratory responses to pharmacological agents. In the last decades, pharmacogenetics has expanded rapidly and has gained wider acceptance in parallel with the development of genetic science. It now includes genomics, transcriptomics, proteomics and metabolomics, and has evolved into "pharmacogenomics" (67,68).

How do genetic variations affect drug metabolism and outcomes? The genetic variations may alter the expression and function of certain drug-metabolizing enzymes, drug-binding or processing proteins, which in turn cause variations of drug plasma levels and therapeutic effects. In addition, genetic variations may change the structure of the target molecules for any given drug. The best-known drug-metabolizing enzymes are the cytochrome P-450 family members, sulfotransferases, methyltransferases, and uridine diphosphate-glucuronic transferases (67,68).

Pharmacogenetic-based drug selection is very important in some clinical situations. For example, clopidogrel is an irreversible platelet ADP receptor antagonist which inhibits platelet activation and aggregation and is used for the prevention or the treatment of arterial thrombosis (69). Aspirin and clopidogrel combination are standard dual antiplatelet therapy in acute myocardial infarction patients and in coronary stent implementation (70). Clopidogrel is a prodrug that must be converted to an active metabolite by the enzyme CYP2C19. Patients with *CYP2C19* loss-of-function polymorphisms are unable to metabolize clopidogrel, the drug remains ineffective, and the risk of thrombosis and death increases (71). If a patient has a *CYP2C19* loss-of-function polymorphism, it is recommended to use other anti-platelet drugs, or the clopidogrel dose should be increased with appropriate drug monitoring (72). In 2010, the FDA attached a black box warning

to the clopidogrel label to inform physicians and patients regarding this issue. Although clinical practice guidelines in cardiology are still not clear about the recommendations on genetic testing for clopidogrel users, recent studies showed that the selection of antiplatelet drugs with genotyping improves the clinical outcomes of percutaneous coronary implementation procedures in high-risk patients (72,73).

There was limited information regarding the complex genetic basis of drug metabolism and effectiveness until the "Human Genome Project". Initially, the high cost of genetic testing and lack of studies showing the clinical utility of genetic information in real life has created a challenge. In the last two decades, however, the data obtained by NGS and Genome-wide Association Study revealed an enormous diversity of genetic variants that potentially affect the metabolism of drugs. The next step, the functional studies showing how these variants affect the level of a given drug, is proceeding rapidly. Now in many centers in Europe, Canada, and the United States, the aim is to combine this information with the electronic health record systems for the realization of highly individualized treatment (74).

The serious side effects and limited success of conventional cytotoxic cancer treatment have been the driving force for the development of more effective therapies. In the last decades, the distinct molecular mechanisms involving the development of certain cancers have been elucidated. This data opened the era of the targeted therapy approach. Cancer cell-specific monoclonal antibodies, small molecules, enzymes, hormones, microRNAs, and genetically modified host T-cells are important in modern cancer treatment. In any cancer center in developed countries, the treatment plan is now determined according to the specific genetic characteristics of the cancer of an individual patient. If a patient has *BCR/ABL*-positive chronic myeloid leukemia, first-generation tyrosine kinase inhibitors are started as initial therapy. The efficacy of the treatment is monitored by regular *BCR-ABL* analysis by quantitative PCR test. If this analysis shows inadequate response, an NGS analysis is performed for evaluating additional mutations in the *BCR/ABL* molecule from the patient's CML cells. NGS data will specify which type of tyrosine kinase is more effective for this patient. With this approach, it is possible to achieve complete remission in more than 95% of CML patients. The same steps are now true for many cancers (74,75).

NGS studies have provided data on both individual cancer-related and drug-metabolizing enzymes-related variables very quickly and cost-effectively. This makes it possible to select more potent and less toxic targeted therapies which are especially important in elderly and frail patients (76).

Discussion

There has been a dramatic growth in the availability and application of genomic tests and this development is expected to continue. The application of WGS as a standard measure for each patient is foreseeable, given the expanding knowledge of genotype-phenotype relationships and reducing the sequencing costs. The majority of genomic research focuses on finding new genes and determining the clinical validity and utility of new tests. However, translating genomic technology and NGS into personalized preventive and medical care continues to be a significant challenge. Especially, new technological advancements allow for extensive testing, sometimes conducted outside of traditional laboratories, with the goal of improving health outcomes. Personalized medicine approaches in current research have provided search for biomarkers based on the "-omic" profile of individuals with new technological tools.

Conclusion

To sum up, the advent of personalized medicine provides more precise, predictable, and powerful healthcare. The final goal of personalized medicine and also translational genomics is to increase health quality. Further research across translational genomics will be important in improving the effective, efficient, and equitable translation of genomic data into more effective management of cancer, pharmacogenomics, and women's health. A basic understanding of translational genomics' characteristics, limits, and risks are thus important for clinician and scientist.

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What is your diagnosis?

A 25-year-old primigravida, was admitted to the antenatal ward at 32 weeks gestation with decreased fetal movements. The patient lived in a remote hilly region and did not go for antenatal checkups because of the non-availability of transport due to the lockdown imposed during the coronavirus pandemic. The patient did not undergo an anomaly scan in the first or second trimester. The present pregnancy was conceived spontaneously, without any history of ovulation induction. There was no history of consanguineous marriage. There was no history of teratogenic drug exposure in the antenatal period. The patient did not have any risk factors for gestational diabetes, body mass index was 22.6 kg/m^2, and family history was not significant. Blood sugar profile was normal after admission, and during the intrapartum and postpartum periods while hemoglobinA1c was normal at 5.8%.

On examination, the fundal height corresponded to 26 weeks, and fetal parts were palpable superficially, suggesting decreased liquor and fetal growth restriction (FGR). The ultrasound showed a single live fetus in breech presentation, corresponding to gestational age 32 weeks with severe FGR, abdominal circumference less than the third centile, biparietal diameter and head circumference at the fifth centile and femur length at the tenth centile with placenta praevia and almost absent liquor. Due to grossly decreased liquor, the radiologist could not comment on fetal anatomy at this gestation. A Doppler study of the umbilical arteries suggested reversed end-diastolic flow with brain sparing effect. Cardiotocography was suggestive of prolonged late decelerations. After discussion with the parents, the patient was taken for lower segment caesarean section because of primigravida with placenta praevia, breech presentation and Stage 4 FGR with high suspicion of fetal acidosis (1).

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Answer

A live baby, weighing 1.2 kg and with Apgar scores of 3/3/1, was born through lower segment caesarean section. The baby had a phenotype suggestive of Potter sequence, with flattening of the nose, hypertelorism with prominent epicanthal fold, micrognathia, and dysplastic and low set ears. The baby also had webbed neck, flexion deformities of hands and wrist, and fused lower limbs without feet, suggestive of Sirenomelia (Figure 1). A bluish-coloured cystic swelling, approximately 4x4x5 cm in the lumbosacral region, suggestive of lumbar myelomeningocele, was present. The external genitalia and anal openings were absent (Figure 2). There was a single umbilical artery. The baby died 10 minutes after birth. The parents refused an autopsy.

Sirenomelia is a polytopic, multi-systemic congenital anomaly with an unknown etiology. The reported incidence is 1.5-4.2 per 100,000 births (2). It gets its name due to the analogy of the born fetus to the mythological siren or "mermaid" (3). In Greek mythology, these creatures were depicted as half woman/half fish and are believed to sing enchanting songs that lure sailors to death (4). Sirenomelia is characterized by varying degrees of fusion of the lower limbs, usually a single axially positioned lower limb, associated with anomalies of the lower spine and urogenital and lower gastrointestinal tracts. Although the exact etiopathology is unknown, the vascular steal phenomenon and defective blastogenesis (5) are the most widely accepted hypotheses regarding its origin. Maternal age of less than 20 or more than 40 years, diabetes mellitus, genetic predisposition, smoking and cocaine abuse and vascular mal-perfusion have been reported to be risk factors in a few studies (6,7).

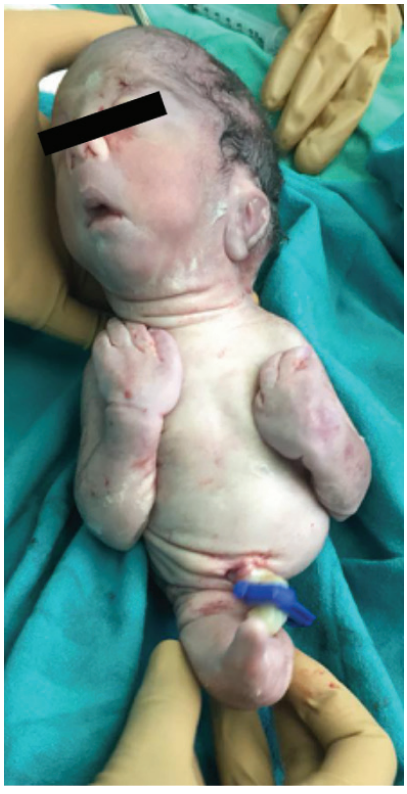

Figure 1. Note the presence of Potter facies, low set ears, micrognathia, club hands and fused lower limbs

Sirenomelia is uniformly associated with poor fetal prognosis because of the associated complications related to abnormal kidney, lung, heart, and bladder development and function (8). Other lethal congenital malformations include body stalk anomaly, anencephaly, autosomal recessive polycystic kidney disease, some forms of skeletal dysplasia, bilateral renal agenesis with pulmonary hypoplasia or fetuses with multiple anomalies, especially associated with a chromosomal abnormality. Ideally, if detected before 24 weeks of gestation, termination of pregnancy is the preferred option. It is always preferable to deliver vaginally in these conditions, and parents should be counselled regarding the poor neonatal prognosis. In the present case, caesarean section was performed due to placenta praevia and poor fetal condition.

The diagnosis is usually easily made by ultrasound at the first-trimester nuchal translucency scan. However, in low and middle-income countries, it is not uncommon for a patient to visit the physician for the first time at advanced gestations. The diagnosis at these times can be challenging due to associated severe oligohydramnios. Any pregnancy, presenting with severe oligohydramnios in the late second or third trimester should be studied in detail with colour Doppler imaging to map the fetal vasculature. Imaging for mid-trimester an-hydramnios should include colour Doppler for renal arteries, especially in a patient who had not undergone an anomaly scan in the first or second trimester. Congenital renal abnormalities in the antenatal period have the highest probability of being associated with oligohydramnios. Aberrant abdominal vasculature or absent

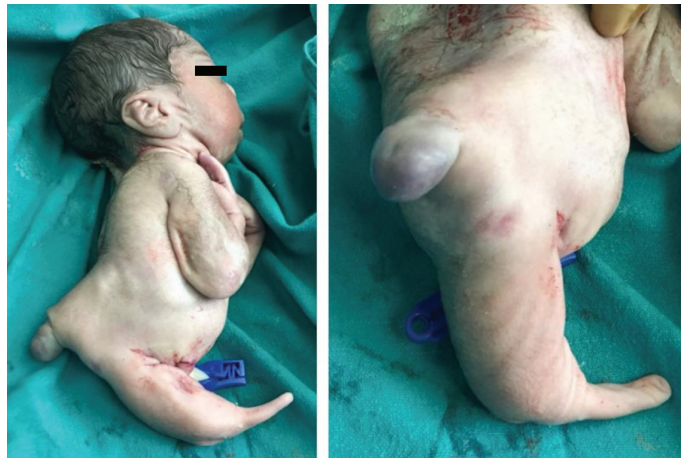

Figure 2. Bluish swelling in the sacral region, suggestive of lumbosacral myelomeningocele

renal arteries may be important clues to the possible diagnosis of sirenomelia (9).

A high index of suspicion is needed to diagnose such cases because, at advanced gestation, the associated oligohydramnios makes it challenging to study the fetal anatomy. Although Sirenomelia is a rare entity, it should be included in the differential diagnosis, when severe oligohydramnios or anhydramnios is detected on antenatal ultrasound.

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Critical analysis of the FIGO 2018 cervical cancer staging

To the Editor,

Cancer staging is a process that changes with technological development leading to improvements in diagnosis, prognosis, and treatment. Therefore, the International Federation of Gynecology and Obstetrics (FIGO) updated the classification of cervical cancer staging in 2018. The main changes in the FIGO 2018 system occurred in stages IA, IB, and IIIC, as well as the inclusion of any imaging modality or pathological findings to allocate the stage (1). However, some conditions still need adjustments to differentiate each stage of the system.

Only the depth of invasion is now considered as the cut-off for stage IA, assigning stage IA as stroma invasion less than 5.0 mm, and further subdivided into stage IA1 and IA2 at a cutoff of 3.0 mm (1). The change at this stage was about the lateral extent of the lesion, which is no longer considered. After removing the lateral extent criterion, there is a concern with different cases being analyzed in the same way. It is also unclear whether clinically visible cases with stromal infiltration up to 3 mm would be IA1 or IB stage.

Tumor size has been recognized as a prognostic factor in stage IB for a long time, with larger tumor sizes displaying higher rates of nodal involvement, and decreased survival rates (2). At this stage, FIGO 2018 has included three substages, rather than two.

In terms of stage IIIB, Katanyoo (3) demonstrated that patients with a lower third vaginal invasion associated with parametrial involvement have poorer survival outcomes than patients at the same stage without a lower third of vaginal invasion. More studies are needed to verify these findings. However, if the finding of vaginal invasion in IIIB has worse prognosis, our suggestion is that stage IIIB should be subdivided into stage IIIB1, with involvement of only the parametrium, and IIIB2, with involvement of the lower third of the vagina and parametrium.

In FIGO 2018, any patient with positive lymph nodes automatically gets upstaged to stage IIIC (1). Ayhan et al. (2) suggested an increase in the number of sub-stages. This classification might be more prognostic than the current 2018 FIGO staging system, as more patients would be allocated to each sub-stage (2). We suggest that lymph node involvement accompany each stage without modifying the original stage instead of grouping them in stage IIIC.

Radiotherapy may be of limited value for patients with cervical adenocarcinoma and may not represent the best treatment, being an important prognostic factor for local failure (4). Different prognoses and treatment needs within the same stage would require some differentiation, as in endometrial cancer, where the serous papillary type is considered high-grade endometrial carcinoma (FIGO grade 3) (5).

An optimal staging system should assign cases to prognostic categories, define the anatomical extent of disease, refer patients for individualized treatments, and compare patients and their outcomes between centers (1,2). These observations on staging, considering new discriminations, could contribute to better understanding and planning through better prognostic accuracy for cervical cancer, reflecting differences in survival and guiding treatment.

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Can prenatal renal pelvicalyceal echogenic foci support the diagnosis of cystinuria?

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Abstract

Cystinuria is an inherited disease caused by a defect in renal and intestinal tubular transport affecting cystine and dibasic amino acids (lysine, ornithine and arginine). It is transmitted as an autosomal recessive disease. On fetal ultrasound, the colon is usually seen as hypoechoic or isoechoic. Antenatal hyperechoic appearance of the fetal colon was previously considered as a normal variant. However, recent studies have shown that hyperechoic colon is associated with cystinuria. We present a case of cystinuria, who was referred to us due to fetal hyperechogenic colon at 32 weeks of gestation. Additional fetal pericalyceal echogenic focal structures were observed on ultrasonography. The diagnosis of cystinuria was confirmed in the postnatal period. (J Turk Ger Gynecol Assoc 2022; 23: 327-9)

Keywords: Cystinuria, hyperechogenic colon, pelvicalyceal echogenic foci

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Introduction

Cystinuria is an autosomal recessive disease characterized by renal tubular reabsorption defect of cystine, which is a dibasic amino acid, and cystine is the only dibasic amino acid that is insoluble at normal urine pH (1). Cystine stones make up 6-8% of childhood urinary tract stones (2).

During the prenatal period, the fetal colon usually appears as either hypoechoic or isoechoic. When the fetal colon has a hyperechoic appearance, this was previously considered to be a normal variant (3). However, in subsequent studies, this finding was discovered to be associated with cystinuria (4,5). Cystinuria is a urinary tract, lithogenic, congenital disease characterized by a cystine resorption dysfunction due to a defect in the rBAT/b0, + AT amino acid transporter which is expressed in the apical border of the proximal renal tubule and epithelial cells of the digestive tract. In fetal life, tubular maturation begins after the 14th week of pregnancy, and after 20 weeks the kidney is responsible for more than 90% of the amniotic fluid volume. Kidney-defective cystine transport results in increased urinary excretion of this amino acid, and the digestive defect reduces digestive absorption, both of which result in cystine accumulation in the amniotic fluid. Swallowing of amniotic fluid begins at week 12 and leads to ingestion of large volumes of cystine. Since the anal sphincter is not physiologically functional at this time, colonic cystine does not accumulate until the 22nd gestational week. However, from 22 weeks on, the closure of the anal sphincter due to the maturation of the three anal sphincter muscles leads to a progressive accumulation of cystine in the colon. At high concentration, cystine precipitates to form radio-opaque stones, which on ultrasound show as hyperechogenicity of the colon. In a series of 16 patients, Amat et al. (5) showed that this finding was associated with cystinuria in 50% of the cases. These authors reported that if a hyperechogenic colonic appearance is observed before the 36th gestational week, the diagnosis may be cystinuria with a probability of 88.9%. Written informed consent was obtained for publication of this report.

Case Report

A 27-year-old mother presented during her first pregnancy. The parents had no history of any disease or kidney stones. In the family history the mother's grandmother had a history

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of hypertension and sabulous urolithiasis. There was rhesus incompatibility between her and her husband. Consanguinity was not present between his parents and family history was negative for any renal diseases. During the pregnancy, the patient was diagnosed with gestational diabetes mellitus, which was adequately controlled by diet. No fetal anomaly was detected until the 32nd week of the pregnancy. However, at the 32nd gestational week, she was referred to us because the fetal colon was found to have a hyperechoic appearance. This finding was confirmed by ultrasonography (USG) performed at our center where the hyperechogenic appearance extended throughout the entire colon to the sigmoid level. During the ongoing examination, the same hyperechogenic appearance was found in the pelvicalyceal and peripyramidal regions of the lower regions of both kidneys (Figure 1, Video 1). The entire colonic segment had a hyperechogenic appearance and there was no dilatation. The anal sphincter had a normal appearance. Existing findings were thought to be related to cystinuria. No invasive procedure was performed on the patient. The family was also informed about the prognosis of the disease.

There were no additional problems during follow-ups and spontaneous labor started at 39 gestational weeks. She was later taken to cesarean section (C/S) with the indication of arrested labor. A baby boy with a birth weight of 3940 grams was delivered via C/S with APGAR scores 7 and 9 at the 5th and 10th minutes, respectively. Newborn assessment revealed nothing abnormal. Spontaneous stool and urine output were detected. On the abdominal USG examination, crystalloid structures were observed in both kidneys. Cystine level in 24-hour urine and urinary cystine/creatinine ratio were requested. This showed a cystine output of 60.96 mg/day (normal range: 0-13 mg/day) and a urinary concentration of 1180.30 mg/g creatinine (normal range: 50-163 mg/g creatinine). Amoxicillin suspension (Largopen, Bilim, Turkey) was started. At the time of writing the baby is six months old and has only had one urinary tract infection. Due to persistent pericalyceal echogenic foci, prophylactic treatment continues.

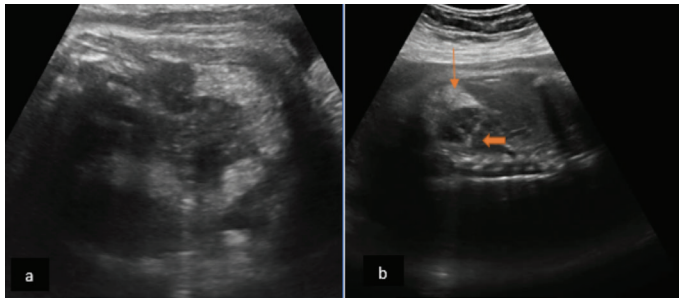

Figure 1. a) Fetal hyperechogenic colon. b) Fetal pericalyceal hyperechogenicity (thin arrow: colon, thick arrow: renal pelvis

In the postnatal period, a heterozygous mutation in the *SLC7A9* gene was detected in the genetic analysis of our patient.

Written informed consent was obtained from the patient.

Discussion

The prevalence of cystinuria in the European population is around 1 in 7000 (6). Cystine stones account for about 1% to 2% of all kidney stones but represent variably 6% to 8% of all pediatric calculi. Eighty percent of cystinuria patients will have their first stone during their first two decades of life. Compared to calcium stone formers, cystine nephrolithiasis patients will be likely to make larger stones, need more urological procedures, make stones more often, and start at an earlier age. They also face a greater risk of subsequent kidney damage and chronic renal failure compared to calcium nephrolithiasis patients. Cystinuria patients also report relatively poor health-related quality of life scores as a result of multiple recurrent stone episodes and related surgical procedures.

The clinical spectrum of the disease depends on the type of mutation and is very variable. It causes infections and stones in the kidneys and impairs kidney function. In patients with cystinuria, renal function is monitored regularly and the urine should be alkalized to prevent the progression of the disease. The aim of follow-up and treatment is to prevent renal failure due to disease progression (7).

It was previously reported that fetal hyperechogenic colon should raise suspicion of cystinuria. However, as far as we know, there is no published evidence that the stones seen in people with cystinuria can also form antenatally and that these structures can also be seen as hyperechogenic pelvicalyceal anomalies in the kidneys of affected fetuses. We suggest that a high degree of cystinuria, when the excess cystine is not absorbed and the level of which increases in the renal pelvis, will lead to a hyperechogenic appearance of the fetal renal pelvis that can be detected by USG in the prenatal period. The present case became symptomatic within the first week after birth, and renal hyperechogenic structures were detected on USG examination. We propose that monitoring renal hyperechogenic pelvicalyceal structures together with fetal hyperechogenic colon will increase the accuracy of cystinuria diagnosis in the prenatal period.

Video 1.

https://www.doi.org/10.4274/jtgga.galenos.2022.2021-11-5.video1

Informed Consent: *Written informed consent was obtained for publication of this report.*

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2022 Referee Index

Acknowledgements for the Year 2022
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CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.medical.theconferencewebsite.com/conferences/obstetrics-and-gynaecology)

January 02-07, 2023	38th Annual Conference of Obstetrics, Gynecology, Perinatal Medicine, Neonatology and the Law, Phoenix, Arizona, United States
January 13-15, 2023	Maternal-fetal Imaging – Advances in Ob-gyn Ultrasound 2023, San Antonio, Texas, United States
March 16-18, 2023	9th Congress of the Society of Endometriosis and Uterine Disorders (SEUD), Abu Dhabi, UAE
March 19-22, 2023	Society for Gynecologic Surgeons (SGS) 49th Annual Meeting, Tucson, Arizona, United States
March 21-25, 2023	Society for Reproductive Investigation (SRI) 70th Annual Scientific Meeting, South Brisbane, Quennsland, Australia
May 02-06, 2023	15th World Congess on Endometriosis, Edinburgh, Scotland Great Britain
May 03-05, 2023	14th European Congress on Menopause and Andropause, Florence, Tuscany, Italy
May 04-07, 2023	ASCCP 2023 Scientific Meeting, Houston, Texas, United States
May 07-10, 2023	World Congress of Perinatal Medicine, Milano, Italy
May 19-21, 2023	American College of Obstetricians and Gynecologists (ACOG) 2023 Annual Clinical and Scientific Meeting, Baltimore, Maryland, United States
May 21-25, 2023	American Society for Reproductive Immunology (ASRI) Annual Meeting 2023, Santa Fe, New Mexico, United States
May 24-27, 2023	International Society of Gynecological Endocrinology 21st World Congress, Bali, Indonesia
June 06-09, 2023	The Society of Obstetricians and Gynecologists of Canada Annual Clinical Scientific Conference, Ottawa, Ontario,Canada
June 21-24, 2023	International Urogynecological Association (IUGA) 48th Annual Meeting, The hauge, South Holland, Netherlands
June 25-28, 2023	European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting, Copenhagen, Denmark
September 10-13, 2023	International Federation of Fertility Societies (IFFS) World Congress, Athens, Greece
October 14-18, 2023	American Society for Reproductive Medicine (ASRM) 79th Annual Meeting, New Orleans, LA, United States
October 16-19, 2023	33rd ISUOG World Congess, Seoul, South Korea
October 18-22, 2023	19th World Congress on Menopause, Melbourne, Australia
November 05-07, 2023	International Gynecologic Cancer Society (IGCS) 2023 Meeting, Seoul, Souh Korea
November 05-09, 2023	The 52nd American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Nashville, Tennessee, United States
November 23-25, 2023	The 31st World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Vienna, Austria

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2022.com)

January 20-22, 2023	Ulusal Jinekolojik Onkoloji Kongresi ve Ulusal Servikal Patolojiler ve Kolposkopi Kongresi, Ankara, Türkiye
February 23-26, 2023	6. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, İstanbul, Türkiye
March 05-08, 2023	17. Uludağ Jinekoloji ve Obstetrik Kış Kongresi ve 1. Marmara Kadın Sağlığı Kongresi, Bursa, Türkiye
March 16-19, 2023	CİSEF 3. Uluslararası Cinsel Sağlık Kongresi, Antalya, Türkiye
March 17-18, 2023	11. İstanbul Kadın Doğum Günleri, İstanbul, Türkiye
April 17-21, 2023	20. Ulusal Jinekoloji ve Obstetrik Kongresi, K.K.T.C.
October 05-08, 2023	5. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Muğla, Türkiye