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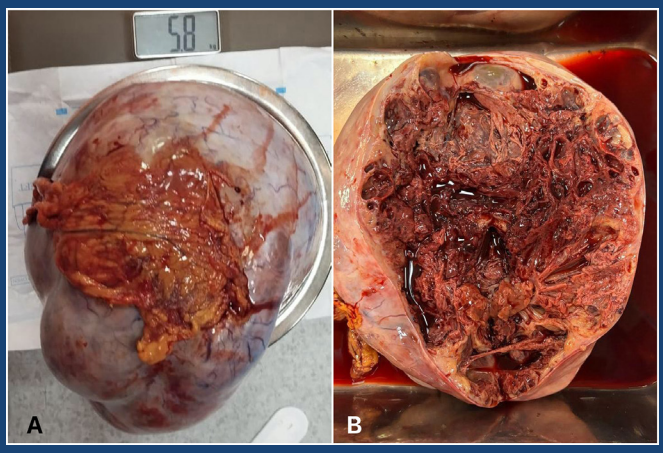

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Aims and Scope

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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The ''Journal of the Turkish-German Gynecological Association'' (EISSN 1309-0380; Abbreviated as "J Turk Ger Gynecol Assoc") is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and the Turkish-German Gynecological Association. Formerly named "ARTEMIS", the journal is published quarterly (March, June, September, December) in English and publishes original peer-reviewed articles, reviews, and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Case reports are not accepted for publication. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

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PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

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In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals (http://oacu.od.nih.gov/regs/guide/guide.pdf) and they should obtain animal ethics committee approval.

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Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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State the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with those of others. Provide information on the limitations and strengths of the study. No new data are to be presented in this section.

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the third issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2025. This issue is consisted of seven articles, and two reviews that we hope you will read with interest. Also you may have the oppurtunity to read the quiz. Here we share some of our favorite articles that were published in this issue of the journal.

When using assisted reproductive technology (ART), poor ovarian responders pose a significant challenge because, even with high-dose gonadotropin treatment, they have a poor fertility outcome, produce few oocytes, are more likely to experience premature ovulation, and are more likely to experience cycle cancellation. About 0.34-8.0% of patients were reported to experience an early luteinizing hormone surge. The size of the leading follicle or follicles typically determines the time of the trigger in ART cycles. It is currently unclear how the leading follicle size affects the rate of oocyte maturation and the risk of premature ovulation. In order to maximize the mature oocyte rate and avoid premature ovulation, a study examining the ideal size of the leading follicle prior to initiating final oocyte maturation will be available for you to read.

Women frequently suffer from stress-type urinary incontinence (SUI), which has a detrimental impact on their quality of life. In cases of SUI that do not improve with conservative measures, surgery provides an efficient solution. For many years, Burch colposuspension has been the method of choice in this regard due to its established efficacy and reliability. You will also have the opportunity to read an article assessing and comparing patients who underwent Burch colposuspension for SUI utilizing the L/S or L/T techniques.

Dear Esteemed Readers, Authors and Reviewers,

Numerous researchers find it challenging to gain recognition, or collaborate, as well as to enhance their h-index. Prior to submission, it is crucial to check a journal's status through Scopus or Web of Science databases and to steer clear of predatory journals entirely. Each year, many researchers waste money, time, and credibility by publishing in predatory journals. To avoid falling into a predatory publication, it's important to assess the journal's scope and consistency, and to be cautious of promises of rapid publication.

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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 relationship between serum estradiol and progesterone levels one day before frozen embryo transfer and pregnancy rates in artificially prepared frozen embryo cycles: are there any threshold serum hormone levels to predict pregnancy in luteal support by the vaginal and subcutaneous route combined?

Levent Dikbaş[1], Michael H. Dahan[2]

[1]Reyap Hospital IVF Center, Tekirdağ, Türkiye

[2]Department of Obstetrics and Gynecology, McGill University, Québec, Canada

Abstract

Objective: To investigate the potential influence of serum estradiol (E_2) and progesterone (P_4) levels, measured one day before artificially prepared frozen embryo transfer (FET), on pregnancy rates in women who received combined vaginal and injectable P_4.

Material and Methods: This retrospective cohort study analyzed the association between serum E_2 and P_4 levels on the day before FET in 167 cases prepared with hormone replacement therapy between February 2022 and October 2023. The primary outcomes assessed were the pregnancy and live birth rates. We modeled a cut-off serum value based on luteal support for pregnancy. Luteal support was through a combination of vaginal suppositories and subcutaneous injections. Multivariate logistic regression was used to test relationships between pregnancy outcomes and independent variables. Cut-off values were evaluated using receiver operating characteristic (ROC) analysis and percentile analysis.

Results: No significant relationships were found between serum E_2 or P_4 levels on the day before FET and pregnancy rates. The mean E_2 level was 169.0±51.9 pg/mL for individuals who achieved conception and 177.7±56.9 pg/mL for individuals who did not conceive (p=0.45). The corresponding values for P_4 were 28.1±18.4 ng/mL and 31.2±25.4 ng/mL, respectively (p=0.73). No differences were observed in body mass index (BMI) or endometrial thickness between the groups. Cut-off values for predicting pregnancy using E_2 and P_4 could not be determined using ROCs. However, no one in the lowest 10th percentile of serum P_4 levels conceived (range 10.0-15.6 ng/mL). When multivariate logistic regression was used, this finding lost significance suggesting that low serum levels are related to age, BMI, and/or other factors.

Conclusion: In artificially prepared FET cycles, the serum E_2 and P_4 levels one day before embryo transfer do not significantly affect pregnancy rates in women with serum E_2 levels between 150-300 pg/mL and P_4 between 10-40 ng/mL when ROC was used for evaluation. However, percentile analysis suggests that serum P_4 levels should be more than 15.6 ng/mL when combined injectable and vaginal P_4 is used for programmed FET. Although this finding may be due to the confounding effects of age, BMI, and other factors affecting steroid metabolism, when controlled for in the multivariate logistic regression. [J Turk Ger Gynecol Assoc. 2025; 26(3): 157-66]

Keywords: Estradiol, progesterone, frozen embryo transfer, pregnancy

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Introduction

Progesterone (P_4) plays a vital role in implantation, as it leads to endometrial differentiation, myometrial quiescence, and immune modulation and possesses anti-inflammatory properties (1). It plays this role in both natural ovulations, fresh in vitro fertilization (IVF) cycles, and frozen embryo transfer (FET) cycles. The advantages of embryo vitrification include reduced rates of ovarian hyperstimulation syndrome and possibly higher pregnancy rates than fresh IVF cycles, although this remains controversial (2,3). The high survival rates of vitrified-thawed embryos have made FET very common. In the United States of America (USA), FET is practiced in approximately 70% of cases (4).

During hormone replacement therapy (HRT) cycles for FET, exogenous P_4 is the only means of providing luteal support when the corpus luteum is absent. In natural conceptions, the production of P_4 for implantation during the first trimester is roughly 50-55 mg/day, and serum values during this period typically range between 25-30 ng/mL (5). It is conceivable that these values could serve as the target levels for FET cycles. Nevertheless, this range may vary significantly in supplemented FET cycles because of the diverse characteristics of patients, including body mass index (BMI), vaginal and peripheral blood supply, and age.

For luteal support in HRT cycles, exogenous P_4 can be administered through vaginal, subcutaneous, intramuscular (IM), oral, or rectal routes. Vaginal P_4 exerts a uterine effect by bypassing the first-pass effect of the liver seen in oral and injectable routes. Vaginal P_4 results in lower serum levels but higher concentrations in endometrial tissue when compared to other routes of administration. In prior studies, micronized vaginal P_4, 800 mg/day yielded a high endometrial tissue level of 11.5 ng/mL, however, the serum level was 11.9 ng/mL, which was a sub-physiological level. When IM P_4 was used, 100 mg/day the serum level was on average 69.8 ng/mL, while the endometrial tissue level remained at 1.4 ng/mL (6). However, the endometrial biopsies in both the injectable and vaginal groups showed similar levels of secretory transformation, indicating a low threshold for such alteration (7,8). When administered vaginally, the serum P_4 levels consistently remain sub-physiological, ranging from 10 to 15 ng/mL (9,10). In contrast with intra-muscular P_4, uterine P_4 remains in a sub-physiological state even though supra-physiological serum levels are obtained. The administration of P_4 in combination, with both vaginal and intra-muscular or subcutaneous combined, ensures that serum and endometrial levels both remain within physiological ranges. Thus, attaining blood and endometrial levels comparable to a natural pregnancy (11). However, whether this is important for success remains controversial, because in many studies pregnancy rates are excellent with vaginal P_4 supplementation alone (12,13).

Despite extensive research, the most effective route and dosage of P_4 administration for luteal support in FET cycles has not been established. Europe favors vaginal administration, while the USA tends to favor the IM route or IM and vaginal combined (14). Subcutaneous P_4 is not available in North America. Despite studies suggesting a correlation between vaginal P_4 administration and low pregnancy rates (15), the literature contains conflicting results (16,17). These findings would suggest variations in patient response and pregnancy rates when using the same P_4 delivery type and dose. Therefore, the administration of luteal phase support could be customized based on the patient's age, weight, genetic profile, and hormonal metabolism (18,19). Some recent studies have suggested that monitoring serum P_4 levels before or during embryo transfer can provide valuable insights into reproductive outcomes (20). Poor obstetric outcomes have been linked to low pre-transfer P_4 levels, and administering an extra (rescue) dose of P_4 might improve outcomes (21-23).

As combined P_4 administration yields physiological serum P_4 levels in the range of those observed during natural pregnancy, we opted for this protocol in our facility, aiming to attain enhanced physiological P_4 levels by employing a combination of vaginal micronized P_4 ovules and subcutaneous P_4, quantified by measuring serum levels of P_4 and estradiol (E_2) on FET day-1. Our hypothesis proposes that pre-FET serum P_4 and E_2 levels may influence pregnancy outcomes. The threshold values for the administration of combined P_4 during pregnancy have not been adequately researched. Thus our aim was to determine if there is a specific threshold value for E_2 or P_4 in patients who are undergoing combined subcutaneous and vaginal P_4 treatment for luteal phase support.

Material and Methods

All ethics protocols are followed as per the Declaration of Helsinki. This study was approved by the İstanbul Atlas University Non-Interventional Research Ethics Committee (approval number: 03, date: 04.03.2024). All women had signed an informed consent that their data may be used in research studies.

The evaluation focused on FET cycles conducted in a single center from February 2022 to October 2023. In this retrospective cohort study, the predictive value of serum E_2 and P_4 levels on implantation rates in hormone-supplemented FET cycles was evaluated. The present study investigated if specific cut-off values for serum E_2 and serum P_4 could predict pregnancy when measured one day before FET (FET-1). A cohort of 167 patients who underwent FET were studied. A comparison was made between 79 patients who successfully conceived and 88 patients who failed to conceive. This study subsequently investigated the cut-off value of serum P_4 level for predicting pregnancy in 72 patients who did and did not conceive (52 pregnancies), who received combined route (vaginal + subcutaneous) P_4 for

luteal phase support. Natural and modified natural cycles of FET were excluded. Due to the prohibition of gamete donation in our country, all subjects used autonomous gametes.

The vitrification of the embryo was performed using an equilibration solution comprising 7.5% ethylene glycol and 75% dimethyl sulfoxide for 8-12 minutes. They were subsequently exposed to a vitrification solution of 15% ethylene glycol, 15% dimethyl sulfoxide, and 0.5 molar sucrose for 60-90 seconds. The specimens were loaded into a hemi-straw using drops smaller than 1 μ and then submerged in liquid nitrogen. Processing was maintained at room temperature. The embryos underwent a warming process at 37 °C for 1 minute in a 1 mL solution of 1M sucrose, followed by 3 minutes in 1 mL solution of 0.5M sucrose. The embryos were then exposed to a 10-minute incubation in a 1 mL HEPES solution containing 20% human serum albumin. Subsequently, the embryos were placed in a culture solution and kept for 2-4 hours until transfer.

The expanded embryos underwent transfer with FET, the predominant approach for embryo transfers in our center. The FET endometrial preparation protocol we used was a step-up oral E_2 method. Administration of E_2 tablet 2 mg orally (Estrofem® tablet 2 mg, Novo Nordisk, Malov, Denmark) twice a day for seven days was started and then was increased to three times a day for six days, commencing on days 2-3 of menstruation. In patients who were unable to tolerate E_2 orally, who exhibited insufficient endometrial thickness (ET), or who had a serum E_2 level of less than 150 pg/mL, we implemented the administration of supplementary E_2 via a vaginal or transdermal patch.

This treatment was preceded by transvaginal ultrasonography (TVUSG) (Voluson P8, General Electric Company, WI, USA) to confirm the absence of early selected follicles (>11 mm) or functional ovarian cysts. The ET and ovaries were evaluated using TVUSG. If the ET was ≥7 mm, the serum P_4 level <1.5 ng/mL, and the E_2 level >150 pg/mL after at least 10 days of E_2 use, luteal phase support was started. To achieve this, support was given using a combined route involving vaginal micronized P_4 (4x200 mg) and subcutaneous water-based P_4 (2x25 mg). Other routes and dosages were also used, including vaginal P_4 only. These subjects using other routes were included in the evaluation of serum levels on pregnancy outcomes but excluded from the analysis on factors for prediction of pregnancy that only included the combined vaginal and subcutaneous P_4 group.

Oral P_4 was not used because of technical difficulties measuring its serum levels. Our decision to opt for the combined route was driven by the objective of achieving more consistent physiological blood levels, mitigating potential absorption issues associated with the vaginal route, as well as addressing the challenges associated with IM administration, such as sterile abscesses, and pain.

In patients with a P_4 level below 10 ng/mL, we added additional P_4. Before transfer, we tried maintaining the serum E_2 level between 150-300 pg/mL and P_4 between 10-40 ng/mL. If the P_4 level was low, we employed the IM route for rescue in patients receiving single drugs and in obese patients receiving combined drugs. Post-rescue, we re-evaluated serum hormone levels on the day of transfer and proceeded with embryo transfer in patients who achieved the predetermined target values. We discontinued the cycle when hormone levels reached highs or lows outside of physiologic parameters. PGT-A was not performed except in a single case. If the serum beta-human chorionic gonadotrophin (β-hCG) value exceeded 5 mIU/mL within 10-12 days following transfer, we considered this a pregnancy. The hormone tests were performed using chemiluminescence immunoassay (Abbott Alinity Analyzer, Abbott Laboratories, Chicago, IL, USA). The Abbott Alinity P_4 assay has a linear measuring range of 0.5-40.0 ng/mL (1.6-127.2 nmol/L), with intra-assay coefficients of variation (CV%) ranging from 2.7% to 5.6% and inter-assay (within-laboratory) CV% ranging from 3.1% to 6.1%. The Abbott Alinity E_2 assay demonstrated a linear measuring range of 5 to 5,000 pg/mL, with intra-assay CV% ranging from 2.5% to 5.3% and inter-assay CV% ranging from 3.1% to 7.3%.

Statistical analysis

The data analysis was conducted using IBM SPSS, version 23 (SPSS corporation, Chicago IL, USA). The presence of a normal distribution was evaluated through the Kolmogorov-Smirnov and Shapiro-Wilk tests. In Table 1, Mann-Whitney U test was used for the comparison of age, embryo cryopreservation age (ECA), gravidity, parity, BMI (kg/m^2), FET CL (day), E_2 (pg/mL), luteinizing hormone (LH) (mIU/mL), P_4 (ng/mL) variables that did not conform to normal distribution, while independent samples t-test was used for the comparison of max ET (mm) and post-IM P_4 variables that conformed to normal distribution. In Table 2, Pearson chi-square test was used to compare the number of ET and ET day according to the groups. In Table 3, receiver operating characteristic (ROC) analysis was used to determine cut-off values for P_4 and E_2 variables in predicting pregnancy. Table 4 shows the percentile values of E_2 and P_4 variables. In Table 5, independent variables affecting the biochemical pregnancy probability were analyzed by Binary Logistic Regression Analysis. In Table 6, the independent variables affecting the clinical pregnancy probability were analyzed by binary logistic regression analysis. In Table 7, the independent variables affecting the probability of live birth were analyzed by binary logistic regression analysis. The analysis results are presented as frequency (percentage) for categorical variables, mean ± standard deviation, and median (minimum-maximum) for quantitative variables. The significance level was set at $p<0.05$. Data was divided into percentile groupings to further understand relationships with pregnancy outcomes.

Results

The parameters of the patients who achieved conception following FET (group A, n=79) and those who did not (group B, n=88) are presented in Table 1. The two groups displayed similar

demographic characteristics including age, BMI, gravidity, and parity. No significant differences were observed between the groups regarding the FET cycle duration, maximal ET, ECA, and pre-transfer E_2, LH, and P_4 values.

Interestingly, in cycles where initial P_4 levels were low and rescue supplementation was needed, the serum P_4 level among individuals who achieved conception was 20.5±5.4 ng/mL, while in those who did not conceive it was 46.4±13.7 and this difference was approaching significance (p=0.08).

The pregnancy rates as a function of the number of embryos transferred and the day of development are displayed in Table 2. The pregnancy rate following the transfer of two embryos vs. single (53.2% vs. 46.8%) was higher but not significantly so. Women primarily had blastocyst transfer, with 71% in group A and 92% in group B.

A ROC analysis was conducted to determine the optimal cut-off value for P_4 and E_2 the day before embryo transfer, in predicting pregnancy among patients using combined P_4 for luteal support in FET. The area under the curve was 0.427 for P_4 (Figure 1) and 0.465 for E_2 (Figure 2). There were no significant cut-off values for P_4 and E_2 parameters in predicting pregnancy in combined P_4 users (p=0.166 and p=0.441, respectively) (Table 3). The serum P_4 and E_2 values in FET cycles were similar in those who did and did not conceive, leading to the absence of significant discriminating cut-off values. Of note, the E_2 value was not assessed before FET in seven patients who achieved pregnancy.

The serum E_2 and P_4 levels measured one day before FET were divided into percentiles to further investigate if certain non-binomial distributions could be detected in predicting outcomes and are presented in Table 4. Among 72 patients, the mean E_2 value within the 0-10 percentile range was recorded as 97.7±8.8 pg/mL, with a minimum value of 85.0 and a maximum value of 107.0 pg/mL, within the 11-90 percentile range as 165.9±35.9 pg/mL, with a minimum value of 108.0 and a maximum value of 247.0 pg/mL, and in the 91-100 percentile range as 280.2±42.7 pg/mL, with a minimum value of 251.0 pg/mL and a maximum value of 360.0 pg/mL (Table 5).

Among the 60 patients in the group who experienced pregnancy (11-90th percentile), the median E_2 values were 165.9 pg/mL (129.9-201.9 pg/mL) one day before FET.

The percentiles of the P_4 parameter in pregnant women using combined P_4 were examined, with no pregnant women identified within the 0-10 range. The mean P_4 value within the 0-10 percentile range was 12.6±2.4 ng/mL, with a minimum value of 10.0 ng/mL and a maximum value of 15.6 ng/mL. Within the 11-90 percentile group the mean was 29.7±12.0 ng/mL, with a minimum value of 16.7 ng/mL and a maximum value of 65.6 ng/mL. Within the 91-100 percentile group, the P_4 serum value exhibited a mean of 78.0±15.7 ng/mL, with a minimum of 67.5 ng/mL and a maximum of 105.7 ng/mL.

Serum P_4 levels before FET were assessed in a cohort of 53 patients who underwent combined P_4 supplementation and successfully achieved pregnancy. Among this group (11th-90th percentile), the mean P_4 level was 29.3 ng/mL (15.2-43.5 ng/mL) in 49 individuals.

The rate of pregnancies achieved by vaginal P_4 was 41.9%, whereas combined (vaginal + subcutaneous) P_4 users had a similar pregnancy rate of 50.0% (p=0.36).

Independent variables affecting the probability of biochemical pregnancy, clinical pregnancy, and live birth were analyzed by multivariate binary logistic regression analysis when controlling for confounding effects and the data is presented in Tables 5-7. When the model was analyzed, the independent variables lost significance for the probability of a positive pregnancy, clinical pregnancy, or live birth, including E_2 or P_4 levels.

Table 1. Comparison of parameters between the groups

	Group				p
	Patients who achieved pregnancy (n=79)		Patients without pregnancy (n=88)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age (years)	31.6±5.56	32 (18-44)	32.25±5.75	32 (21-44)	0.587
ECA (ng/mL)	30.19±5.55	30 (18-42)	31.51±5.99	31 (21-44)	0.210
Gravidity	0.68±0.97	0 (0-5)	0.67±1.22	0 (0-7)	0.420
Parity	0.25±0.47	0 (0-2)	0.19±0.54	0 (0-3)	0.147
BMI (kg/m²)	27.82±6.32	26.7 (17-57.6)	26.45±4.99	24.6 (20-37.4)	0.153
FET CL (day)	19.19±2.32	19 (13-28)	19.26±1.47	19 (15-24)	0.193
Max ET (mm)	9.94±1.51	10 (6.9-14)	9.61±1.61	9.83 (6.3-15)	0.180
E_2 (pg/mL)	169.75±51.88	162.5 (85-360)	177.68±56.91	168.5 (92-318)	0.449
LH (mIU/mL)	5.15±4.56	3.91 (0.1-21)	5.71±4.79	4.8 (0.1-26.81)	0.332
P_4 (ng/mL)	28.07±18.39	23.3 (6.5-105.7)	31.15±25.35	23.05 (2.4-117.6)	0.732
Post-IM P_4	20.5±5.43	20 (15-26)	46.4±13.65	46.5 (33-60)	**0.008**

BMI: Body mass index, CL: Corpus luteum, ECA: Embryo cryopreservation age, FET: Frozen embryo transfer, LH: Luteinizing hormone, max: Maximum, min: Minimum, Post-IM: Post–intramuscular, SD: Standard deviation

Table 2. Distribution of the number of embryo transfers and embryo transfer days according to groups

	Group		Test statistics	p*
	Patients who achieved pregnancy (n=79)	Patients without pregnancy (n=88)		
Number of ETs				
1	37 (46.8%)	48 (54.5%)	0.990	0.320
2	42 (53.2%)	40 (45.5)		
ET day				
3	6 (7.6%)	7 (8%)	2.256	0.324
4	2 (2.5%)	0 (0%)		
5	71 (89.9%)	81 (92%)		
*Pearson's chi-square test, ET: Embryo transfer				

Table 3. ROC analysis results for cut-off values for P_4 and E_2 parameters in determining pregnancy in combined vaginal and subcutaneous progesterone users

Parameter	AUC (%95 CI)	p
P_4	0.421 (0.309-0.533)	0.166
E_2	0.456 (0.345-0.568)	0.441
ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, E_2: Estradiol, P_4: Progesterone		

Table 4. Percentile distribution of E_2 value and progesterone according to groups

	Group		
	Patients who achieved pregnancy (n=79)		Patients without pregnancy (n=88)
Percentile	**E_2**	**Progesterone**	**E_2**
0-10	10 (11.4%)	0 (0%)	6 (8.3%)
11-90	68 (77.3%)	48 (92.3%)	60 (83.3%)
91-100	10 (11.4%)	4 (7.7%)	6 (8.3%)
E_2: Estradiol			

Table 5. Logistic regression analysis of independent variables affecting the probability of pregnancy among those with an embryo transfer

	Biochemical pregnancy		Multiple	
	No biochemical pregnancy (n=88)	Biochemical pregnancy (n=79)	OR (95% CI)	p
Age (years)	32.25±5.75	31.6±5.56	1.107 (0.885-1.386)	0.372
Embryo freezing age	31.51±5.99	30.19±5.55	0.853 (0.693-1.05)	0.134
Gravidity	0.67±1.22	0.68±0.97	0.789 (0.509-1.223)	0.290
Parity	0.19±0.54	0.25±0.47	1.89 (0.647-5.524)	0.245
BMI (kg/m^2)	26.45±4.99	27.82±6.32	1.053 (0.984-1.127)	0.137
FET CL (days)	19.26±1.47	19.19±2.32	1.105 (0.889-1.374)	0.369
Max endometrial thickness (mm)	9.61±1.61	9.94±1.51	1.113 (0.873-1.42)	0.387
E_2 (pg/mL)	177.68±56.91	169.75±51.88	0.998 (0.991-1.005)	0.599
LH (mIU/mL)	5.71±4.79	5.15±4.56	0.976 (0.897-1.061)	0.561
P_4 (ng/ml)	31.15±25.35	28.07±18.39	0.991 (0.974-1.008)	0.288
No of ET				
1	48 (56.5%)	37 (43.5%)	Reference	
2	40 (48.8%)	42 (51.2%)	1.557 (0.683-3.552)	0.292

Table 5. Continued

	Biochemical pregnancy		Multiple	
	No biochemical pregnancy (n=88)	Biochemical pregnancy (n=79)	OR (%95 CI)	p
HRT protocols				
E_2 + P_4 (vaginal + subcutaneous)	52 (50%)	52 (50%)	1.527 (0.616-3.786)	0.361
E_2 + P_4 (single drug)	36 (57.1%)	27 (42.9%)	Reference	

Mean ± standard deviation; frequency (percentage)
OR: Odds ratio, CI: Confidence interval, E_2: Estradiol, LH: Luteinizing hormone, P_4: Progesterone, BMI: Body mass index, FET: Frozen embryo transfer, ET: Embryo transfer, HRT: Hormone replacement therapy, Max: Maximum

Table 6. Logistic regression analysis of independent variables affecting the probability of clinical pregnancy among those who conceived

	Clinical pregnancy		Multiple	
	No clinical pregnancy (n=13)	Clinical pregnancy (n=66)	OR (95% CI)	p
Age (years)	31±6.66	31.71±5.39	1.218 (0.717-2.068)	0.465
Embryo freezing age	30.23±6.08	30.18±5.49	0.844 (0.516-1.382)	0.501
Gravidity	0.62±0.87	0.7±0.99	2.022 (0.479-8.534)	0.338
Parity	0.31±0.48	0.24±0.47	0.099 (0.006-1.757)	0.115
BMI (kg/m^2)	29.42±10.17	27.51±5.31	0.942 (0.837-1.061)	0.325
FET CL (days)	18.46±1.81	19.33±2.39	1.327 (0.79-2.229)	0.284
Max endometrial thickness (mm)	9.72±1.18	9.98±1.57	1.729 (0.873-3.424)	0.116
E_2 (pg/mL)	160±50.73	171.9±52.32	1.006 (0.989-1.024)	0.473
LH (mIU/mL)	5.62±4.02	5.05±4.69	1.051 (0.865-1.277)	0.616
P_4 (ng/mL)	30.5 ±20.23	27.58±18.14	1.003 (0.959-1.049)	0.899
No of ET				
1	9 (24.3%)	28 (75.7%)	Reference	
2	4 (9.5%)	38 (90.5%)	5.209 (0.633-42.862)	0.125
HRT protocols				
E_2 + P_4 (vaginal + subcutaneous)	10 (19.2%)	42 (80.8%)	0.154 (0.014-1.739)	0.130
E_2 + P_4 (single drug)	3 (11.1%)	24 (88.9%)	Reference	

Mean ± standard deviation; frequency (percentage)
OR: Odds ratio, CI: Confidence interval, E_2: Estradiol, LH: Luteinizing hormone, P_4: Progesterone, BMI: Body mass index, FET: Frozen embryo transfer, ET: Embryo transfer, HRT: Hormone replacement therapy, Max: Maximum

Table 7. Logistic regression analysis of independent variables affecting the probability of live birth among those who had a clinical pregnancy

	Live birth rate		Multiple	
	No live birth (n=6)	Live birth (n=53)	OR (95% CI)	p
Age (years)	31±5.4	31.45±5.13	1.099 (0.741-1.629)	0.639
Embryo freezing age	29.17±6.77	30.04±5.19	---	---
Gravidity	0.83±0.75	0.62±1	---	---
Parity	0.33±0.52	0.23±0.42	---	---
BMI (kg/m^2)	31.37±6.28	26.64±4.83	0.697 (0.481-1.009)	0.056
FET CL (days)	18.67±1.63	19.42±2.21	2.424 (0.548-10.72)	0.243
Max endometrial thickness (mm)	9.83±1.27	9.96±1.63	1.615 (0.672-3.881)	0.284
E_2 (pg/mL)	145.33±42.6	171.91±46.4	0.998 (0.972-1.025)	0.901
LH (mIU/mL)	6.34±6.49	4.62±3.44	0.812 (0.494-1.334)	0.411

Table 7. Continued

	Live birth rate		Multiple	
	No live birth (n=6)	**Live birth (n=53)**	**OR (95% CI)**	**p**
P_4 (ng/mL)	19.07±9.16	29.18±19.42	1.103 (0.915-1.328)	0.304
No of ET				
1	4 (16.7)	20 (83.3)	Reference	
2	2 (5.7)	33 (94.3)	1.031 (0.045-23.413)	0.985
HRT protocols				
E_2 + P_4 (vaginal + subcutaneous)	3 (8.3)	33 (91.7)	1.685 (0.097-29.222)	0.720
E_2 + P_4 (single drug)	3 (13)	20 (87)	Reference	

Mean ± standard deviation; frequency (percentage)
OR: Odds ratio, CI: Confidence interval, E_2: Estradiol, LH: Luteinizing hormone, P_4: Progesterone, BMI: Body mass index, FET: Frozen embryo transfer, ET: Embryo transfer, HRT: Hormone replacement therapy, Max: Maximum

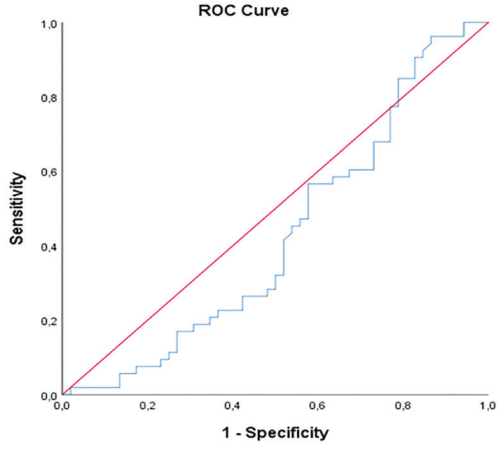

Figure 1. ROC curve for serum progesterone level in determining pregnancy
ROC: Receiver operating characteristic

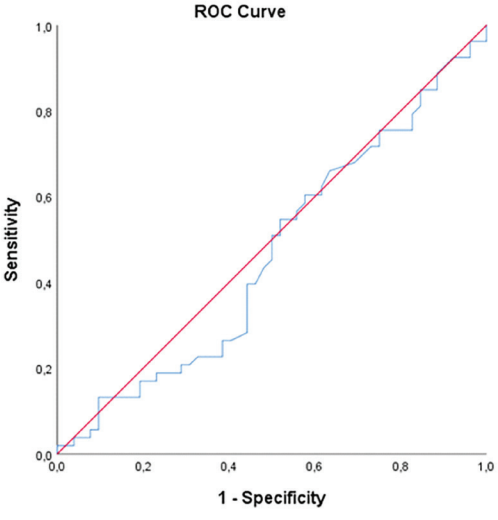

Figure 2. ROC curve for serum estradiol level in determining pregnancy
ROC: Receiver operating characteristic

Discussion

Our findings indicate that serum E_2 and P_4 measurements measured one day before transfer do not serve as predictive factors for pregnancy rates in autologous FET cycles when different routes of E_2 supplementation and combined vaginal and injectable P_4 were used. The only exception to this was the group with a serum P_4 level of less than 15.5 ng/mL, who should likely have the embryo transfer aborted, since no pregnancies were seen in this group. This finding of P_4 cut-off is likely related to different P_4 metabolism due to patient age and BMI, since it was not significant in a multivariate logistic regression analysis controlling for confounding effects.

Similar to our results, previous studies have reported that pre-transfer E_2 monitoring did not affect pregnancy outcomes. Niu et al. (12) investigated the serum E_2 level on the day of P_4 initiation and determined no notable difference in ET and pregnancy rates. They reported E_2 levels at 25, 25-75, and 75-100 percentile as 110, 191, and 299 pg/mL ($p<0.01$) and pregnancy rates of 44%, 40.8% and 41.9% ($p>0.05$ for all comparisons), respectively. In addition, they found that ET did not correlate with serum E_2 level (23). These authors concluded that the serum E_2 level did not predict pregnancy in an E_2 step-up artificial endometrial preparation protocol in the absence of pituitary down-regulation. Comparable findings have been documented in other studies (24,25).

In contrast, Goldman et al. (26) reported that the quartile with the highest serum E_2 levels (mean 528 pg/mL) on the day of P_4 initiation had significantly lower ongoing pregnancy (OP) and live birth rates (LBR) compared to the quartile with the lowest levels (mean 212 pg/mL) (relative risk 0.66 and 0.70 for OP and LBR, respectively). No discrepancies were observed between the groups regarding ET and miscarriage rates. These findings led the researchers to conclude that elevated E_2 levels on the day of P_4 initiation in FET cycles with artificial preparation could be deleterious to implantation and live LBR.

In a randomized controlled study, Racca et al. (27) examined the effects of 7 and 14 days of E_2 priming in the artificial cycle for FET. They reported no significant differences regarding pregnancy, miscarriage, and LBR rates. The study observed similar serum E_2 levels after 7 and 14 days of E_2 priming, measuring 225.0±73.8 pg/mL and 228.0±100.8 pg/mL, respectively (p=0.84). The measurement of comparable serum E_2 levels among individuals who conceived and those who did not conceive in our study, suggests that assessing E_2 before transfer may lack practical utility.

Considering individualized luteal phase support to attain physiological P_4 levels during natural pregnancy is a rational approach to possibly enhance the pregnancy rate in FET (20,21,28). One study reported that the vaginal-only administration of P_4, widely used in Europe, exhibited lower OP rates compared to IM or IM and vaginal administration. For that reason, the vaginal-only arm of the study was prematurely halted (15). A consensus has yet to be reached regarding the optimal serum P_4 level before or during transfer in artificial FET cycles. Melo et al. (29) conducted a thorough multicentre prospective cohort study to investigate the effect of frozen embryo transfer regimen on the association between serum P_4 and live birth. Their study reported serum P_4 levels <7.8 ng/mL were associated with reduced odds of live birth and the mean adjusted probability of live birth increased non-linearly from 37.6% to 45.5% as serum P_4 rose between the 10^{th} (7.8 ng/mL) and 90^{th} (24.0 ng/mL) centiles.

A separate study indicated that administering 40 mg IM P_4 might rescue results if serum P_4 levels were low on the day of FET (<10 ng/mL) (30). In their study, Labarta et al. (22) found that the minimum threshold for rescue was 9.2 ng/mL in patients who received vaginal P_4 alone. Our study primarily evaluated the combined route (vaginal 600 mg/day plus subcutaneous 50 mg/day) for luteal support in FET cycles, while P_4 levels were assessed one day before transfer. Our study showed no significant discrepancy in serum P_4 levels between patients who achieved pregnancy and those who did not. From our finding, we infer that serum P_4 on FET-1 does not independently predict conception when considering other factors. The optimal threshold for combined P_4 administration remains inadequately investigated.

Based on our findings, we conducted a subgroup analysis of patients who achieved pregnancy. Our aim was to ascertain whether there was a predictive threshold for pregnancy when implementing the combined P_4 regimen. No significant threshold value could be identified for pregnancy determination because of the similarity in serum P_4 levels among patients who achieved pregnancy with the combined application. Similarly, an analysis was conducted for the E_2 value, and no threshold value was identified. However, using percentiles suggested that a low P_4 level may affect outcomes, with a level of less than 15.5 ng/mL failing to result in any pregnancies. Although this was a small group the results are interesting and warrant further study. As the debate persists, well-designed prospective studies are necessary. When using multivariate logistic regression to control for confounding effects, the results lost significance, suggesting that the variables used in the analysis may contribute to alterations in P_4 metabolism that caused these low levels and the lack of pregnancies in this group.

Study limitations

While acknowledging the limitations of the study, such as the small number of cases and the retrospective nature, it is worth noting that the study's strength lies in the homogeneity of the patient group's demographics. The study yielded no serum E_2 and P_4 cut-off values to predict pregnancy on FET day 1 when using ROCs. The observation that individuals who conceived displayed serum P_4 levels between 15 and 43 ng/mL suggest potential lower limits for P_4 on FET-1.

Conclusion

Our findings indicate that striving to attain physiologic levels comparable to natural pregnancy through measuring serum E_2 and P_4 levels one day before transfer in autologous artificial FET cycles does not yield noteworthy variations in pregnancy outcomes. The study yielded no serum E_2 and P_4 cut-off values to predict pregnancy on FET day 1 by ROC analysis. In artificially prepared FET cycles, the serum E_2 and P_4 levels one day before embryo transfer did not significantly affect pregnancy rates in women with serum E_2 levels between 150-300 pg/mL and P_4 between 10-40 ng/mL, again using ROC curve analysis. However, the observation that all individuals who conceived had serum P_4 levels above 15.5 ng/mL suggests a lower limit for for P_4 on the day before embryo transfer. Women with P_4 levels less than this value should be considered for cycle cancellation. Of note, multivariate logistic regression analysis suggested that these findings may be due to confounding factors affecting P_4 metabolism. Larger, prospective studies are needed to validate our findings.

Ethic

Ethics Committee Approval: *This study was approved by the İstanbul Atlas University Non-Interventional Research Ethics Committee (approval number: 03, date: 04.03.2024).*

Informed Consent: *All women had signed an informed consent that their data may be used in research studies.*

Footnotes

Author Contributions: *Surgical and Medical Practices: L.D., Concept: L.D., Design: L.D., Data Collection or Processing: L.D., Analysis or Interpretation: L.D., M.H.D., Literature Search: L.D., Writing: L.D., M.H.D.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

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Prevalence of high-grade cervical intraepithelial neoplasia in Mexican women aged under 40 years: a cross-sectional study

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Abstract

Objective: Cervical cancer is the second leading cause of cancer mortality among Mexican women aged 20-39 years, driven primarily by persistent human papillomavirus (HPV) infection. To determine the prevalence of high-grade squamous intraepithelial lesions (HSIL) in women under 40 years of age and identify associated risk factors.

Material and Methods: An observational, cross-sectional study was conducted, including 359 women under 40 years old who were evaluated at the Gynecology and Obstetrics Medical Unit of Centro Médico Nacional de Occidente. Cervicovaginal cytology results indicative of HSIL were analyzed to determine prevalence and assess correlations with demographic and gynecological factors.

Results: The prevalence of HSIL was 39%, with the highest proportion of cases observed in women aged 35-39 years. The average age of sexual debut was 18.5 years, with an average of 2.93 sexual partners. Women diagnosed with HSIL were more likely to be older, married, and homemakers. HPV infection was highly prevalent across both low-grade squamous intraepithelial lesion and HSIL groups.

Conclusion: A high prevalence of HPV infection was found, mostly in a relatively young population. A significant association between infection and risk factors, like marital status and gynecological/obstetric history, was also demonstrated. The findings also confirmed a relationship between HPV and HSIL. [J Turk Ger Gynecol Assoc. 2025; 26(3): 167-73]

Keywords: Pap smear, cervical cancer, cervical intraepithelial lesion, HSIL, cervical screening

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Introduction

Among women aged 20-39 years, cervical cancer (CC) is the second leading cause of cancer mortality, causing 10 deaths per week (1). In Mexico, CC was the second leading cause of death in women, with an estimated 9,439 new cases and 4,335 deaths in 2020 (2). Most cases in the country are diagnosed at the locoregional stage (3).

Persistent infection by carcinogenic types of human papillomavirus (HPV) is the main cause triggering CC development (4). HPV in the cervical epithelium causes alterations in the host genome, leads to downregulated tumor suppressor factors, and induces aberrant functioning of several tumor-promoting factors (5).

The transformation zone at the junction between the ectocervix and endocervix (i.e., the squamocolumnar junction) serves as the usual origin of cervical lesions (6). Cervical preneoplasia, also called cervical intraepithelial neoplasia (CIN), corresponds to low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL). In the latter, the extent and degree of atypia generally exceed the limits described in flat or exophytic condylomas (7,8).

Early detection is essential to identify the disease in its early stages when it is more treatable and associated with better outcomes. This can be achieved by cytology or HPV testing to identify cervical cell abnormalities. The pap smear test reveals cervical cell morphological alterations that indicate precancerous changes, while the HPV test detects the presence of the virus based on its genetic material in cervical cells, with a sensitivity of 90% for precancer detection. In both cases, follow-up colposcopy is necessary to identify precancerous lesions (9,10).

According to the American Cancer Society, the recommended age to initiate screening is 25 years, and a primary HPV screening test is recommended, as is a concomitant test or cytology alone (11). However, considered as screening after the age of sexual activity onset, which detects more than 97% of young women (12).

In unscreened women, the prevalence of LSIL tends to decrease with age. In contrast, the rates of HSIL tend to increase with age, establishing the importance of performing such cancer screening tests early (13).

In Latin American countries, screening coverage in 2019 was over 50%, as early testing, including annual cytology, is performed according to national recommendations (14). In Mexico, it is estimated that about 4.1% of women in the general population harbor a cervical HPV- 16/18 infection at any given time, while 65% of invasive CCs are attributed to HPV- 16/18. In addition, there is a population of 49.6 million women aged 15 years and older who are at risk of developing CC (15). Therefore, timely detection of cervical lesions in the young female Mexican population is of great public health importance. The aim of this study was to determine the prevalence of HSIL in a cohort of patients aged under 40 years.

Material and Methods

For this cross-sectional, observational study, patients were included from January 1, 2019, to January 1, 2023. The study focused on women aged under 40 years who were evaluated at the Gynecology and Obstetrics High Specialty Medical Unit of the National Western Specialty Hospital, Mexican Social Security Institute. These patients underwent cervicovaginal cytology, either for screening purposes or as part of the protocol for gynecologic hysterectomy, and their results corresponded to an HSIL. In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the editorial team for the purposes of additional data analysis or for the reproducibility of this study in other centers, if such is requested.

Patient selection

Female patients under 40 years of age were included if they had undergone cervicovaginal cytology. Exclusion criteria included patients aged 40 years and older, those with immunosuppressive conditions (e.g., HIV infection or autoimmune diseases), or patients receiving immunosuppressive or immunomodulatory therapies, which may alter susceptibility to or increase the risk of cervical premalignant or malignant lesions.

Measuring instruments

Cervical cytology samples were collected using two techniques. The first technique employed the Ayre spatula for exocervical sampling. The bifurcated end of the spatula was inserted into the cervical orifice and rotated 360° clockwise with gentle pressure to ensure a comprehensive sample of the exocervical epithelium, paying particular attention to irregular areas. For endocervical sampling, the conical portion of the spatula was inserted into the cervical canal and rotated 360° counterclockwise. The sample was then spread onto a slide and fixed with 96% alcohol.

The second technique used an endocervical brush or swab, which was gently introduced into the cervical canal, rotated clockwise, and then removed for sample placement onto a slide.

To ensure sample adequacy, specimens had to contain cells from the transformation zone. Samples were deemed inconclusive if the transformation zone was everted or significantly reduced. In cases where the transformation zone was retracted into the endocervical canal, a cotton swab moistened with physiological saline or sterile water was used.

The cytological results were classified using the Bethesda system and correlated with the Mexican official standard (NOM-014-SSA2-1994). All cytology slides were reviewed

by a cytopathologist, and results were categorized as either low-grade intraepithelial lesions (e.g., HPV, mild dysplasia, CIN 1) or high-grade intraepithelial lesions (e.g., moderate dysplasia, severe dysplasia, carcinoma *in situ*, CIN 2, CIN 3). HPV infection was confirmed by the identification of hallmark cytopathological changes, including koilocytosis, dyskaryosis, and nuclear enlargement.

Statistical analysis

The results are expressed as mean and standard deviations (SDs) or numbers and percentages. Descriptive statistics were calculated using percentages for categorical variables and means ± SDs for continuous variables. Categorical data were analyzed using the chi-square test. Differences were considered significant at $p<0.05$. All odds ratios (ORs) were given with 95% confidence intervals (CIs). SPSS, version 21 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Ethical considerations

The study adhered to the stipulations of the 2013 Declaration of Helsinki and its amendments, the General Health Law, and the regulations of the host institution regarding research in humans. The study was approved by the Research and Ethics Committee of the Instituto Mexicano del Seguro Social (approval number: R-2022-1301-123, date: 23.012022).

Results

A total of 359 patients aged under 40 years who met all inclusion criteria were included. The mean age was 32.5±5.37 years. The youngest patient was 15 years old, and the biggest age group was 35-39 years making up 42.3% of the sample, while the group with the lowest representation was aged 15-19 years (Figure 1).

In terms of marital status, 162 (45.1%) reported that they were married, followed by 124 single patients (34.5%). Two hundred fifty-seven (71.6%) reported having a paid job, 98 (27.3%) were homemakers, and 4 (1.1%) were students (Table 1).

Regarding comorbidities, 296 (82.5%) reported having none, 11 (3.1%) reported having hypertension, 8 (2.2%) reported having hypothyroidism, and 7 (1.9%) reported having type 2 diabetes mellitus. Additionally, 28 (7.8%) reported having two or more chronic diseases. The mean patient body mass index was 26.7±5.02 kg/m^2. Forty-six (12.8%) reported active smoking.

The obstetric and gynecological history of the sample is listed in Table 2. Twenty-nine percent reported never having been pregnant, followed by 21.7% with two pregnancies. The least common parities were 7 and 8, with one patient in each case.

The mean age of sexual activity onset was 18.5±3 years, with a mean of 2.93±1.85 sexual partners. The most frequent number of sexual partners was 2 or 3.

Table 1. Sociodemographic characteristics

Marital status	**Number of patients**	**%**
Married	162	45.1
Divorced	14	3.9
Single	124	34.5
Cohabiting	56	15.6
Widow	3	0.8
Occupation		
Paid employment	261	72.7
Homemaker	98	27.3

Table 2. Obstetrical and gynecological history

	Number of patients	**%**
Gestations		
0	104	29
1	72	20.1
2	78	21.7
3	56	15.6
4	35	9.7
5	9	2.5
6	3	0.8
7	1	0.3
8	1	0.3
Family planning method		
None	155	43.2
Abstinence	1	0.3
Contraceptive ring	2	0.6
IUD	22	6.1
Medical IUD	7	1.9
Injected hormone	3	0.8
Oral hormonal	17	4.7
Subdermal implant	21	5.8
BTO	60	16.7
Patches	16	4.5
Preservative	55	15.3
Number of sexual partners		
1	81	22.6
2	90	25.1
3	90	25.1
4	43	12
5	27	7.5
6	12	3.3
7	3	0.8
8	5	1.4
9	0	0
10	8	2.2

IUD: Intrauterine device, BTO: Bilateral tubal occlusion

Regarding family planning, 43.2% of the sample reported not using any contraceptive method, 16.7% had bilateral tubal occlusion, 15.3% used condoms, and 5.8% used a subdermal implant as their family planning method.

The most prevalent gynecological diseases were endometriosis and uterine myomatosis (2.5% and 2.2%, respectively), while 81.9% reported no history of gynecological disease. HPV infection was present in 87.7% of patients and thus only 4.2% were not carriers of the infection.

All patients had a diagnosis by exfoliative cytology (Figure 2). Regarding the prevalence of cytological diagnoses by age group, older patients (30-39 years) more commonly presented with HSIL (p=0.016; OR, 1.723; 95% CI: 1.067-2.783) compared with younger patients (15-29 years). There was a higher percentage of patients who were homemakers in the group who did not have HSIL (p=0.001; OR, 2.356; 95% CI: 1.467-3.782). Other variables are shown in Table 3.

There were no significant between-group differences in histo/cytopathological history, although the percentage of patients with some chronic disease was higher in the group with HSIL (22.9% versus 14.16% in the group without HSIL). The HSIL group n=140 (39%) also included a higher percentage of tobacco users n=128 (91.4%) including those who had former use or were active smokers at the time of the study compared with n=185 (84.5%) in the group without HSIL.

Finally, the group with HSIL was more likely to use family planning methods, with the intrauterine device most common (10%, contrasted with 3.7% in the group without HSIL). The HPV infection distribution was similar between these groups.

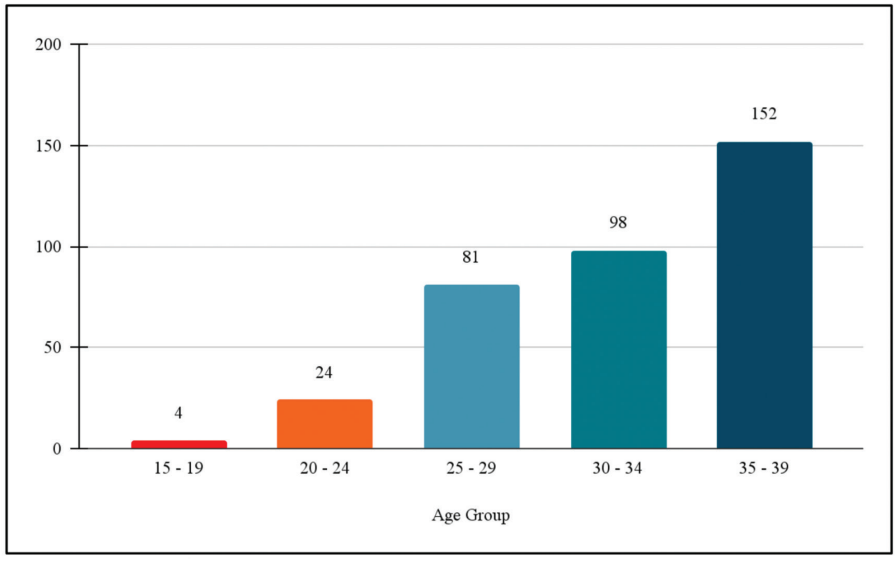

Figure 1. Participant distribution by age group

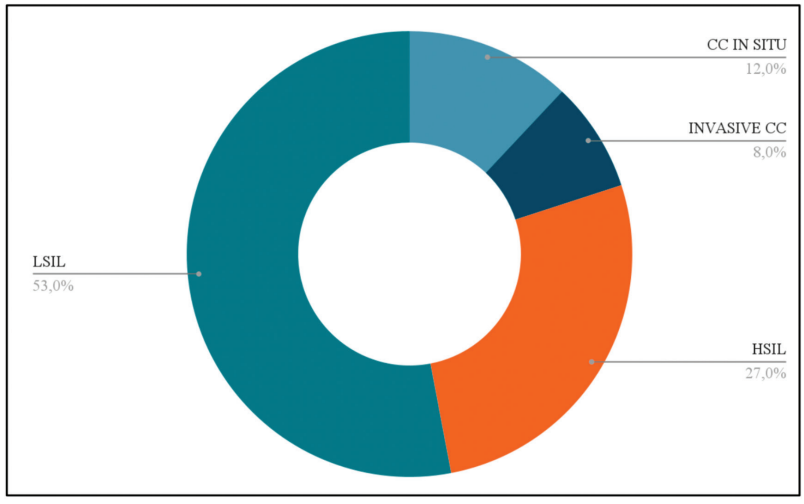

Figure 2. Distribution of diagnoses by cytology
LSIL: Low-grade squamous intraepithelial lesions, HSIL: High-grade squamous intraepithelial lesions, CC: Cervical cancer

Table 3. Analysis of variables

	HSIL	No HSIL	Total	p-value	OR	95% CI
Age of onset of sexual activity						
≤17 years	52	70	122	0.185*	0.795	0.509-1.241
18–39 years	88	149	359			
Number of sexual partners						
≤3 partners	103	158	261	0.432*	0.930	0.577-1.501
≥4 partners	37	61	98			
Number of pregnancies						
≤2 pregnancies	95	159	254	0.199*	1.255	0.790-1.994
>3 pregnancies	45	60	105			

*p-value calculated with chi-square test.
HSIL: High-grade squamous intraepithelial lesion, OR: Odds ratio, CI: Confidence interval

Discussion

HSIL has been shown to be remarkably predictive of CC development. As such, early identification of lesions, particularly in early life, is critical for preventing the establishment of malignant disease.

Herein, the average age of the study sample was 32.5 years, with the youngest patient being 15 years old at diagnosis. In the study by Bonas et al. (16) of patients younger than 30 years, 46 were younger than 25 years and 20 were aged 25-30 years. Thus, the youngest patients were most prevalent in their study, in contrast with the present study in which the most highly represented age group was women aged 35-39 years (152 patients) and there were only four patients in the 15-19 years age group. This finding aligns with that of, Possati-Resende et al. (17) who reported a mean age of 37.9 years for patients with HSIL.

Kalavathy et al. (18) divided patients according to marital status (i.e., living with or without a husband). The group not living with a husband predominated, with 53.8%. Herein, the marital status of patients with HSIL was in contrast to that reported by Kalavathy et al. (18) that is, married patients made up 45.1% of our total sample. According to our findings and those of Darré et al. (19), married women and those whose occupation is homemaker may engage in more regular sexual activity, increasing their risk of developing precancerous cervical lesions. Similarly, Ssedyabane et al. (20) reported a higher prevalence of cervical lesions among married women compared with those with a different marital status.

The mean number of gestations in our study was 1.7±1.5. Twenty-nine percent were

nulligravid and 78 (21.7%) had two pregnancies. Patients with seven or eight gestations were less common, with one patient in each case. Mukhtar et al. (21) highlighted that one-third of the women in their sample were nulligravid (31.9%). The median gestational age of their pregnancies was 30.5 weeks. In their sample, 97.8% had only one sexual partner. Five hundred and two patients (85.5%) initiated sexual intercourse between the ages of 20 and 30 years. Compared with our cohort, the age of sexual activity was 18.5 (±3) years and the average number of sexual partners was 2.93 (±1.85). These results might be explained by cultural differences. The relevance of gynecological/obstetric characteristics and history is in the important associations between them and possible cytological changes. As described by Rasheed et al. (22), a significant association was found between cervical cytology results and advanced age, increased number of sexual partners since coitarche, and parity.

Alarcón-Romero et al. (23) reported an overall HPV prevalence of 54.16%, while 91.39% of patients with HSIL were HPV-positive. This is similar to our findings, in which 87.7% of the sample was HPV-positive. Similarly, Campos et al. (24) reported that 79.2% of their patients had HPV infection, including those with normal cytology, LSIL, HSIL, and CC.

According to Xu and Wang (25), there was a higher prevalence of HPV infection (98.0%) in their group with CIN (26). HPV infection was also significantly more prevalent in older age groups compared with perimenopausal patients, mainly due to factors such as sexual behavior, educational level, history of genital tract diseases, multiple pregnancies, contraceptive methods without tubal ligation, and postcoital hygiene practices.

Herein, diagnoses according to exfoliative cytology were LSIL in 53% and HSIL in 27%, followed by 12% with cancer *in situ*, and 8% with invasive cancer. In the study by Mishra et al. (27), the histological abnormalities were LSIL in 950 (11.52%) patients, HSIL in 851 (10.32%) patients, and CC in 207 (2.51%) patients. Consistent with our results, that group reported that the most frequent cytological diagnosis was LSIL, followed by HSIL, and then some cancer types. However, we differentiated cancer *in situ* and invasive cancer into different groups.

We recognize the limitations of our study regarding the HPV diagnostic method. Although exfoliative cytology varies based on coinfection, diagnosis by other methods like polymerase chain reaction would allow viral identification even before cervical modifications appear and distinguish virus strains. This study showed the presence of HSIL diagnosis and the presence of HPV infection, in addition to sociodemographic characteristics that are consistent with the international literature. We also recognized our limitations on the sample and the number of patients included, due to some deficiencies of the care unit itself, thus we encourage to further explore this topic on a larger scale. The cumulative findings support the importance of determining these characteristics in the Mexican population, toward prevention and timely detection.

Implications for practice and policy

The findings of this study underscore the crucial role of early detection and prevention strategies in reducing the incidence of CC among young women. Routine screening through HPV testing and cytological analysis is essential for the timely identification of HSIL, which is highly predictive of CC development. For healthcare practitioners, integrating HPV testing with cytology as part of routine cervical screening, particularly in women aged 25 and older, should be prioritized to ensure early detection and intervention, which can significantly improve patient outcomes and reduce the risk of CC progression. In addition, practitioners should leverage the study's findings that link sociodemographic factors, such as marital status and parity, to increased HSIL risk. This information can be used to target high-risk groups with more tailored educational and screening interventions.

This study highlights the need to strengthen national screening programs and expand access to routine cervical screening services, especially in areas with below-optimal coverage. Moreover, vaccination policies should focus on increasing accessibility to the HPV vaccine, particularly for adolescents, to prevent infections linked to CC. Public health campaigns should raise awareness about the importance of HPV vaccination and regular CC screening to promote early detection and adherence to screening guidelines.

Future research and implementation strategies must prioritize culturally sensitive and accessible screening programs for underserved populations. Policymakers must wholeheartedly support ongoing research into the effectiveness and cost-efficiency of HPV screening and vaccination programs to seamlessly integrate them into healthcare systems. These efforts will be central to significantly reduce the incidence of CC and thus improve health outcomes for at-risk women.

Study limitations

The limitations of our study were the retrospective design and the lack of evaluation of molecular markers to confirm the results.

Conclusion

Our sample of relatively young adults, with an average age of 32.5 years, had a high prevalence of HPV infection (87.7%). A significant association was observed between HSIL and risk factors including age, marital status, and gynecological/obstetric history. Furthermore, the relationship between HPV infection and diagnosis of HSIL was confirmed. Although the results regarding the distribution of lesions and cytological diagnoses are consistent with the international literature, they highlight the need for more sensitive HPV diagnostic methods.

Ethics

Ethics Committee Approval: *The study was approved by the Research and Ethics Committee of the Instituto Mexicano del Seguro Social (approval number: R-2022-1301-123, date: 23.01.2022).*

Informed Consent: *The study adhered to the stipulations of the 2013 Declaration of Helsinki and its amendments, the General Health Law, and the regulations of the host institution regarding research in humans.*

Footnotes

Author Contributions: *Surgical and Medical Practices: E.G.J.P., L.P.L.T., L.G.C.B., Concept: E.G.J.P., L.P.L.T., L.G.C.B., A.G.O., C.F.O., Design: E.G.J.P., A.G.O., C.F.O., Data Collection or Processing: E.G.J.P., L.P.L.T., L.G.C.B., Analysis or Interpretation: A.G.O., E.C.P., J.M.G.D., V.T.H.R., C.F.O., Literature Search: G.C.G., E.C.P., S.R.O., S.J.V.S., S.E.G.M., K.D.M.M., J.M.G.D., V.T.H.R., A.S.A.V., C.E.C.T., Writing: E.G.J.P., S.E.G.M., K.D.M.M., J.M.G.D., V.T.H.R., A.O.C.F.*

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Twin pregnancy: adolescents versus adults

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Abstract

Objective: Various nations, and this could create a new era of very young mothers which apply an additional pressure on obstetrical and neonatal health system. In cases of twin pregnancy, the burden would be maximized. The aim was to highlight the differences of obstetrical and neonatal outcomes of twin adolescent pregnancy compared to adults.

Material and Methods: Data were collected prospectively over five years from a tertiary obstetric and neonatal center. Two categories of twin pregnancies were formed from adolescents as the case group and adults as controls.

Results: The adolescent group included 59 women and adults numbered 782. The adolescents had significantly higher rates of very preterm delivery, defined as gestational age [(GA) 28≤32 weeks] [odds ratio (95% confidence interval) 2.64 (1.26-3.92)], p<0.05], and significantly lower mean GA than adults (36.6±4.1 versus 37.8±2.6, weeks respectively). Babies delivered to adolescents had significantly lower mean birth weight (1936.5±0.604 g), birth height (43.4±4.3 cm), and occipitofrontal circumference (OFC) (30.8±3.3 cm). Moreover, there was a significantly higher frequency of neonates with APGAR score <7 at the fifth minute [31 (52.54)], low birth weight [53 (89.83)], and neonatal intensive care unit (NICU) admission [38 (64.41)].

Conclusion: Twin adolescent pregnancy had significantly elevated metrics for obstetric and neonatal complications, which were especially notable for very preterm delivery, low neonatal birth weight and short birth length, and reduced OFC, APGAR score <7 at the fifth minute, and NICU admission rate. [J Turk Ger Gynecol Assoc. 2025; 26(3): 174-9]

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Introduction

Pregnancy between the ages of 10-19 years is considered adolescent pregnancy, while any age older than that is defined as adult pregnancy (1).

Although adolescent pregnancy is not common, it has shown an increasing trend worldwide although the rates vary widely from country to country, and have been reported to range from 0.1% to over 20%. The incidence tends to be higher in developing countries compared to developed countries, however (2,3).

The rate of twin adolescent pregnancy is much lower at about 1.5% globally. Assisted reproductive technologies (ART) have significantly increased this rate (up to 32.1%), but ART is more easily accessible in the developed parts of the world (4,5). However, the present study only examined spontaneous twin pregnancies and thus focused on natural twinning rates.

In most of the developing countries in the Middle East and North Africa, the rates of adolescent pregnancy are among the highest in the world due to many factors. These include the social

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belief of early marriage, and background cultural acceptance of pregnancy at a very young age. These beliefs extend beyond pregnancy through all age groups and involve the use of certain drugs and remedies to support the health of adolescent pregnant women and her neonate based on traditional beliefs. As a result, the rate of twinning in adolescents may be as high as 16 per 1,000 births (6-9).

In general, twin pregnancy carries risks to the mother and her babies and more risks are associated with adolescents as these women are not biologically and mentally mature enough to face the burden of this health-related event. Many complications may arise, such as preterm delivery, gestational hypertension (GH), gestational diabetes (GDM), higher cesarean section (CS) rates, and low birth weight (LBW) with higher chances of the newborn baby needing neonatal intensive care unit (NICU) admission. Similarly, advanced maternal is also associated with more complications with higher rates of maternal and neonatal morbidities (10-12).

The limited published data about adolescent twin pregnancy and the expected load on the health system dealing with twinning pregnancy at different maternal ages (2,6) are the major stimuli for this study. The aims are to examine and report obstetrical and neonatal outcomes of twin pregnancy in adolescents compared to twin pregnancies in adults.

Material and Methods

Twin pregnant women who visited obstetrics and gynecology department at a tertiary medical center over five years, from November 2019 to October 2024 were prospectively included. Data were obtained from the attending obstetrical and neonatal units' records under the supervision of the researchers.

Exclusion criteria were: previously diagnosed chronic maternal disease, including hematological, cardiovascular, immunological, endocrinological, and oncological abnormalities; fetal retardation-associated pregnancies; pregnancies resulting from in vitro fertilization (to decrease bias in results when comparing twin pregnancy outcomes in adolescents versus (vs) adults); premature delivery before 28 weeks gestation; VLBW below 1,000 g; congenital and/or chromosomal neonatal defects; and missing and incomplete data. Two groups were formed; the study group included adolescent twin pregnant women and the control group included adult twin pregnant women aged (20-34) years.

Definitions

The adolescent pregnant women were defined as women aged (10-19) years, while pregnant women aged ≥20 years were defined as adult (13,14).

Preterm pregnancy was defined as gestational age (GA) birth below 37 completed weeks, and late preterm pregnancy was defined as GA between 32-37 weeks. If GA was 28 to <32 weeks, this was categorized as a very preterm pregnancy, while an extremely preterm pregnancy was one when birth occurred with GA <28 weeks (15,16).

Premature rupture of membranes (PROM) as defined as rupture occurring before 37 weeks GA (17).

LBW, and VLBW neonates were defined when birth weight was <2.5 kg, and <1.5 kg, respectively (18,19).

The definition of GH follows the guidelines set by the American College of Obstetricians and Gynecologists. This is characterized by a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg on two separate readings taken at least 4 hours apart after 20 weeks of pregnancy in a woman with previously normal blood pressure (20,21). Women with GH were managed according to the hospital's guideline with labetalol and/or methyldopa.

Maternal anemia was defined as a hemoglobin level less than 11 g/dL measured at birth (14,22).

GDM was diagnosed after 20 weeks of pregnancy following the criteria established by the International Association of Diabetes in Pregnancy Study Groups. Diagnosis involved a fasting plasma glucose level exceeding 91.8 mg/dL, or elevated postprandial levels during a 75 g oral glucose tolerance test, with thresholds of over 180 mg/dL at one hour and over 153 mg/dL at two hours (11,22). Women with GDM were managed according to the hospital's guideline and started with diet and healthy lifestyle, and if that failed, metformin was tried before the use of insulin which was considered the last treatment option.

Body mass index was calculated using the standard formula: body weight (kg)/ height (m^2) (23).

Stillbirth was defined as a baby that died after 28 weeks of GA, but before or during delivery (24).

The attending obstetrician and neonatologist completed all the needed measurements according to standard hospital guidelines, under observation of the authors.

This study was approved by the Al-Kindy College of Medicine University of Baghdad (approval number: 89, date: 23.09.2019).

Statistical analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corporation, Armonk, New York, USA), with a significance threshold set at $p<0.05$ for all tests. The normality of the data was assessed using the Kolmogorov-Smirnov test. Parametric data were analyzed with Student's t-test, and results are presented as mean ± standard deviation. For non-parametric data, the Mann-Whitney U test was applied, with results reported as

median (minimum, maximum). Categorical variables were assessed using the chi-square test, and odds ratios with 95% confidence intervals were calculated.

Results

The study group of adolescent twinning pregnancies included 59 women, and the control group of adult twinning pregnancies included 782 women.

Table 1 shows the general sociodemographic characteristics. Evidently, median age (years) differed significantly between the adolescent and adult groups and multiparity was more frequent in adults. Both groups have comparable rates of CS, and the adolescent group included a larger percentage of primary CS. Mean stillbirth values were higher in adolescents without being significanct. Mean GA at birth was significantly lower in the adolescent group in comparison with the adult group (36.6±4.1 and 37.8±2.6, respectively), with approximately one week difference.

In terms of maternal outcomes (Table 2), very preterm delivery has was significantly more common in adolescents than adults [31 (52.54) and 232 (29.67), respectively]. Conversely, late preterm delivery, extremely preterm delivery, and GDM were more common in the adult group, but not significantly so. In addition, preterm delivery, PROM, GD, GH, and maternal anemia were more common in adolescents.

In terms of neonatal outcomes (Table 3), mean birth weight (g), birth length (cm), and occipitofrontal circumference (OFC; in cm) were significantly less in babies born to adolescents compared to those born to adults (1936.5±0.604 vs. 2181.7±0.522, 43.4±4.3 vs. 44.6±4.1, and 30.8±3.3 vs. 31.9±3.8, respectively). Proportion of neonates with APGAR score <7 at the fifth minute, LBW, and NICU admission were significant larger in the adolescent group than the adult group [31 (52.54) vs. 367 (46.93), 53 (89.83) vs. 527 (67.39), and 38 (64.41) vs. 1.76 (1.1-3.2), respectively]. However, although the APGAR score <7 at the first minute and VLBW were more frequent in the adolescent group than in adults, these variables failed to reach statistical significance [31 (52.54) vs. 367 (46.93), and 8 (13.56) vs. 81 (10.36), in corresponding order].

Discussion

Although twin pregnancy at any age is a major health concern, adolescent population may fare worse. In the present study, median ages of adolescent and adult pregnant women was

Table 1. General demographic characteristics of adolescent versus adult twin pregnancies

Parameter	Adolescent group (n=59)	Adult group (n=782)	p-value
Age (years): median (min, max)	18 (12-19)	28 (20-34)	<0.05
Parity: n (%)			<0.05
Nulliparous	57 (96.61)	556 (71.10)	
Multiparous	2 (3.39)	226 (28.90)	
Body mass index: mean ± SD	24.6±1.7	25.9±3.2	0.09
Residence: n (%)			0.24
Urban	46 (77.97)	568 (72.64)	
Rural	13 (22.3)	214 (27.36)	
Mode of delivery: n (%)		36.6±4.1 and 37.8±2.6	
Vaginal	3 (5.08)	28 (3.58)	
Cesarean section: n (%)	56 (94.92)	754 (96.42)	
Primary: n (%)	54 (96.43)	567 (75.20)	<0.05
Repeated: n (%)	2 (3.57)	187 (24.80)	
Gestational age at delivery: mean ± SD	36.6±4.1	37.8±2.6	0.36
Chorion type, n (%)			0.27
Mono-chorionic	23 (38.98)	386 (49.36)	
Di-chorionic	36 (61.02)	396 (50.64)	
Neonatal sex: n (%)			0.89
Male	66 (55.93)	822 (52.56)	
Female	52 (44.07)	742 (47.44)	
Stillbirth: mean ± SD	4 (6.78)	46 (5.88)	0.74
Gestational age (GA): mean ± SD weeks	36.6±4.1	37.8±2.6	<0.05

SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Obstetrical complication by different maternal age groups

Complication: n (%)	Adolescent group (n=59)	Adult group (n=782)	OR 95% CI	p-value
Preterm delivery	51 (86.44)	605 (77.37)	1.78 (0.89-3.51)	0.28
Late preterm delivery	19 (32.20)	358 (45.78)	0.83 (0.61-1.73)	0.07
Very preterm delivery	31 (52.54)	232 (29.67)	2.64 (1.26-3.92)	<0.05
Extremely preterm delivery	1 (1.67)	15 (1.92)	0.68 (0.44-2.53)	0.43
Premature rupture of membranes (PROM)	16 (27.12)	176 (22.51)	1.2 (0.39-5.37)	0.31
Gestational hypertension (GH)	5 (8.47)	51 (6.52)	1.1 (0.35-3.46)	0.72
Anemia	52 (88.14)	670 (85.68)	1.57 (0.73-4.29)	0.69
Gestational diabetes (GD)	2 (3.39)	31 (3.96)	0.82 (0.24-3.13)	0.54
OR: Odds ratio, CI: Confidence interval				

Table 3. Neonatal complication by different maternal age groups

Complication	Adolescent group (n=59)	Adult group (n=782)	OR 95% CI	p-value
Birth weight (g) (mean ± SD)	1936.5±0.604	2181.7±0.522		<0.05
Birth height (cm) (mean ± SD)	43.4±4.3	44.6±4.1		<0.05
Occipitofrontal circumference (cm) (mean ± SD)	30.8±3.3	31.9±3.8		<0.05
APGAR score <7 at 1st minute: n (%)	31 (52.54)	367 (46.93)	1.38 (0.94-2.25)	0.14
APGAR score <7 at 5th minute: n (%)	15 (25.42)	126 (16.11)	1.47 (1.08-2.39)	<0.05
Low birth weight: n (%)	53 (89.83)	527 (67.39)	2.98 (1.64-5.13)	<0.05
Very low birth weight: n (%)	8 (13.56)	81 (10.36)	1.57 (0.61-2.72)	0.29
Neonatal intensive care unit admission	38 (64.41)	428 (54.73)	1.76 (1.1-3.2)	<0.05
OR: Odds ratio, CI: Confidence interval, SD: Standard deviation				

around 18 and 28 years, respectively. This is in line with other local and international figures (3,6,25). Parity in adults was much higher than in adolescents, unsurprisingly, as with age progression the number of deliveries is likely to increase (2,26). Operative delivery by CS had similar rates in both groups, possibly because of obstetrician's choice for twin pregnancies (25,27). Primary CS was predominant in adolescents while adults had predominantly repeated CS. This is obvious as adolescent pregnancy is a risk factor by itself and with elevated parity numbers the possibility of repeated operative delivery and CS increases (2,27,28).

There was a one-week difference in GA at birth between adolescents and adults. However, it has been shown that GA at birth is shortened in both adolescent pregnancies and twin pregnancies (29,30).

Although preterm delivery was more frequent in the adolescent group, very preterm delivery was the only definition of prematurity to exhibit a significant difference. Conflicting previous reports have shown various results. One much earlier study found no difference in preterm rates between adolescents and adults, while a more recent paper revealed a higher occurrence of very advanced preterm labor with less than 28 weeks in twin adolescent pregnancy. However, a third paper reported higher preterm deliveries of less than 33 weeks in twin adolescent pregnancy (31-33). These contradictory results could be related to the number and ethnic background of involved samples, and the criteria used for defining different categories of preterm delivery.

Obstetric complications including PROM are more common in both adolescent pregnancies and twin pregnancies, which is in parallel with our results (2,26,27).

GH was more common in our adolescent pregnancy cohort. Again, published evidence is contradictory about this. Some reports found no differences in GH in different age groups, while others observed a higher incidence in adolescents (12,29,31,32). The multifactorial etiology of GH may explain these contrary results.

Anemia is a common feature of adolescents in general, especially nutritional anemia due to iron deficiency since they have elevated iron requirements because their physical development is not yet finished. Besides, pregnancy is a known cause of iron deficiency. Accordingly, anemia is more common in all age groups during pregnancy but slightly more so in adolescents (14,34).

As individuals grow older the sensitivity of pancreatic beta cells decreases. Pregnancy also increases demand on the maternal beta-cell function. Given this, adult pregnant women have a higher chance to develop GDM than adolescents, and that is what we found in our sample (11,21).

With respect to neonatal complications, we found that neonatal weight, length, and OFC measurements were significantly less in babies born to adolescents. This is in line with the published evidence. Furthermore, adolescents may focus on their body shape, even during pregnancy, using various approaches like fasting, lowering amount and type of daily food and calories, and even vomiting. Besides, adolescent physical development may not be complete, especially in younger adolescents, and this could lead to conflicting needs for nutrient absorption and utilization between the developing body of the adolescent and their fetuses. Given these factors, and the one week difference in GA at birth, the findings concerning neonatal anthropometry in the two groups in our study may be unsurprising (2,6,35,36).

In the present study, being adolescent when pregnant was significantly associated with reduced rates of APGAR score <7 at 5th minute, LBW, and NICU admission were found. Many earlier investigations had the same opinion showing poor neonatal parameters and outcomes (2,6,25,37,38).

Study limitations

Strengths of this work include prospective data collection over five years and being conducted at the largest tertiary medical facility in Iraq.

Yet, some limitations should be acknowledged, including the single-center nature of the study, the relatively small number of women with twin pregnancies, especially adolescents, leading to limited statistical power to detect differences in rare outcomes, such as GDM and GH, and lack of nutritional data for the pregnant women. Finally, the sociodemographic characteristics of the Iraqi population mean that the findings may not be generalizable. Thus more studies with expanded international diversity are suggested.

Conclusion

This study investigated outcomes of twin pregnancies in adolescents and adult women where adolescent pregnancy was considered a high-risk medical concern. It was found that adolescent twin pregnancy was associated with increased complications and morbidities, both for the mother and the twins. Of note, there was a heightened vulnerability of very preterm delivery, APGAR score <7 at the fifth minute, LBW, and NICU admission in the adolescent group. Furthermore, neonatal birth weight, birth length, and OFC were all significantly lower in twins born to adolescents.

Ethic

Ethics Committee Approval: *This study was approved by the Al-Kindy College of Medicine University of Baghdad (approval number: 89, date: 23.09.2019).*

Informed Consent: *Helsinki declaration guidelines were applied, and an instructed consent was gathered from all participants.*

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Footnotes

Author Contributions: *Surgical and Medical Practices: S.K.J., R.D., A.O.O., H.A.M, R.A., Concept: S.K.J., R.D., R.A., Design: S.K.J., R.D., A.O.O., H.A.M, Data Collection or Processing: S.K.J., R.D., A.O.O., Analysis or Interpretation: S.K.J., R.D., H.A.M, Literature Search: R.D., A.O.O., H.A.M, R.A., Writing: S.K.J., R.D., A.O.O., H.A.M, R.A.*

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Retrospective evaluation of transvaginal cervical cerclage cases in a tertiary reference center: comparison of indications and suture materials

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Abstract

Objective: To compare history-indicated cervical cerclage (HICC), ultrasound-indicated CC (UICC) and physical examination-indicated CC (PEICC) in terms of obstetric outcomes and to compare the outcomes related to braided and non-braided suture materials (Prolene suture vs. Mersilene tape).

Material and Methods: We retrospectively evaluated 173 transvaginal CC procedures performed in a single center. Cases were classified based on procedure indications and the type of suture material used.

Results: Of the 173 cases reviewed, 103 (59.5%), 45 (26.0%) and 25 (14.4%) cases were in the HICC, UICC and PEICC groups, respectively. Patients in the PEICC group underwent cerclage at significantly later gestational weeks, had higher hospitalization rates, longer hospital stays following the procedure, a shorter interval between cerclage and delivery, and a higher rate of procedure-related pregnancy loss compared to the other groups ($p<0.05$ for all). Both the gestational age at delivery and the take-home baby rate were lower in this group compared to the other groups ($p<0.05$ for both). There were no significant differences identified in terms of suture materials used. Subgroup analyses revealed similar obstetric outcomes between different suture materials.

Conclusion: PEICC had worse perinatal outcomes compared to HICC and UICC procedures. CC indication was the major determinant of perinatal outcome in this cohort while suture material had no significant effect on perinatal outcomes. [J Turk Ger Gynecol Assoc. 2025; 26(3): 180-9]

Keywords: Cervical cerclage, indication, mersilene suture, prolene suture, suture material

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Introduction

Cervical cerclage (CC) is a procedure performed to reinforce the cervix in certain circumstances. Transvaginal CC was first described by Shirodkar and modified by McDonald to its most widely used technique (1,2). Several surgical techniques have been described, such as a transabdominal or laparoscopic approach, especially in cases with previous transvaginal CC failure (3,4).

The indications for the cerclage procedure are mainly categorized into three groups; history-indicated CC (HICC), ultrasound-indicated CC (UICC) and physical examination-indicated CC (PEICC) (5). The patient selection for the procedure must also be within the defined indications as

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the procedure has also some important complications that may even result in pregnancy loss. Membrane rupture, intra-amniotic infection or suture migration are the most commonly reported complications of cerclage procedure. The rate of complications has been reported to increase with maternal age and advanced cervical dilatation (6). However, there are also numerous studies showing similar results between different group of patients, including UICC and PEICC, in terms of procedure related complications (7).

Success of a cerclage procedure strictly depends on the indication for the procedure as well as the used surgical technique and surgical materials. Despite transabdominal or laparoscopic routes for CC being associated with higher morbidity, these procedures may be preferred for patients with a prior transvaginal CC failure (8). Furthermore, placement of suture material and the remaining intact cervical height have been associated with greater success of the procedure (9).

Beyond surgical techniques, the association between suture material type and pregnancy outcomes has been widely studied. Braided suture materials, such as Mersilene tape, are the most widely used material for this procedure (10). However, there are numerous studies evaluating the appropriateness of non-braided, non-absorbable sutures, such as Prolene, for CC. This question has been investigated in a multicenter randomized trial and the authors found no differences between braided and non-braided suture materials (11). However, due to lack of further randomized studies confirming these results, we believe that additional data may be helpful.

The aim of this study was to evaluate the obstetric and neonatal outcomes in pregnancies with CC according to cerclage indication and suture materials used.

Material and Methods

All CC procedures were performed between January 1, 2004 and December 31, 2023 in the Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, were evaluated in this retrospective cohort study. Study data were extracted from the electronic database of Hacettepe University. Singleton pregnancies undergoing CC procedure were included. All the procedures were performed by maternal fetal medicine specialists. Multiple pregnancies and pregnancies with transabdominal cerclage procedures were excluded from the study. Patients who were lost to follow-up were also excluded. The study was performed in accordance with the Declaration of Helsinki. This study was approved by the Hacettepe University Health Sciences Research Ethics Committee (approval number: 2023/03-08, date: 19.09.2023).

CC procedures were performed according to McDonald's technique based on three main indications: 1) HICC which was based on a prior history of one or more second-trimester losses associated with painless cervical dilation (12); 2) UICC defined as singleton pregnancy, prior preterm birth or a second-trimester loss, and a short cervical length (≤25 mm) on transvaginal ultrasound examination at 16 to 23 weeks of gestation; and 3) PEICC which was performed in cases of cervical insufficiency based on a dilated cervix on a digital or speculum examination at 16 to 23 weeks of gestation (5).

Patients were evaluated in terms of obstetric histories, antenatal risk factors and cervical assessment before the operation. Fetal anomalies incompatible with life, intrauterine infection, active vaginal bleeding, active preterm labor, preterm premature rupture of membranes (PPROM) and fetal demise were considered as contraindications for the CC procedure (12). Cerclage procedures included in the cohort were primarily performed at or before 24 weeks of gestation. In five cases (four PEICC, one UICC), the procedure was performed beyond 24 weeks (25-26 weeks) following detailed counseling with the patient and family regarding potential risks and benefits. A comprehensive informed consent was provided for all patients including estimated success rates, procedure related complications and possible neonatal adverse outcomes. After obtaining required written permissions, the patients were placed in lithotomic position, the operation field was cleansed with aseptic solutions, surgical drapes were placed and sedoanalgesia was administered in the operating room. All patients received a single prophylactic dose of 2 g intravenous cefazolin prior to the procedure, following institutional standard protocol. The anterior and posterior lips of the cervix were grasped by two ring forceps. Then sutures (either Prolene or Mersilene tape) were inserted at 12, 3, 6 and 9 o'clock positions circumferentially around the entire cervix as high as safely possible, avoiding the bladder, rectum, and uterine vessels (9,12). The lateral positions (3 and 9 o'clock) were approached with particular caution to avoid uterine artery injury, and the suture pathway was adjusted according to the cervical anatomy (5). Either outpatient approach or hospitalization was chosen according to individual patient clinical picture. Mersilene tape (5-0 Mersilene™ white 1X18" S-14 double armed, Ethicon, Johnson & Johnson, New Jersey, USA) or Prolene suture (Prolene™#1, polypropylene suture, Ethicon, Johnson & Johnson, New Jersey, USA) were used in all cases. Pregnancies were closely followed-up at the division of perinatology until delivery.

Pregnancies included in the study were divided into three groups based on CC indications: 1) HICC group; 2) UICC group; and 3) PEICC group. Maternal age, gravidity, parity, previous miscarriage, number of living children, multiparity, gestational week of cerclage procedure, suture material, hospitalization rate, duration of hospitalization after the cerclage procedure, procedure related pregnancy loss (pregnancy losses that occurred within a week after the CC procedure), preterm labor/PPROM rate, rates of deliveries at $<34^{th}$, 34^{th}-$<37^{th}$, and $\geq 37^{th}$ weeks of gestation, duration between cerclage procedure

and delivery, birth weight, route of delivery, rate of any Apgar score less than 7 in the first ten minutes, admission to neonatal intensive care unit (NICU), neonatal infection rate (presence of neonatal sepsis and/or congenital pneumonia) and take-home baby rates were compared between the groups. Thereafter, pregnancies were divided into groups based on suture material, either 1) Prolene suture group and 2) Mersilene tape group. The same set of variables were compared between the groups. Preterm birth rate was considered the primary outcome of the study. Other outcomes, including gestational age at delivery, birthweight, NICU admission, take-home baby rate, perinatal mortality, and procedure-related pregnancy loss, were evaluated as secondary outcomes.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 22 (IBM Inc., Armonk, NY, USA). Variables were investigated using visual and analytical methods to determine whether they were normally distributed. Descriptive analyses are presented as medians and interquartile range for non-normally distributed variables. As continuous variables were not normally distributed, Kruskal-Wallis or Mann-Whitney U tests were performed to compare the median values between the groups. A p value of <0.05 was used to infer statistical significance. Categorical variables were defined based on numbers and percentages. Categorical variables were compared with Fisher's exact or chi-square test as appropriate. Pairwise compasions were performed by Mann-Whitney U test for continuous variables and post-hoc analyses were performed for significantly different categoric variables.

Results

A total of 173 transvaginal CC procedures were performed during the study period, including 103 (59.5%) in the HICC group, 45 (26.0%) in the UICC group, and 25 (14.4%) in the PEICC group. Significant differences were found for gravidity, number of previous miscarriages, gestational week of cerclage procedure, hospitalization after CC rate, duration of hospitalization after the cerclage procedure, procedure related pregnancy loss, pregnancy outcome, preterm labor rate, PPROM rate, gestational week at delivery subgroups, gestational week at delivery, duration between cerclage procedure and delivery, birth weight, admission rate to NICU and take-home baby rate ($p<0.05$ for all) (Table 1). Although the median number of previous miscarriages was zero in the UICC group, all patients had qualifying risk factors, such as prior spontaneous preterm birth or second-trimester loss, consistent with guideline-based indications for UICC. Median values for gestational week of CC procedure were 13, 20 and 21 weeks for HICC, UICC and PEICC groups, respectively ($p<0.001$). Hospitalization rates after cerclage procedures were 29.1%, 51.1% and 92% for HICC, UICC and PEICC groups, respectively ($p<0.001$). Duration of hospitalization after CC was significantly different between all groups ($p<0.001$). The procedure-related pregnancy loss rate was significantly higher in the PEICC group (40%) compared to HICC (1.9%) and UICC groups (6.6%, $p<0.001$ for both). Pregnancy outcomes differed among groups as to whether they ended in miscarriage or delivery. Miscarriage rates were 8.7%, 6.6% and 36% for HICC, UICC and PEICC groups, respectively. Preterm labor rate was higher in the PEICC and UICC group

Table 1. Characteristics of the patient groups based on cervical cerclage indications

Variables	History indicated cerclage group (n=103)	Ultrasound indicated cerclage group (n=45)	Physical examination indicated cerclage group (n=25)	p values
Maternal age (median, p25-p75)	32 (29-35)	33.5 (30-37.5)	33 (28.5-34.5)	0.309
Gravidity (median, p25-p75)	3.5 (3-5)	2 (1-3)	2 (2-4)	**<0.001**[a]
Parity (median, p25-p75)	1 (0-2)	1 (0-1)	0 (0-1)	0.050
Previous miscarriage (median, p25-p75)	1 (1-2)	0 (0-1)	1 (0-2)	**0.009**[b]
Living child (median, p25-p75)	0 (0-1)	0 (0-1)	0 (0-1)	0.411
Multiparous n, (%)	67 (65.1)	23 (51.1)	11 (44)	0.083
Gestational week of cerclage procedure (median, p25-p75)	13 (12-14)	20 (17.5-22)	21 (19-24)	**<0.001**[c]
Suture material n (%)				0.867
Prolene	63 (61.1)	26 (57.7)	16 (64)	
Mersilene tape	40 (38.9)	19 (42.3)	9 (36)	

p25-p75: 25th and 75th percentiles, NICU: Neonatal intensive care unit, PPROM: Preterm prelabor rupture of membranes
Pairwise comparison revealed significant differences between;
[a]Ultrasound indicated and history indicated groups
[b]Ultrasound indicated and other two groups
[c]History indicated and other two groups

compared to HICC group (p=0.005). Median gestational week at delivery was lowest in the PEICC group (34) and this value was significantly lower than the HICC (37) and UICC (36) groups (p=0.025). Median duration between the CC procedure and delivery was longest in the HICC (24) group and shortest in the PEICC group (11). This difference was significant between all groups by pairwise analyses (p<0.001 for both). Median birth weight was 3050 g, 2850 g and 2340 g for HICC, UICC and PEICC groups, respectively, with a significant difference between HICC and PEICC groups. Rate of any first ten minute Apgar score <7 was similar between groups (p=0.420). Admission rates to NICU were highest for the PEICC group (56.2%) in comparison with HICC (20.2%) and UICC (30.9%) (p=0.008). Take-home baby rate was significantly lower in the PEICC group (64%) in comparison with the HICC (91.2%) and UICC (88.8%) groups (p=0.001).

Prolene suture and Mersilene tape was used in 105 (60.7%) and 68 (39.3%) cases, respectively. Both groups were comparable in terms of study parameters. CC indications were similar between groups. We could not demonstrate any significant difference regarding neonatal and perinatal outcomes (Table 2).

Table 2. Clinical outcomes of the patient groups based on cervical cerclage indications

Variables	History indicated cerclage group (n=103)	Ultrasound indicated cerclage group (n=45)	Physical examination indicated cerclage group (n=25)	p values
Hospitalization after cerclage, n (%)	30 (29.1)	23 (51.1)	23 (92)	**<0.001**[a]
Duration of hospitalization after the cerclage procedure (days) median, (p25-p75)	0 (0-1)	0.5 (0-1)	3 (1-7.5)	**<0.001**[a]
Procedure related pregnancy loss n (%)	2 (1.9)	3 (6.6)	10 (40)	**<0.001**[b]
Pregnancy outcome, n (%) Miscarriage Delivery	 9 (8.7) 94 (91.3)	 3 (6.6) 42 (93.4)	 9 (36) 16 (64)	**0.001**[b]
Preterm labor[¥]	27 (28.7)	23 (54.7)	9 (56.2)	**0.005**[c]
PPROM (n, %)	10 (10.6)	9 (21.4)	7 (43.7)	**0.003**[b]
Gestational week at delivery subgroups, n (%)[¥]				**0.003**[c]
<34th weeks	10 (10.6)	11 (26.1)	7 (43.7)	
34th-<37th weeks	17 (18.1)	12 (28.5)	2 (12.5)	
≥37th weeks	67 (71.3)	19 (45.4)	7 (43.7)	
Gestational week at delivery median, (p25-p75)[¥]	37 (36-38)	36 (31.5-38)	34 (20.5-37)	**0.025**[b]
Duration between cerclage procedure and delivery (weeks) median, (p25-p75)[¥]	24 (20-25)	16 (10.5-19.5)	4 (0.5-12)	**<0.001**[a]
Birth weight (g), median (p25-p75)[¥]	3050 (2715-3295)	2850 (2335-3255)	2340 (987.5-2955)	**0.005**[d]
Route of delivery, n (%)[¥]				
Spontaneous vaginal delivery	24 (25.5)	14 (33.3)	8 (50)	0.126
Cesarean section	70 (74.5)	28 (66.7)	8 (50)	
5th minute Apgar <7 n (%)[¥]	15 (15.9)	10 (23.8)	2 (12.5)	0.420
Admission to NICU, n (%)[¥]	19 (20.)	13 (30.9)	9 (56.2)	**0.008**[d]
Neonatal infection, n (%)[¥]	6 (6.3)	6 (14.2)	3 (18.7)	0.163
Take-home baby rate, n (%)	94 (91.2)	40 (88.8)	16 (64)	**0.001**[b]

p25-p75: 25th and 75th percentiles, NICU: Neonatal intensive care unit, PPROM: Preterm prelabor rupture of membranes
[¥]Analyses were performed after exclusion of cases with abortion
Pairwise comparison revealed significant differences between;
[a]All groups
[b]Physical examination indicated group and others
[c]History indicated and other two groups
[d]Physical examination indicated and history indicated groups

We performed further statistical analyses regarding the suture material in each indication group (Table 3). There were no significant differences in obstetric and neonatal outcomes between suture material groups by indication group. However, the take-home baby rate was slightly higher for the Prolene group compared to the Mersilene group in PEICC, although this difference was not significant (75% vs. 44.4%; p=0.127) (Table 4).

Table 3. Demographic features and clinical characteristics of the patient groups based on suture material

Variables	Prolene suture group (n=105)	Mersilene tape group (n=68)	p value
Maternal age, median (p25-p75)	32 (26-36)	33 (30-35.5)	0.559
Gravidity, median (p25-p75)	3 (2-4)	3 (2-4)	0.489
Parity, median (p25-p75)	1 (0-2)	0 (0-1)	0.614
Previous miscarriage, median (p25-p75)	1 (0-2)	1 (0-3)	**0.115**
Number of living children, median (p25-p75)	0 (0-1)	0 (0-1)	0.270
Multiparous, n (%)	69 (67.6)	32 (47.1)	0.015
Gestational week of cerclage procedure, median (p25-p75)	14 (13-20)	15 (13-20)	0.439
Cerclage indication, n (%)			0.867
History indicated	63 (60)	40 (58.8)	
Ultrasound indicated	23 (21.9)	19 (27.9)	
Physical examination indicated	16 (18.1)	9 (13.2)	
Hospitalization after cerclage, n (%)	48 (45.7)	28 (41.1)	0.557
Duration of hospitalization after the cerclage procedure (days), median (p25-p75)	0 (0-1)	0 (0-1)	0.667
Procedure related pregnancy loss, n (%)	9 (8.8)	6 (8.8)	0.954
Pregnancy outcome, n (%) Miscarriage Delivery	 12 (11.4) 93 (88.6)	 9 (13.2) 59 (86.8)	0.772
Preterm labor¥	40 (43)	19 (32.2)	0.183
PPROM, n (%)¥	18 (19.3)	8 (13.5)	0.355
Gestational week at delivery groups¥, n (%)			0.234
<34th weeks	17 (18.2)	11 (18.6)	
34th-<37th weeks	23 (24.7)	8 (13.5)	
≥37th weeks	53 (56.9)	40 (67.9)	
Gestational week at delivery, median (p25-p75)¥	37 (32-38)	37 (33-38)	0.912
Duration between cerclage procedure and delivery (weeks), median (p25-p75)¥	21 (13-24)	19.5 (13-24)	0.872
Birthweight (g), median (p25-p75)¥	2910 (2430-3270)	3000 (2590-3250)	0.739
Route of delivery, n (%)¥			0.958
Spontaneous vaginal delivery	28 (30.1)	18 (30.5)	
Caesarean section	65 (69.9)	41 (69.5)	
5th minute Apgar <7 n (%)¥	14 (15.1)	13 (22.0)	0.273
Admission to NICU, n (%)¥	25 (26.8)	16 (27.1)	0.925
Neonatal infection, n (%)¥	11 (11.8)	4 (6.7)	0.309
Take-home baby rate, n (%)	91 (86.6)	59 (86.7)	0.985

p25-p75: 25th and 75th percentiles, NICU: Neonatal intensive care unit, PPROM: Preterm prelabor rupture of membranes
¥Analyses were performed after exclusion of cases with abortion

Table 4. Comparison of obstetric and neonatal outcomes according to the suture materials and indications

	History indicated cerclage group		
Variables	**Prolene suture group (n=63)**	**Mersilene tape group (n=40)**	**p value**
Gestational week of cerclage procedure, median (p25-p75)	13 (12-14)	14 (13-14)	0.027
Hospitalization after cerclage, n (%)	20 (31.7)	10 (25)	0.463
Duration of hospitalization after the cerclage procedure (days), median (p25-p75)	0 (0-1)	0 (0-0.5)	0.263
Procedure related pregnancy loss, n (%)	2 (3.1)	0 (0)	0.255
Pregnancy outcome, n (%) Miscarriage Delivery	 6 (9.5) 57 (90.5)	 3 (7.5) 37 (92.5)	0.723
Preterm labor, n (%)¥	20 (35.1)	7 (18.9)	0.091
PPROM, n (%)¥	7 (12.2)	3 (8.1)	0.522
Gestational week at delivery groups, n (%)¥			0.226
<34th weeks	7 (12.2)	3 (8.1)	
34th-<37th weeks	13 (22.8)	4 (10.8)	
≥37th weeks	37 (64.9)	30 (81.1)	
Gestational week at delivery, median (p25-p75)¥	37 (36-38)	37 (37-38)	0.646
Duration between cerclage procedure and delivery (weeks), median (p25-p75)¥	24 (22-25)	23 (21-25)	0.152
Birthweight (g), median (p25-p75)¥	3015 (2657.5-3285)	3100 (2797.5-3300)	0.673
Route of delivery, n (%)¥			0.452
Spontaneous vaginal delivery	13 (22.8)	11 (29.7)	
Cesarean section	44 (77.2)	26 (70.3)	
5th minute Apgar <7, n (%)¥	9 (15.7)	6 (16.2)	0.956
Admission to NICU, n (%)¥	12 (21)	7 (18.9)	0.801
Neonatal infection, n (%)¥	5 (8.7)	1 (2.7)	0.240
Take-home baby rate, n (%)	57 (90.5)	37 (92.5)	0.723
	Ultrasound indicated cerclage group		
	Prolene suture group (n=26)	**Mersilene tape group (n=19)**	**p value**
Gestational week of cerclage procedure, median (p25-p75)	20 (18-22)	20 (17-22)	0.951
Hospitalization after cerclage, n (%)	13 (50)	10 (52.6)	0.862
Duration of hospitalization after the cerclage procedure (days), median (p25-p75)	0.5 (0-1.25)	1 (0-1)	0.488
Procedure related pregnancy loss, n (%)	2 (7.6)	1 (5.2)	0.747
Pregnancy outcome, n (%) Miscarriage Delivery	 2 (7.6) 24 (92.4)	 1 (5.2) 18 (94.7)	
Preterm labor¥	14 (58.3)	9 (50)	0.551
PPROM, n (%)¥	5 (20.8)	4 (22.2)	0.914
Gestational week at delivery groups, n (%)¥			0.729
<34th weeks	6 (25)	5 (27.7)	
34th-<37th weeks	8 (33.3)	4 (22.3)	
≥37th weeks	10 (42.6)	9 (50)	

Table 4. Continued

	History indicated cerclage group		
Variables	**Prolene suture group (n=63)**	**Mersilene tape group (n=40)**	**p value**
Gestational week at delivery, median (p25-p75)¥	36 (31.25-37.75)	36.5 (33-38)	0.823
Duration between cerclage procedure and delivery (weeks), median (p25-p75)¥	15.5 (10.75-19.5)	16 (12.75-20)	0.899
Birthweight (g), median (p25-p75)¥	2910 (1757.5-3295)	2845 (2402.5-3209)	0.755
Route of delivery, n (%)¥			0.508
Spontaneous vaginal delivery	9	5	
Cesarean section	15	13	
5th minute Apgar <7 n (%)¥	4 (16.6)	6 (33.3)	0.209
Admission to NICU, n (%)¥	7 (29.1)	6 (33.3)	0.773
Neonatal infection, n (%)¥	4 (16.6)	2 (11.1)	0.611
Take-home baby rate, n (%)	22 (84.6)	18 (94.7)	0.286
	Physical examination indicated cerclage group		
	Prolene suture group (n=16)	**Mersilene tape group (n=9)**	
Gestational week of cerclage procedure, median (p25-p75)	23.5 (19.25-24.75)	20 (18.5-22.5)	0.417
Hospitalization after cerclage, n (%)	15 (93.7)	8 (88.8)	0.667
Duration of hospitalization after the cerclage procedure (days), median (p25-p75)	3 (1-7)	4 (2-12)	0.397
Procedure related pregnancy loss, n (%)	5 (31.2)	5 (55.5)	0.234
Pregnancy outcome, n (%) Miscarriage Delivery	 4 (25) 12 (75)	 5 (55.5) 4 (44.4)	0.127
Preterm labor, n (%)¥	6 (50)	3 (75)	0.383
PPROM, n (%)¥	6 (50)	1 (25)	0.383
Gestational week at delivery groups, n (%)¥			0.319
<34th weeks	4 (33.3)	3 (75)	
34th-<37th weeks	2 (16.6)	0	
≥37th weeks	6 (50)	1 (25)	
Gestational week at delivery, median (p25-p75)¥	35.5 (27-37)	31.5 (27-36)	0.585
Duration between cerclage procedure and delivery (weeks), median (p25-p75)¥	11 (2.5-16)	10 (6.25-12.25)	0.569
Birthweight (g), median (p25-p75)¥	2515 (987-3030)	1810 (1047-2715)	0.569
Route of delivery, n (%)¥			1.000
Spontaneous vaginal delivery	6 (50)	2 (50)	
Cesarean section	6 (50)	2 (50)	
5th minute Apgar <7, n (%)¥	1 (8.3)	1 (25)	0.383
Admission to NICU, n (%)¥	6 (50)	3 (75)	0.383
Neonatal infection, n (%)¥	2 (16.6)	1 (25)	0.712
Take-home baby rate, n (%)	12 (75)	4 (44.4)	0.127

p25-p75: 25th and 75th percentiles, NICU: Neonatal intensive care unit, PPROM: Preterm prelabor rupture of membranes
¥Analyses were performed after exclusion of cases with abortion

Table 5. Comparison of take home baby rates based on suture materials in each indication group

	History indicated cerclage group (n=103)	Ultrasound indicated cerclage group (n=43)	Physical examination indicated group (n=25)
Prolene suture Mersilene suture	57/63 (90.5) 37/40 (92.5) p=0.723	22/26 (84.6 %) 18/19 (94.7 %) p=0.286	12/16 (75) 4/9 (44.4) p=0.127

Discussion

Cervical insufficiency is a devastating complication which leads to second trimester pregnancy loss (12). Making the correct diagnosis for cervical insufficiency is crucial for deciding if CC surgery would be appropriate. Choosing the appropriate candidates for CC is the key element for achieving favorable obstetric outcomes (13). However, there have been ongoing debates on the optimal technique, suture material, patient selection criteria and gestational week for CC in order to get better results (7,14-16). For these reasons, experiences of tertiary reference centers may be important to enhance knowledge in this field.

In the present study, the obstetric outcomes were significantly affected by cerclage indications. PEICC had worse outcomes compared to HICC and UICC groups for most of the study parameters. In the pregnant women who underwent PEICC, the CC procedures were performed at later gestational weeks, almost all of the patients were hospitalized after the procedure, procedure related pregnancy loss rate was significantly higher, premature delivery and PPROM rate and admission rate to NICU were significantly higher, the duration between CC procedure and delivery was shorter and take-home baby rate was lower. These findings are largely consistent with the current literature. One significant concern related to PEICC cases is the lack of knowledge about the effect of duration of amniotic membrane exposure to the vaginal environment. This duration may lead to increased rates of infection and inflammation and may be a major contributor to adverse outcomes in this indication group. Despite the known risks and relatively high complication rates, the overall take-home baby rate of 64% in this high-risk cohort supports the continued use of cerclage in selected patients with cervical dilatation, suggesting that the potential benefits may outweigh the risks in appropriately counseled cases. We observed that previous studies reported similar perinatal and obstetric outcomes for HICC and UICC groups (17,18). Moreover, Drassinower et al. (19) reported similar rates of perioperative complications for HICC (n=198) and UICC (n=89) in their retrospective observational study. These results were also confirmed by meta-analysis by Chen et al. (20). Our findings were also consistent with Chen et al. (20). However, despite significantly worse results in PEICC group, CC has also been associated with favorable outcomes without increasing maternal morbidity compared to expectant management in this group of patients (21). Thus, despite having significantly worse results than other indications, PEICC still improves perinatal and neonatal outcomes compared to expectant management.

The threshold for HICC varies between major international guidelines and highlights the lack of global consensus on cervical insufficiency diagnosis and management (12,14,22). The definition used in the present study was based on American College of Obstetricians and Gynecologists and Society of Obstetricians and Gynaecologists of Canada Criteria, which allow for consideration of cerclage after a single characteristic second-trimester loss.

We have also compared the obstetric outcomes according to the suture material used and found no significant difference between groups. The selection criteria for the appropriate suture material seem to be operative dependent and the optimal material remains a matter of debate. Braided sutures are favored by physicians mostly due to their physical strength, while non-braided sutures are preferred due to a theoretical decreased surgical infection risk (23,24). More recent studies about this topic have also reported conflicting results. Stafford et al. (16) reported similar outcomes for different suture materials (monofilament, braided, or 5 mm tape cerclages) in their retrospective study consisted of 109 CC procedures. In contrast, Daigle et al. (25) evaluated the outcomes of 34 CC procedures according to suture materials (16 braided, 12 monofilament and 6 5-mm tape sutures). They found that the gestational week at delivery was higher in patients operated with monofilament sutures and concluded that this material was superior to braided sutures. However Sweeney et al. (26) found that the rate of spontaneous preterm delivery was significantly higher in patients managed with monofilament sutures in HICC group. Although there is lack of consensus between retrospective studies, the randomized C-STICH trial concluded that monofilament suture materials did not improve obstetric outcomes (11). This study's conclusion is significant as it is the only randomized trial in the literature with a large number of patients. Our results were consistent with those of the C-STICH trial and we believe that choice of suture material does not significantly change the obstetric outcome. It should be noted that the C-STICH trial consisted of HICC and UICC

patients, but not PEICC patients. Our study uniquely contributes to the literature by providing one of the most comprehensive single-center comparisons of CC outcomes across all indication groups and suture types, including detailed subgroup analyses that highlight nuanced outcome patterns.

Study limitations

The main strengths of this study were relatively high number of cases included, high number of variables and the opportunity to make the comparison of two different suture materials in terms of perinatal outcomes. In addition, subgroup analyses were conducted to compare suture materials across all indication subgroups for more comprehensive results. However, it is important to note that the study was limited by its retrospective design and single-center experience. As this was a retrospective analysis of all eligible cases over two decades, no a priori power calculation was performed. However, the sample size was sufficient to detect significant differences across key variables, as demonstrated in our statistical analysis. Another limitation is the long study period of nearly 20 years, during which clinical practices and patient characteristics might have evolved. However, all procedures were conducted at a single tertiary center by the same specialist team following consistent protocols, which we believe minimized temporal variability. No adjustment for multiple comparisons was performed, which may increase the risk of type-I error. However, results were interpreted cautiously and supported by clinical consistency. Multivariate analysis was not performed, which may limit confounder control; however, groups were based on clear clinical indications and had comparable baseline characteristics. Furthermore, potential confounding variables were not adjusted for using multivariate models, which is a notable limitation. While our subgroup comparisons were based on predefined clinical indications and groups were generally similar in baseline characteristics, we acknowledge that residual confounding may still be present. Future studies with prospective designs and multivariate modeling are warranted to strengthen the findings.

Conclusion

Perinatal outcomes, with preterm birth rate as the primary outcome, significantly varied depending on the indication for CC. The PEICC group had the highest rate of preterm birth and the poorest perinatal outcomes overall. Conversely, the type of suture material (braided or monofilament) did not significantly affect obstetric or neonatal outcomes, and the choice was left to the discretion of the operating surgeon. These findings emphasize that the indication for cerclage is a more critical determinant of perinatal prognosis than the suture material used.

Ethic

Ethics Committee Approval: *This study was approved by the Hacettepe University Health Sciences Research Ethics Committee (approval number: 2023/03-08, date: 19.09.2023).*

Informed Consent: *A comprehensive informed consent was provided for all patients including estimated success rates, procedure related complications and possible neonatal adverse outcomes.*

Footnotes

Author Contributions: *Surgical and Medical Practices: U.K., E.F., Ö.D., Concept: U.K., E.F., Ö.D., Design: U.K., E.F., Ö.D., Data Collection or Processing: U.K., E.F., A.Ç.B., İ.A., E.A.K., Ö.D., Analysis or Interpretation: U.K., İ.A., E.A.K., Literature Search: E.F., A.Ç.B., Ö.D., Writing: U.K., E.F., Ö.D.*

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Comparison of laparoscopic and laparotomic Burch colposuspension in the treatment of stress urinary incontinence

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Abstract

Objective: To evaluate patients who underwent Burch colposuspension due to stress-type urinary incontinence (SUI) in terms of laparoscopic (L/S) and laparotomy (L/T) approaches.

Material and Methods: Women aged 40-70 years who were admitted to our hospital with symptoms of SUI between 2017 and 2024, who underwent surgical treatment for SUI, and who met the inclusion criteria were included. The women were divided into two groups, those who received L/T and those who underwent L/S Burch colposuspension. To assess the impact of SUI on quality of life, several quality-of-life questionnaires, including the urinary distress inventory (UDI-6), the incontinence impact questionnaire (IIQ-7), the short-form-36 (SF-36) physical component summary, and the mental component summary (MCS), were evaluated. Post-operative pain was assessed with a Visual Analog Scale (VAS).

Results: The cohort consisted of 74 patients. The surgical time and estimated blood loss in the L/S group was significantly lower than in the L/T group (both $p<0.001$). The sixth and 48th-hour VAS score in the L/S group was significantly lower than in the L/T group (both $p<0.001$). There was a significant decrease in UDI-6 and IIQ-7 score in patients who underwent L/S-Burch colposuspension and L/T-Burch colposuspension at the 6th-month follow-up ($p<0.001$ and $p<0.001$, respectively). At the sixth-month follow-up, the SF-36 MCS score was significantly lower in the L/S group compared with the L/T group ($p=0.014$).

Conclusion: In our study, the results of Burch colposuspension methods were consistent with the literature. L/S-Burch colposuspension is superior in terms of surgical time, blood loss, hospital stay, pain management, and recovery time. The significant decrease in UDI-6 and IIQ-7 scores at the 6-month follow-up shows that both methods provide improvement in urinary incontinence symptoms and increase quality of life. [J Turk Ger Gynecol Assoc. 2025; 26(3): 190-4]

Keywords: Burch colposuspension, laparoscopy, laparotomy, stress urinary incontinence

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Introduction

Stress-type urinary incontinence (SUI) is a common health problem among women and negatively affects quality of life (QoL) (1). Surgical treatment offers an effective solution in SUI cases that do not respond to conservative methods. In this context, Burch colposuspension has been preferred as a procedure with proven reliability and effectiveness for many years (2). Traditionally this procedure has been performed via laparotomy (L/T). However, Burch colposuspension can now be performed using minimally invasive methods with the development of laparoscopic (L/S) techniques. Burch colposuspension, performed either through an open or a L/S approach, is an effective surgical treatment for SUI (3). The advantages of L/S surgery, such as smaller incisions, less postoperative pain, faster recovery time and shorter hospital stay, have increased the preference for this method (4). However, the technical difficulties of the L/S approach and the length of the surgical learning curve make it important to compare its effectiveness and safety with the L/T method (5). L/T surgery is still preferred by some surgeons because it offers a wider field of view and requires relatively less experience. Evaluation of the advantages and disadvantages of L/S and L/T Burch colposuspension procedures may contribute to determining the optimal approach in the surgical treatment of SUI (6). Thus, the aim of the present study was to evaluate and compare patients who underwent Burch colposuspension for SUI using either the L/S or L/T approaches.

Material and Methods

This study was a retrospective, observational study. This study was approved by the Başkent University Rectorate Medical and Health Sciences Research Board (approval number: KA25/70, date: 10.04.2025). The study complied with the Helsinki Declaration and informed consent was obtained from all patients. Women aged 40-70 years who were admitted to our hospital with symptoms of SUI between 2017 and 2024, who underwent surgical treatment for SUI, and who met the inclusion criteria were included. The women were divided into two groups, those who received L/T and those who received L/S Burch colposuspension. Classified as L/S-Burch colposuspension surgery (group 1) and L/T-Burch colposuspension surgery (group 2). In patient selection, previous pelvic surgery, active pelvic infection, medical treatment history in the preceding six months, neurogenic bladder, history of malignancy and current pregnancy were considered as exclusion criteria. All surgeries were performed by experienced pelvic surgeons and the same surgical protocols were followed. The presence of preoperative SUI in all women participating in the study was confirmed from patient files. Anamnesis, physical examination, cystourethroscopy and urinalysis data of all women were evaluated retrospectively. Physical examinations included bimanual pelvic examination and focused neurologic examinations. SUI was defined as the involuntary loss of urine through the urethra attributable to a sudden increase in intra-abdominal pressure. All patients were evaluated for the type of incontinence, presence and degree of cystocele, rectocele, enterocele, and other pelvic floor abnormalities, such as uterine hypermobility. All data, including age, parity, body mass index (BMI), menopausal status, hormone replacement status, delivery type, incontinence type, concomitant diseases, surgical time, intraoperative blood loss, intraoperative fluid requirements, preoperative and postoperative hematocrit, postoperative analgesic requirements, length of hospital stay, and complications, were obtained from patient records. Exclusion criteria were: history of SUI surgery; intrinsic sphincter deficiency in SUI; urinary retention; neurogenic bladder; suspected malignancy; urge incontinence only; chronic cystitis; pelvic inflammatory diseases; urinary tract infection; use of anticoagulant drugs and/or anti-psychiatric drugs; and coagulation disorders.

Visual Analog Scale (VAS) scores were recorded six and 48 hours after the procedure to assess postoperative pain. On the VAS scale, 0 represents no pain and 10 represents the worst conceivable pain. Dyspareunia was scored by participants on a range of 0 to 10 (7). In the clinical examination, cough stress test data were evaluated during the sixth month postoperative follow-up to evaluate the response to treatment. In addition, at the sixth month follow-up, the urinary distress inventory (UDI-6) and incontinence impact questionnaire (IIQ-7) data were examined to evaluate the subjective response to treatment (8). The short-form-36 (SF-36) QoL questionnaire was used to evaluate baseline and six months postoperative subjective QoL for the patients (9). This form compares eight scales that can be combined into two summary measures assessing physical and mental health. These are the physical component summary (PCS) and mental component summary (MCS), respectively. In addition, the SF-36 has a general health question (excellent, very good, good, fair, and poor). Only the summary scales and the general health question are reported for the present study (10). Lower scores using the SF-36 questionnaire indicate better general, physical, and mental health. These instruments assess symptom distress and life impact of urinary incontinence, respectively. The Genitourinary Treatment Satisfaction Scale (GUTSS) was used to evaluate satisfaction with the surgery at the sixth month postoperative follow-up (10). The GUTSS consists of 10 items on two scales measuring satisfaction with care and outcome. The scale range is 0-32, with higher scores indicating greater satisfaction.

Statistical analysis

Statistical analysis was performed using SPSS, version 26.0 (IBM Inc., Armonk, NY, USA). The normality of data distribution was measured using the Kolmogorov-Smirnov test. Quantitative data are reported as mean ± standard deviation. Numbers (n) and percentages (%) were used for describing categorical data. The independent samples t-test was used to compare paired groups, the matched test was used to ascertain the changes that occurred before and after the treatment, and the chi-square test was used to compare qualitative data. The results were evaluated at a 95% confidence interval so a p-value of <0.05 was considered to indicate statistical significance.

Results

A total of 74 women were included with a mean age of 49.58±7.16 years, and mean BMI of 25.57±4.45 kg/m^2. The mean parity of the women was 3.05±1.12, and the mean gravidity was 3.61±1.35. No significant difference was found between the L/S group (n=34) and the L/T group (n=40) in terms of demographic or obstetrics characteristics (Table 1).

Several variables were significantly improved in the L/S group compared to the L/T group (Table 2). These included operation time, blood loss, duration of hospital stay, sixth hour and 48th hour VAS scores, and time to return to normal activity (all p<0.001 except for duration of hospital stay when p=0.036).

There was a significant decrease in UDI-6 scores in patients who underwent L/S-Burch colposuspension and L/T-Burch colposuspension at the 6th-month follow-up (p<0.001 and p<0.001, respectively). There was also a significant decrease in IIQ-7 scores in patients who underwent L/S-Burch colposuspension and L/T-Burch colposuspension at the sixth-month follow-up (p<0.001 and p<0.001, respectively). However, there was no significant baseline to follow-up improvement in general health. There was a significant increase in SF-36 PCS scores in patients who underwent either L/S-Burch colposuspension or L/T-Burch colposuspension at the sixth-month follow-up (p=0.014 and p=0.046, respectively). At baseline, the SF-36 MCS score was significantly lower (43.26±10.18) in the L/S-Burch colposuspension group compared with the L/T-Burch colposuspension group (47.38±10.36) (p=0.018). At the sixth-month follow-up, the SF-36 MCS score remained significantly lower (43.68±10.26) in the L/S-Burch colposuspension group compared with the L/T-

Table 1. Comparison of demographic and obstetric characteristics of the participants

	L/S-Burch colposuspension n=34	L/T-Burch colposuspension n=40	p-value
Age (year)	49.76±7.38	49.44±6.98	0.82
BMI (kg/m^2)	25.62±4.58	25.52±4.34	0.84
Gravidity	3.68±1.42	3.56±1.32	0.56
Parity	3.06±1.08	3.04±1.15	0.62
Smoking, n (%)	16 (47%)	20 (50%)	0.36
*Type of delivery, n (%)			0.32
NSVD	27 (79.4%)	33 (82.5%)	
C/S	7 (20.6%)	7 (17.5%)	

Data are mean ± SD or n (%) unless otherwise speciified
BMI: Body mass index, NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section, SD: Standard deviation, L/S: Laparoscopic, L/T: Laparotomy

Table 2. Comparison of the surgical and postoperative characteristics of the participants

	L/S-Burch colposuspension n=34	L/T-Burch colposuspension n=40	p-value
Operation time (min)	94.38±11.46	62.18±12.58	<0.001
Estimated blood loss (mL)	74.26±21.58	108.58±20.52	<0.001
Hospital stays (days)	2.08±0.88	2.56±0.78	0.036
6th hour VAS (pain)	5.12±0.76	7.22±0.82	<0.001
48th hour VAS (pain)	3.12±0.56	5.82±0.64	<0.001
Return to normal activity time (days)	18.26±2.36	25.32±3.28	<0.001

Data are mean ± SD or n (%) unless otherwise speciified
VAS: Visual Analog Scale, min: Minutes, SD: Standard deviation, L/S: Laparoscopic, L/T: Laparotomy

Burch colposuspension group (47.88±10.42) (p=0.014). No significant difference was found between the groups in terms of GUTSS at the sixth-month follow-up (Table 3).

Discussion

Although there are many published studies about Burch colposuspension, there are limited comprehensive evaluations of L/S-Burch versus L/T-Burch procedures in terms of patient satisfaction in the postoperative period. The findings of the present study showed that both methods effectively reduced urinary incontinence symptoms and improved patients' QoL. However, the L/S method was found to be superior to the L/T method in terms of surgical time, estimated blood loss, length of hospital stay, and postoperative pain management, supporting the findings of Dean et al. (6) who showed a trend toward fewer perioperative complications, less postoperative pain, and shorter hospital stay for L/S compared with open colposuspension. There was no significant difference in the reported short and long-term subjective recovery rates of the two procedures. We also observed no significant differences in postoperative evacuation dysfunction or perioperative complications. There was a significantly longer surgical time and hospital stay for L/S colposuspension.

The minimally invasive technique used in the L/S approach is seen as one of the main advantages of this method. In addition, patients are able to return to their daily activities more quickly following L/S surgery supports the benefits of this method in terms of patient comfort and satisfaction. In the literature no significant difference was found between the groups in terms of surgical time. However, intraoperative blood loss and postoperative analgesic requirements were lower in the L/S group than in the L/T group. The duration of hospital stay was also significantly shorter in the L/S group. Similarly, Obaid et al. (11) reported that L/S-Burch colposuspension provided advantages, such as shorter hospital stay, less estimated blood loss, less postoperative pain, and faster recovery time compared with L/T-Burch colposuspension for the treatment of SUI. However, in contrast to the present study, the surgical time was found to be longer in the L/S method (12). The significant decrease in UDI-6 and IIQ-7 scores in both groups at the 6th-month follow-up indicated that both methods improved urinary incontinence symptoms and improved patients' QoL.

Ünal and Karadeniz (12) found no significant differences between the groups in terms of subjective recovery rates (UDI-6 and IIQ-7) in the postoperative period of L/S and L/T-Burch colposuspension surgeries (13). The SF-36 PCS showed a significant increase in both groups. However, the SF-36 MCS, which was lower at the beginning in the L/S method, was also lower at six months compared with the L/T method. This suggests that psychological recovery after L/S surgery may progress more slowly and should be evaluated in more detail. In

Table 3. Comparison of intergroup and intragroup results before and after treatment

		L/S-Burch colposuspension n=34	L/T-Burch colposuspension n=40	p-value
UDI-6	Baseline 6 months later	51.16±18.92 24.86±11.62 p<0.001***	50.32±19.26 25.12±10.92 p<0.001***	0.68** 0.72**
IIQ-7	Baseline 6 months later	49.82±19.84 24.12±10.71 p<0.001***	49.52±19.52 23.82±11.12 p<0.001***	0.84** 0.78**
General health	Baseline 6 months later	2.82±1.12 2.71±1.03 p=0.11***	2.42±1.21 2.32±1.06 p=0.08***	0.016** 0.012**
SF-36 PCS	Baseline 6 months later	44.26±11.84 47.36±10.92 p=0.014***	44.42±11.78 47.24±10.68 p=0.046***	0.76** 0.82**
SF-36 MCS	Baseline 6 months later	43.26±10.18 43.68±10.26 0.76***	47.38±10.36 47.88±10.42 0.82***	0.018** 0.014**
GUTSS (median-IQR)	6 months later	28.5±6.8	28.1±7.2	0.56**

Data are mean ± SD or n (%) unless otherwise speciified
**Independent Samples t-test, ***Match t-test, UDI-6: Urinary distress inventory, IIQ-7: Incontinence impact questionnaire, SF-36 PCS: Physical component summary, SF-36 MCS: Mental component summary, GUTSS: Genitourinary Treatment Satisfaction Scale, IQR: Interquartile range, SD: Standard deviation, L/S: Laparoscopic, L/T: Laparotomy, SF-36: Short-form-36

the study by Carey et al. (13), at baseline, the L/T group reported significantly better general health and better mental health by SF-36 compared with the L/S group. The baseline differences in general health between the L/T and L/S groups were maintained at follow-up. In the present study, no significant differences were found between the groups in terms of GUTSS scores at the sixth-month follow-up. These results show that both methods have similar effects on general satisfaction and lower urinary tract symptoms. Carey et al. (13) also used GUTSS to assess their cohort and reported that scores were high in both groups in terms of satisfaction with treatment results at the sixth month follow-up, and no difference was found between the treatment groups.

Study limitations

The main limitation of our study is that it was retrospective, and only the post-treatment 6th-month data of all patients in the surgical treatment groups were available. Another limitation was that the data on the long-term effectiveness of the treatment methods within and between groups are not yet available. When the cost difference between the two surgical methods was compared, although it was higher in the L/S group, cost-effectiveness could not be evaluated as a factor due to its retrospective nature. The strengths of this study are the use of various QoL questionnaires (UDI-6, IIQ-7, PCS, and MCS) and the assessment of how treatment effects affect symptom control and the patient's overall QoL.

Conclusion

The present study compared the short- and mid-term clinical results of L/S and L/T-Burch colposuspension methods. The findings were consistent with the existing literature. L/S-Burch colposuspension was superior to the L/T method in terms of surgical time, blood loss, hospital stay, pain management, and recovery time. The significant decrease in UDI-6 and IIQ-7 scores in both groups at the six-month follow-up showed that both methods provided improvement in urinary incontinence symptoms and increased the QoL of all patients. However, prospective studies are needed to evaluate long-term outcomes for both procedures with larger patient groups.

Ethics

Ethics Committee Approval: *This study was approved by the Başkent University Rectorate Medical and Health Sciences Research Board (approval number: KA25/70, date: 10.04.2025).*

Informed Consent: *The study complied with the Helsinki Declaration and informed consent was obtained from all patients.*

Footnotes

Author Contributions: *Surgical and Medical Practices: U.A., M.U.M., Concept: M.E.P., Design: B.Ö., Data Collection or Processing: U.A., Analysis or Interpretation: U.A., Literature Search: U.A., Writing: U.A.*

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Optimal leading follicle size for final oocyte maturation in POSEIDON group 3 and 4 poor responders undergoing assisted reproductive technology cycles

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Abstract

Objective: The aim of this retrospective cohort study was to evaluate the relationship between leading follicle size at the time of human chorionic gonadotropin (hCG) trigger and live birth rates in Patient-Oriented Strategies Encompassing Individualised Oocyte Number (POSEIDON) groups 3 and 4 undergoing assisted reproductive technology cycles using a gonadotropin releasing hormone (GnRH) antagonist protocol. The objective was to identify the optimal leading follicle size for maximizing live birth outcomes in this challenging patient population.

Material and Methods: This retrospective cohort study included POSEIDON groups 3 and 4 poor responders aged 20-42 years undergoing intracytoplasmic sperm injection with GnRH antagonist protocol between January 2015 and July 2021. Patients were categorized based on the occurrence of premature ovulation. The primary outcome measures were number of oocytes retrieved, number of metaphase II (MII) oocytes, MII oocyte ratio and follicle oocyte index (FOI). These outcomes were compared across different leading follicle size categories at the time of hCG trigger.

Results: Among the 294 subjects included, 47 (16.2%) had premature ovulation between the trigger and oocyte pick-up days. The mean size of the leading follicle on the day of trigger was significantly higher in the premature ovulation group (19.8±2.4 mm vs.18.7±2 mm, respectively; $p<0.001$). Multivariate logistic regression analyses identified baseline luteinizing hormone [odds ratio (OR) 1.144, 95% confidence interval (CI) 1.052-1.243; $p=0.002$], number of follicles >11 mm on the day of trigger (OR 0.580, 95% CI 0.438-0.767; $p<0.001$), and leading follicle size (OR 1.361, 95% CI 1.130-1.641; $p=0.001$) as independent predictors of premature ovulation. The FOI and MII/antral follicle count ratios peaked when the leading follicle size was between 16-17 mm.

Conclusion: Individualized triggering based on leading follicle size may provide optimal oocyte retrieval after ovarian stimulation in POSEIDON expected poor responders. While a late trigger may result in premature ovulation, an early trigger may also result in less MII. Triggering when the leading follicle size is between 16.5 and 17 mm may help to prevent these negative outcomes and achieve optimal cycle outcome. [J Turk Ger Gynecol Assoc. 2025; 26(3): 195-203]

Keywords: Assisted reproductive technology, final oocyte maturation, follicle diameter, poor responder, POSEIDON

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Introduction

Poor ovarian responders (PORs) represent a major challenge when undergoing assisted reproductive technology (ART), as they experience a poor fertility outcome, yield low number of oocytes, have an increased risk of premature ovulation and a greater likelihood of cycle cancellation, despite high-dose gonadotropin treatment (1). Gonadotropin-releasing hormone (GnRH) antagonists are useful in PORs to suppress pituitary activity and prevent a premature luteinizing hormone (LH) surge during controlled ovarian stimulation (COS). However, despite GnRH antagonist administration, the occurrence of premature LH surge was reported in approximately 0.34-8.0% of patients (2-4). Cycle management for premature ovulation may involve attempting to retrieve all oocytes by aspirating the free fluid from the posterior cul-de-sac under transvaginal sonographic guidance or switching to intrauterine insemination (IUI) protocol when all follicles are ruptured (5,6). Even with optimal convertion to IUI, these patients were 2.6 times less likely to have a live birth after IUI compared to in vitro fertilization (IVF) (7). When the larger follicles prematurely rupture before oocyte pick-up, the rate of harvesting metaphase II (MII) oocytes will decrease from the remaining smaller follicular pool. In addition, premature progesterone rise may lead to endometrial asynchrony, necessitating cryopreservation of the embryos (5,6). All of these challenges are exacerbated by a scarcity of evidence regarding the ideal leading follicle diameter and the optimal timing for final oocyte maturation.

While some studies have claimed that follicle diameter of ≥16 mm leads to higher pregnancy rates because of optimized growth factors and steroid hormones in the follicular fluid (8-11), other studies have shown no differences between follicle size and embryo quality and/or implantation rate (12,13). In ART cycles, the timing of trigger usually depends on the size of the leading follicle/s, which is generally accepted as >17-18 mm. Early implementation of trigger leads to an early LH surge, thus follicular atresia, and obtaining a lower number of mature oocytes (14). On the other hand, a delayed trigger carries the risk of premature ovulation and oocyte deterioration (14).

The Patient-Oriented Strategies Encompassing Individualised Oocyte Number (POSEIDON) group classification system was introduced to improve pregnancy rates (15). Several suggestions have been made to improve outcome for each sub-group. However, premature LH surge and premature ovulation still remain one of the main challenges, particularly in POSEIDON groups 3 and 4 poor responders. The relationship between the leading follicle size and the risk of premature ovulation and oocyte maturation rate is not yet clear. The aim of the present study was to determine the optimal size of the leading follicle before triggering final oocyte maturation in order to prevent premature ovulation and maximize the mature oocyte rate in POSEIDON groups 3,4.

Material and Methods

In this single-center, retrospective cohort study, data from women in POSEIDON groups 3 and 4 poor responders aged between 20-42 years who underwent intracytoplasmic sperm injection (ICSI) following a GnRH antagonist cycle between January 2015 and July 2021 were reviewed. The study protocol was approved by the Ankara University Ethical Committee for Human Research (approval number: I8-567-21, date: 15.10.2021). All included subjects fulfilled the POSEIDON criteria for the definition of expected POR; antral follicle count (AFC) <5 and/or serum anti-Müllerian hormone level <1.2 ng/mL (15). All data on COS were extracted from patient records and the hospital database, and cycles were categorized into two groups according to occurrence of premature ovulation. Premature ovulation was defined as visualization of rupture of at least one of the leading follicles on the day of oocyte retrieval. The inclusion criteria were fulfilment of the criteria for POSEIDON groups 3 or 4, a starting dose of gonadotropin stimulation of 225-300 IU/day, and body mass index between 20 and 35 kg/m^2. The exclusion criteria were the use of long agonist or natural cycle protocols, progestin-primed ovarian stimulation, presence of any untreated thyroid dysfunction, adrenal disease, or hyperprolactinemia, administration of non-steroidal anti-inflammatory drugs to suppress ovulation or all the above factors.

Before initiation of treatment, all patients underwent vaginal ultrasound examination to eliminate presence of >10 mm follicles on day 2 of the cycle. Baseline hormonal profile was also assessed. Ovarian stimulation was carried out with recombinant follicle stimulating hormone (rFSH) (Gonal-F; Merck-Serono, Geneva, Switzerland) and/or human menopausal gonadotropin (Menopur; Ferring GmbH, Wittland, Kiel, Germany) from the second or third day of the menstrual cycle with an initial dose of 225-300 IU/day. Dose adjustment was performed individually according to ovarian response, which was determined on the basis of serum estradiol levels and ultrasound examination. The maximum dose of rFSH was 375 IU/day. The GnRH antagonist Cetrorelix 0.25 mg/day (Cetrotide; Merck-Serono, Geneva, Switzerland) was initiated on day 6 of stimulation in a fixed manner. All oocyte retrieval procedures were performed under inhalation anaesthesia using a 16-gauge double-lumen oocyte retrieval needle under transvaginal ultrasound guidance 36 hours after the final oocyte trigger by recombinant human chorionic gonadotropin (Ovitrelle 250 micrograms, Merck Serono, Modugno, Italy). The timing of trigger related to the follicle size was performed based upon the experience and preference of the treating physician.

The primary outcome measures were number of oocytes retrieved, number of MII oocytes, MII oocyte ratio and follicle oocyte index (FOI). FOI was calculated as the ratio between the number of oocytes retrieved at oocyte pick-up and the number of antral follicles at the start of stimulation (16). MII oocyte ratios were calculated as MII/AFC and MII/follicles >11 mm on trigger day. In addition, the ratio of oocytes retrieved by number of follicles >11 mm on the day of final oocyte maturation was further calculated.

Statistical analysis

Data analysis was performed using SPSS, version 21.0 (IBM Inc., Armonk, NY, USA). Samples were tested with the Shapiro-Wilk test to determine normality of distribution. The results of this analysis meant that parametric tests were preferred. Continuous variables were compared with Student's t-test and One-Way ANOVA test where appropriate. Categorical variables were compared with chi-square test. Multivariate logistic regression models were created to determine independent predictors of premature ovulation in POSEIDON groups 3 and 4 patients undergoing COS. A $p<0.05$ was considered statistically significant. In addition, assuming a non-linear relationship between maximal follicle size on the day of trigger and follicle output parameters, non-linear quadratic curve models are created to estimate the optimal time for triggering.

Results

A total of 456 POSEIDON patients assessed to be in groups 3 and 4 were assessed for eligibility. Among those, 342 patients between 20 and 42 years of age who underwent COS along with GnRH antagonist suppression were included. However, 12 patients were excluded due to untreated thyroid dysfunction or hyperprolactinemia, and 36 patients were excluded due to administration of non-steroidal anti-inflammatory drugs before oocyte retrieval. Thus, 294 patients were included in the final analyses.

Four patients did not respond to COS and cycles were cancelled. Among those who were scheduled for oocyte retrieval, 47 (16.2%) had premature ovulation. Table 1 shows the comparisons between the patients who ovulated prematurely and the controls. In the premature ovulation group, serum FSH and LH levels were significantly higher and AFC was significantly lower when compared to controls (Table 1). The distribution of the POSEIDON groups was similar between the premature ovulation and control groups ($p=0.512$). The mean serum progesterone and LH levels on the day of hCG trigger were significantly higher in the premature ovulation group compared to control subjects (Table 1). The mean size of the leading follicle on the day of hCG trigger was significantly higher in the premature ovulation group than in the control group (19.8±2.4 mm vs. 18.7±2 mm, respectively; $p<0.001$). The mean number of follicles >11 mm on the day of hCG trigger was significantly lower in the premature ovulation group than in the control group (2.5±1.8 vs. 3.6±2, respectively; $p<0.001$).

The cycle outcome parameters in the study and control groups are summarized in Table 2. The mean number of oocytes retrieved and MII oocytes were significantly lower in the premature ovulation group, as well as the rates of oocytes retrieved/AFC, oocytes retrieved per total of >11 mm follicles, MII/AFC, and MII/>11 mm follicles than in the control subjects.

After adjusting for parameters that differed significantly between the premature ovulation cases and controls (baseline FSH, AFC), baseline LH, number of follicles >11 mm on the day of hCG trigger, and leading follicle size were identified as independent determinants for the probability of premature ovulation (Table 3). An increasing number of follicles >11 mm on the day of hCG trigger decreased the likelihood of premature ovulation [odds ratio (OR) 0.580, 95% confidence interval (CI) 0.438-0.767; $p<0.001$]. Increasing size of the leading follicle on the day of hCG trigger increased the likelihood of premature ovulation (OR 1.361, 95% CI 1.130-1.641; $p=0.001$)

Figure 1 illustrates the distribution of premature ovulation among the different sizes of leading follicles on the day of hCG. Premature ovulation was observed when the leading follicle exceeded 16 mm: 10% between 16.1-17 mm, 16.9% between 17.1-18 mm, 25% between 18.1-19 mm, 15% between 19.1-20 mm, and 22.6% above 20 mm.

The FOI and the MII/AFC rate were significantly different between subgroups based on different leading follicle sizes (Table 4). The highest values of FOI, MII/AFC, oocytes retrieved />11 mm follicle, and MII/>11 mm follicle were observed when the leading follicle size was between 16.1-17 mm. Figures 2 and 3 show the non-linear curve estimates for the best outcome in terms of the number of oocytes and MII per AFC and retrieved oocyte and MII per >11 mm follicle. The FOI and MII/AFC rate peaked when the leading follicle sizes were 17.5 mm and 16.5 mm, respectively. In addition, the oocytes retrieved />11 mm follicle and MII/>11 mm follicle rates peaked when the leading follicle sizes were 17.5 mm and 16.0 mm, respectively.

Table 1. Comparison of baseline and cycle parameters between study and control groups

	Premature ovulation n=47	Control n=243	p value
Age, years	35.3±6.2	35.7±5.4	0.736
Body mass index, kg/m²	25.3±3.1	25±2.7	0.544
Baseline estradiol, pg/mL	40.2±23.3	44.3±19	0.273
Baseline progesterone, ng/mL	0.7±0.4	0.7±0.6	0.913
Baseline FSH, mIU/mL	16±8.7	12±5.5	0.004
Baseline LH, mIU/mL	8±5.9	5.6±3.3	0.009
Baseline TSH, mIU/L	2.1±1.2	1.9±0.9	0.347
Baseline Prolactin, ng/mL	13.3±8.5	16.1±11.7	0.107
Baseline AMH, ng/mL	0.4±0.3	0.5±0.9	0.148
Antral follicle count	3.5±2.1	4.2±2.2	0.031
POSEIDON group, n (%) Group 3 Group 4	 15 (31.9) 32 (68.1)	 91 (37.4) 152 (62.6)	0.512
Number of prior IVF attempts	1±1.7	1±1.5	0.868
Duration of stimulation, days	10.8±4.7	9.8±3	0.181
Total dose of gonadotropins, IU	2735±1529	2750±1080	0.947
Serum estradiol/>11 mm follicle on trigger day, pg/mL	262.4±122.5	260.3±171.3	0.073
Serum progesterone on trigger day, ng/mL	0.98±0.43	0.79±0.55	0.020
Serum LH on trigger day, mIU/mL	20.5±18.7	5.4±5.6	<0.001
Leading follicle size on trigger day, mm	19.8±2.4	18.7±2	0.005
Number of follicles >11 mm	2.5±1.8	3.6±2	<0.001
Number of follicles >17 mm	1.4±0.8	1.5±1.1	0.629

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, AMH: Anti-müllerian hormone, IUI: Intrauterine insemination, IVF: In vitro fertilization, MII: Metaphase II, AFC: Antral follicle count, POSEIDON: Patient-Oriented Strategies Encompassing Individualised Oocyte Number. The mean numbers of oocytes retrieved and MII oocytes are significantly lower in the premature ovulation group, as well as the rates of oocyte/AFC, oocyte/>11 mm follicle, MII/AFC, and MII/>11 mmfollicle

Table 2. Comparison of outcome parameters between study and control groups

	Premature ovulation n=47	Control n=243	p value
Number of oocytes retrieved	0.9±1.5	2.8±1.8	<0.001
Number of MII oocytes	0.5±0.9	2±1.7	<0.001
Retrieved oocyte/AFC ratio	0.24±0.34	0.76±0.6	<0.001
Retrieved oocyte/>11 mm follicle ratio	0.28±0.4	0.87±0.58	<0.001
Retrieved oocyte/>17 mm follicle ratio	0.55±0.79	1.93±1.33	<0.001
MII/AFC ratio	0.15±0.27	0.53±0.45	<0.001
MII/>11 mm follicle ratio	0.21±0.39	0.63±0.47	<0.001
MII/>17 mm follicle ratio	0.34±0.59	1.39±1.07	<0.001

AFC: Antral follicle count, MII: Metaphase II

Table 3. Multivariate logistic regression analysis presenting risk factors for premature ovulation

	Odds ratio	95% CI	p value
Baseline serum LH level	1.144	1.052-1.243	0.002
Number of >11 mm follicles on trigger day	0.580	0.438-0.767	<0.001
Leading follicle size	1.361	1.130-1.641	0.001
LH: Luteinizing hormone, CI: Confidence interval			

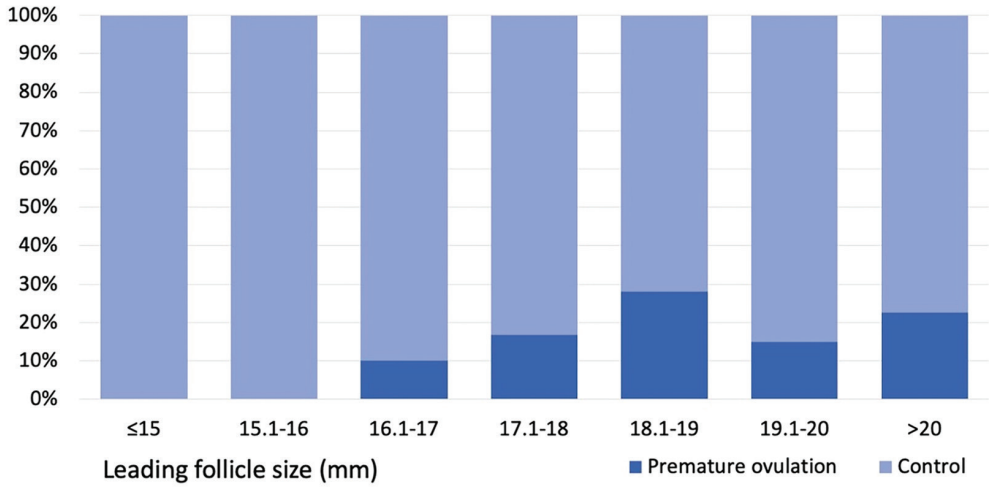

Figure 1. Distribution of premature ovulation cases among different leading follicle sizes on the day of trigger

Table 4. Comparison of outcome parameters between different leading follicle size groups

LFS (mm)	≤15 n=9	15.1-16 n=20	16.1-17 n=30	17.1-18 n=77	18.1-19 n=32	19.1-20 n=60	>20 n=62	p value
Oocyte/AFC	0.17±0.25	0.48±0.24	**0.92±0.54**	0.75±0.55	0.63±0.72	0.64±0.60	0.54±0.55	0.003[a]
Oocyte/>11 mm follicle	0.36±0.45	0.56±0.24	**0.83±0.62**	0.77±0.48	0.66±0.43	0.82±0.66	0.67±0.63	0.120
MII/AFC	0.10±0.15	0.40±0.15	**0.56±0.40**	0.54±0.43	0.31±0.28	0.44±0.47	0.43±0.42	0.012[b]
MII/>11 mm follicle	0.25±0.43	0.50±0.30	**0.57±0.47**	0.57±0.43	0.38±0.31	0.56±0.51	0.54±0.45	0.214

LFS: Leading follicle siz, AFC: Antral follicle count, MII: Metaphase II. [a]The statistical significance stems from the differences between groups ≤15 mm vs. 16.1-17 mm (p=0.010) and groups 16.1-17 mm vs. >20 mm (p=0.039); [b]The statistical significance stems from the differences between groups ≤15 mm vs. 16.1-17 mm (p=0.048) and groups ≤15 mm vs. 17.1-18 mm (p=0.038)

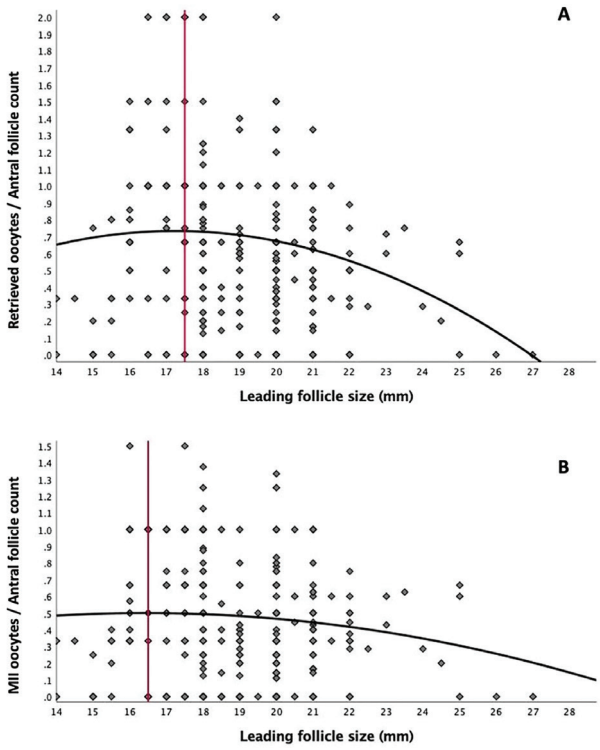

Figure 2. Non-linear quadratic curve estimation for retrieved oocyte and MII oocyte numbers per antral follicle among different leading follicle sizes on the day of trigger. Vertical red lines indicate peak points for tested outcome
MII: Metaphase II

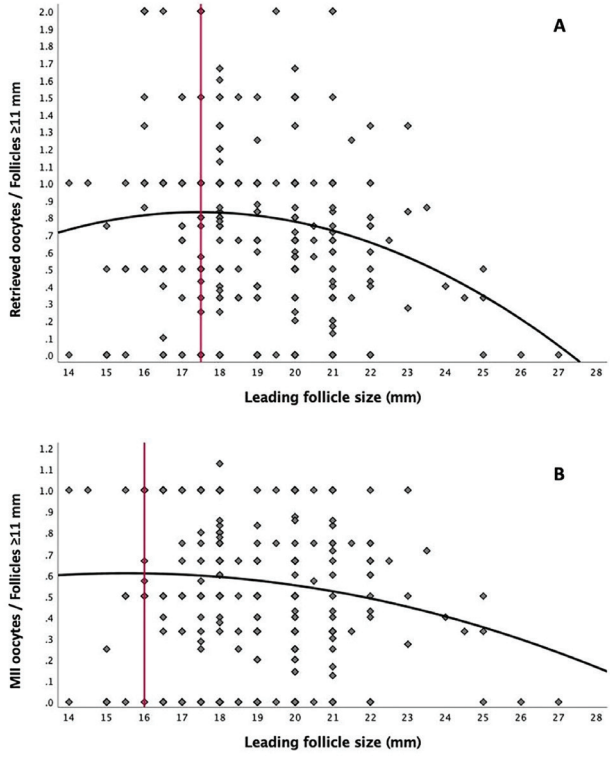

Figure 3. Non-linear quadratic curve estimation for retrieved oocyte and MII oocyte numbers per >11 mm follicle among different leading follicle sizes on the day of trigger. Vertical red lines indicate peak points for tested outcome
MII: Metaphase II

Discussion

The aim of the present study was to investigate the relationship between the leading follicle size on the day of trigger and efficiency of ovarian stimulation cycle by means of premature ovulation rate and oocyte/AFC, MII/AFC ratios in POSEIDON groups 3/4 poor responders. Across the whole study cohort, 16.2% had premature ovulation defined as observing rupture of at least one follicle between trigger day and oocyte pick-up. There were no significant differences between the POSEIDON groups regarding premature ovulation rates. The baseline serum LH level, number of follicles >11 mm on trigger day and leading follicle size were independent predictors for premature ovulation. The optimal follicle diameter to collect MII oocytes at the maximum rate was 16.5-17 mm in POSEIDON 3/4 PORs.

During a COS cycle, a careful frequent measurement of follicles is important in order to obtain the maximum number of mature oocytes and blastocysts (17). Several previous studies have found a relationship between the size of follicles and oocyte maturity, and suggested leading follicle diameters should be between 18 and 24 mm before trigger to obtain optimal MII oocyte and blastocyst numbers (9,10,13,18). Early follicular retrieval to avoid premature ovulation, particularly in patients with low ovarian reserve, can lead to inadequate maturation of the follicles and lower number of mature oocytes (13,19). Rosen et al. (20) suggested that the chances of mature oocyte yield and fertilization rates were significantly lower for 16-18 mm follicles than >18 mm follicles in an unselected IVF population. Similarly, Shapiro et al. (11) have shown that retrieval of follicles 10-12.5 mm size during oocyte retrieval was associated with a significant reduction in the total and MII oocyte retrieval rate. In the same study, follicle size of 19-21.5 mm was associated with the best rates for MII oocytes. Hence, it may be reasonable to extend the duration of stimulation to have a larger follicular pool to obtain more viable embryos (12,20,21). However, patients with low ovarian reserve and/or advanced age have increased risk of premature ovulation, which may result in cycle cancellation (4,11,22,23). Wu et al. (24) showed that an earlier hCG trigger when the leading follicle size was 16 mm and early oocyte retrieval prevents premature luteinization and improves the number and quality of embryos in women >43 years old.

Reichman et al. (3) investigated breakthrough LH surge in GnRH antagonist cycles and found that the risk of premature LH surge and ovulation increased with age in patients with diminished ovarian reserve. These authors found that baseline serum FSH and LH levels were similar between the groups. The largest diameter of two follicles were 17.6 mm and 15.2 mm when the LH surge started in patients who had premature ovulation (3). Our results were in partial agreement with Reichman et al. (3). In our study, higher baseline LH level was an independent risk factor for premature ovulation, which may be the result of investigating a specific population: POSEIDON expected poor responders. We also found that serum LH level on the day of trigger was significantly higher in the premature ovulation group. The mean LH level in this group was approximately 20 mIU/mL indicating the LH surge had already started. There appears to be a fine line between premature ovulation and collecting immature oocytes in poor responders. While infrequent monitoring and late trigger may result in premature ovulation, on the contrary early trigger may result in less MII. In addition, it seems that patients with high baseline LH levels warrant more careful monitoring. The number of follicles responsive to ovarian stimulation was another independent risk factor for premature ovulation in the present study. The fewer the number of follicles >11 mm on trigger day, the greater the risk of premature ovulation. This suggests that the management of POSEIDON expected PORs may be different depending on the ovarian reserve level.

Our results showed that the numbers of retrieved oocytes and MII oocytes were significantly lower in the premature ovulation group. In addition, considering that not all POSEIDON patients who were expected to have a poor response had a uniform ovarian reserve, we attempted to evaluate the ratio of oocytes and mature oocytes obtained per antral follicle rather than the number of oocytes. The non-linear curve estimates showed that the FOI and MII/AFC ratio peaked when the leading follicle sizes were 17.5 mm and 16.5 mm, respectively.

Wu et al. (24) observed that granulosa cell functions including gene expression related to gonadotropin activity, steroidogenesis and apoptosis were all significantly affected by age. These biological changes may imply that intrafollicular growth factors, rather than estrogen per follicle, cause premature ovulation when ovarian reserve is low. Our findings also support this hypothesis because the serum estradiol level per >11 mm follicle on the day of trigger was similar between the premature ovulation and control groups.

Study limitations

To the best of our knowledge, this is the first study to assess optimal leading follicle size in POSEIDON groups 3 and 4. Despite the relatively small sample size and retrospective nature of the analyses, the main limitations of our work, the systematic exploration of individual parameters, the consistency in observed associations between leading follicle size and mature oocyte ratio together with the multivariate approach to identify premature ovulation risk factors add credence to our observations. Another limitation was the lack of information about embryo qualities and pregnancy outcomes. However, in our clinical practice, the collected oocytes are

incubated together and following ICSI individual MII oocytes are not labelled. Therefore, it was not possible to evaluate the fertilization potential of oocytes and embryo quality according to follicle size.

Conclusion

The leading follicle size was an important parameter in deciding the timing of final oocyte maturation in POSEIDON groups 3 and 4 PORs. Individualized triggers based on leading follicle size may provide maximum efficiency in ovarian stimulation in POSEIDON expected PORs. While late trigger may result in premature ovulation, early trigger may also result in a lower MII output. Triggering when the leading follicle size is between 16.5 and 17 mm may help to prevent these unwanted consequences and achieve the optimum cycle outcome. However, randomized controlled trials are needed to confirm our results and to assess the relationship between leading follicle size and embryo quality in POSEIDON group 3 and 4 PORs.

Ethics

Ethics Committee Approval: *The study protocol was approved by the Ankara University Ethical Committee for Human Research (approval number: I8-567-21, date: 15.10.2021).*

Informed Consent: *Not applicable.*

Footnotes

Author Contributions: *Concept: N.A., Y.E.Ş., Design: N.A., Y.E.Ş., B.A., B.Ö., Data Collection or Processing: N.B.K., O.A.A., Analysis or Interpretation: Y.E.Ş., B.A., Literature Search: N.B.K., O.A.A., B.A., Writing: Y.E.Ş., M.S., B.B., C.S.A., R.A., B.Ö.*

Conflict of Interest: *Two of the authors of this article, Yavuz Emre Şükür and Batuhan Özmen, are members of the editorial board of the Journal of the Turkish-German Gynecological Association. However, neither author was involved in any stage of the editorial decision-making process for this manuscript. The manuscript was evaluated by independent editors from different institutions. The other authors have declared no conflicts of interest.*

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Obstetric brachial plexus injury: risk factors and clinical follow-up results

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Abstract

Objective: Obstetric brachial plexus injury is a significant cause of neonatal morbidity. The aim of this study was to evaluate the maternal and perinatal factors associated with plexus injury and to analyze clinical follow-up outcomes and parental caregiving burden.

Material and Methods: This study was conducted as a retrospective descriptive study at the maternity center of a tertiary hospital. Deliveries resulting in obstetric plexus injury between February 2018 and December 2023 were included in the study. Out of 27,695 live births, 28 infants with plexus injury were identified and analyzed.

Results: Of the women who gave birth to infants with brachial plexus injury, 25 (89.3%) were aged 21-34 years, and 22 (78.6%) had a body mass index between 25 and 29.99 kg/m^2. Of the cohort, 16 (57.1%) were multiparous, and 3 (10.7%) had gestational diabetes. In addition, 15 (53.6%) women underwent labor induction, and all had vaginal deliveries. Shoulder dystocia occurred in 11 deliveries (39.3%). Of the newborns with brachial plexus injury, 25 (89.3%) had Erb's palsy. The mean follow-up period for the infants was 12 (3-31) months. Injury recovery occurred in 24 babies (85.7%), while four babies (14.3%) experienced permanent injury. Regarding parental caregiving burden, 22 parents (78.6%) reported "no to mild burden," while six parents (21.4%) reported a "mild to moderate burden." No parents reported "moderate to severe" or "severe burden". All newborns with permanent damage developed shoulder dystocia at delivery (p=0.007).

Conclusion: Most infants with plexus injury recovered, while permanent injury was linked to shoulder dystocia, and parental caregiving burden was generally low. [J Turk Ger Gynecol Assoc. 2025; 26(3): 204-11]

Keywords: Birth injury, macrosomia, neonatal, newborn, shoulder dystocia

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Introduction

Obstetric brachial plexus injury (OBPI) is damage between the fifth cervical nerve root and the first thoracic nerve root during labor. These nerve roots collectively form the brachial plexus, responsible for sensory and motor functions in the shoulder and arm muscles. Manifestations of OBPI include muscle weakness, sensory disturbances, limited arm movements, and potentially the absence of the Moro reflex on the affected side (1,2). Although brachial plexus injury can occur during birth, it may also occur *in utero* before delivery. In such cases, paralysis may be accompanied by findings such as muscle atrophy and

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bone demineralization on the affected side (3). The incidence of OBPI ranges from 0.4 to 3 per 1,000 live births (4). Damage to the fifth and sixth cervical nerve roots is termed Erb (5) paralysis, damage to the eighth cervical and first thoracic nerve roots is referred to as Klumpke (6) paralysis, and damage to all nerve roots from C5 to T1 is defined as total paralysis. In the clinic, 85% of cases result in Erb paralysis and Erb palsy plus. In Erb palsy plus, additional damage to the seventh cervical nerve is involved, along with the typical involvement of C5 and C6 (7). The primary risk factor for the development of OBPI is shoulder dystocia. When shoulder dystocia complicates birth, the main mechanism causing brachial plexus damage is the application of lateral traction to the fetal head towards the posterior shoulder (8). Possible risk factors contributing to an increased occurrence of brachial plexus damage include gestational diabetes mellitus (GDM), labor induction, macrosomic fetus, multiparity, excessive maternal weight gain during pregnancy, breech presentation, and instrumental delivery (9). To prevent OBPI, obstetricians should remain vigilant for the occurrence of shoulder dystocia and be prepared to implement appropriate interventions, such as the Crede maneuver, McRoberts maneuver, and Woods maneuver, when dystocia arises. In addition, clinicians should consider risk factors, including fetal macrosomia, maternal diabetes, and a history of shoulder dystocia, which may predispose to fetal injury, when determining obstetric management strategies (10). Electrodiagnostic tools, such as electromyography and neuroradiological imaging, especially magnetic resonance, can be valuable for evaluating the severity and mapping of brachial plexus damage. While improvement is typically seen with follow-up physical and occupational therapy, if no significant progress occurs within 3 to 9 months, surgical intervention may become necessary (11,12).

The aim of this study was to assess maternal and perinatal factors associated with OBPI cases and to examine the outcomes of clinical follow-up and parental care burden.

Material and Methods

This was a retrospective descriptive study performed in the maternity center of a tertiary hospital. Deliveries resulting in OBPI between February 2018 and December 2023 were reviewed. Patient information was obtained from hospital electronic health records. Fetuses diagnosed with OBPI through newborn examinations and diagnostic methods, such as electromyography, were included in the study. Stillbirths were excluded from the study. We evaluated the characteristics of fetuses with OBPI, their clinical follow-up, recovery status, obstetric parameters of the mothers, and parental care burden. The study was conducted in accordance with the principles of the Declaration of Helsinki and informed consent was obtained from all participants. During the data collection phase, the identification numbers of pregnant women and newborns were anonymized. Mothers' age, gravida, parity, body mass index (BMI), presence of chronic disease, number of antenatal visits, serum calcium levels, gestational weeks, and delivery types were evaluated. Postnatal infants' birth weight, length, activity pulse grimace appearance respiration (APGAR) scores, gender, need for neonatal intensive care unit, and complications were examined. The incidence rates of fetuses with OBPI by year, types of brachial plexus injuries, and clinical follow-up were investigated. We also assessed the parental care burden using the Zarit scale of caregiver burden (ZCB). The ZCB scale, developed by Zarit et al. (13), assesses the psychological and social conditions of caregivers, the impact of the care recipient on the caregiver, and the economic conditions involved. The scale consists of 22 questions and is a Likert-type instrument with five response options for each question: never (0 points), rarely (1 point), sometimes (2 points), quite often (3 points), and almost always (4 points). A minimum of 0 and a maximum of 88 points can be scored on the scale. The total score interpretations are: 0-21 indicates no to mild burden; 21-40 indicates mild to moderate burden; 41-60 indicates moderate to severe burden; and ≥61 indicates severe burden. This study was approved by the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval number: 2024/48, date: 20.02.2024). All vaginal deliveries at our obstetric center are conducted in the delivery room using the lithotomy position, following current guidelines. In cases of shoulder dystocia, appropriate standard maneuvers are promptly performed. All newborns are comprehensively evaluated by a pediatrician, both in the delivery room and in the examination room. The diagnosis of brachial plexus injury is confirmed by the pediatrician through physical examination after delivery. Following discharge and during follow-up visits, electrodiagnostic and neuroradiological assessments are performed when necessary. A consensus diagnosis and management plan are then established through collaboration between specialists in physical therapy, orthopedics, and pediatrics.

Statistical analysis

Data were statistically analyzed using the Statistical Package for the Social Sciences for Windows, v.21.0 (IBM Inc., Armonk, NY, USA). Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to evaluate the study data. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

Between 2018 and 2023, there were 27,695 births in our unit, 28 of whom were infants with OBPI. Our clinic's OBPI rate is 1.01 per 1,000 births. Table 1 shows OBPI rates by year.

Among the women who gave birth to fetuses with brachial plexus damage, 25 (89.3%) were aged 21-34 years, and 22 (78.6%) had a BMI of 25-29.99 kg/m^2. Of the women, 16 (57.1%) were multiparous, 12 (42.9%) were nulliparous, 23 (82.1%) had no additional diseases, and 3 (10.7%) had GDM. While five women (17.9%) did not attend any antenatal care visits, 19 women (67.9%) attended 1-3 visits, and four women (14.3%) attended more than four visits. The presenting symptom at hospital admission was labor pain in 12 (42.9%) women and premature rupture of membranes in 11 (39.3%) women. In addition, 15 (53.6%) women received labor induction, while 13 (46.4%) did not. The mean delivery duration was 6 (1-48) hours. Sixteen women (57.1%) gave birth ante meridiem, and 14 women (50%) underwent an episiotomy (Table 2).

The median APGAR scores of newborns born with brachial plexus injury were 8 (5-9) at the first minute and 9 (8-9) at the fifth minute. The birth weight of 10 newborns (35.7%) was between 3000-3499 grams, 13 newborns (46.4%) weighed between 3500-3999 grams, and 5 newborns (17.9%) weighed 4000 grams or more. The mean length of the newborns was 52.57±1.68 cm, and the mean head circumference was 35.11±1.28 cm. Among them, 18 (64.3%) were female, and 10 (35.7%) were male. Brachial plexus injury occurred on the right side in 22 newborns (78.6%) and on the left side in 6 newborns (21.4%). No complications were observed in 17 newborns (60.7%) after birth, while caput succedaneum was detected in 5 (17.9%), subconjunctival hemorrhage in 4 (14.3%), clavicle fracture in 1 (3.6%), and adrenal region hematoma in 1 (3.6%). Shoulder dystocia occurred in 11 (39.3%) deliveries, while it was not observed in 17 (60.7%) deliveries (Table 3).

Among newborns with brachial plexus injury, 25 (89.3%) had Erb's palsy, 2 (7.1%) had Klumpke's palsy, and 1 (3.6%) had total paralysis. The median follow-up period for the newborns was 12 (3-31) months. The injury healed in 24 (85.7%) babies, while 4 (14.3%) babies experienced permanent injury. Twenty-two parents (78.6%) reported "no to mild care burden", and six (21.4%) reported a "mild to moderate care burden". No parents were identified as "moderate to severe burden" or "severe burden" (Table 4).

There were no significant differences in maternal obesity, rates of multiparity, labor induction, or macrosomia between newborns with permanent and transient injury (p=0.497, p=0.196, p=0.356, and p=0.497, respectively). Shoulder dystocia occurred in all newborns with permanent injury, compared to 7 (29.2%) cases among those with transient injury (p=0.007) (Table 5).

Discussion

In the present study that examined the characteristics of infants born with brachial plexus injuries over a six-year period (2018-2023) at a tertiary hospital, there was an OBPI rate of 1.01 per thousand births. The review, which included 46 studies on the epidemiology of OBPI, reported rates ranging from 0.3 to 3 per 1,000 births (14). We believe that the variation in incidence rates is influenced by countries' levels of development, obstetric care practices, geographical factors, and nutritional habits. An analysis of our clinic's OBPI rates from 2018 to 2023 reveals a variable pattern, with rates alternating between increases and decreases over the years. The peak incidence was 1.91 per thousand in 2021, while the lowest was 0.46 per thousand in 2018. At our clinic, obstetric residents perform deliveries under the supervision of an obstetric specialist. Over time, experienced residents graduate and leave the hospital, while less experienced residents, who are just beginning, take on the task of performing deliveries. We think that this dynamic has influenced the changes in our clinic's OBPI rates over the years, with rates decreasing as the experience of residents performing deliveries increases.

Of the mothers who gave birth to infants with OBPI, only 10.7% were of advanced maternal age (35 years or more). Advanced maternal age may adversely affect birth outcomes. A recent study conducted in California, involving more than 8 million

Table 1. The number of infants born and the rate of obstetric brachial plexus injury

Years	Number of infants	OBPI	OBPI rate/1,000 births
2018	4394	2	0.46
2019	5471	8	1.46
2020	4666	3	0.64
2021	4717	9	1.91
2022	4328	3	0.69
2023	4119	3	0.73
Total	27695	28	1.01

Values are presented n (‰), OBPI: Obstetric brachial plexus injury

participants, found that the rate of brachial plexus injury in advanced-age mothers was 13.6%. The study also reported that the risk of OBPI increased by [aortic outflow region (AOR): 1.16] compared to mothers aged 20-34 years (15). We believe that chronic diseases, maternal exhaustion, and insufficient pushing, which become more common with advanced maternal age, contribute to the increased OBPI rates.

Table 2. Maternal and obstetric characteristics

	n=28
Maternal age (years)	
21-34	25 (89.3)
35 or more	3 (10.7)
Body mass index (kg/m^2)	
18-24.99	3 (10.7)
25-29.99	22 (78.6)
30 or more	3 (10.7)
Gravida	2 (1-6)
Parity	
Nulliparous	12 (42.9)
Multiparous	16 (57.1)
Abortions	0 (0-2)
Maternal chronic diseases	
No	23 (82.1)
Gestational diabetes mellitus	3 (10.7)
Asthma	1 (3.6)
Hepatitis B disease	1 (3.6)
Antenatal care visits	
0	5 (17.9)
1-3	19 (67.9)
4 or more	4 (14.3)
Maternal serum calcium level (mg/dL)	8.87±0.47
Gestational age (weeks)	39 (37-41)
Initial symptoms of admitted	
Labor pain	12 (42.9)
Premature rupture of membranes	11 (39.3)
Post-date pregnancy	3 (10.7)
Oligohydramnios	2 (7.1)
Induction of labor	
Yes	15 (53.6)
No	13 (46.4)
Induction agent	
Oxytocin	10 (66.7)
Dinoprostone	5 (33.3)
Type of delivery	
Vaginal delivery	28 (100)
Cesarean delivery	0 (0)
Time of delivery (hours)	6 (1-48)
Hour of birth	
Ante meridiem	16 (57.1)
Post meridiem	12 (42.9)
Episiotomy	
Yes	14 (50)
No	14 (50)

Values are presented as mean ± standard deviation, median (range), and n (%)

In the present study, we found that 10.7% of women who gave birth to infants with brachial plexus injury had a BMI of 30 kg/m^2 or more. The study conducted by Avram et al. (16) demonstrated that the rate of brachial plexus injury increased with maternal weight. We believe that increased maternal adiposity, both before and during pregnancy, contributes to disproportionate fetal growth and increases the risk of brachial plexus injury. In the present study, 57.1% of brachial plexus injuries occurred in women who had a prior vaginal delivery. In a study examining 78 infants, 58% of cases with brachial plexus injuries were multiparous. Multiparous women give birth to infants with higher birth weights than primiparous. Providers tend to underestimate birth weights in multiparous women and are less likely to perform necessary labor interventions. This approach contributes to an increased rate of brachial plexus injuries in women with a previous delivery (17). We identified GDM in 10.7% of cases involving brachial plexus injury.

A systematic review and meta-analysis encompassing approximately 30 million births reported that GDM significantly increased the risk of brachial plexus injury (odds ratio =5.33). Excessive and disproportionate fetal growth is more common in pregnancies complicated by GDM. Specifically, the ratio of fetal abdominal and head circumference tends to increase. Both excessive and disproportionate fetal growth contributes to the risk of plexus injury (9). We used induction to initiate labor in 53.6% of the women in our cohort. Similarly, Yenigül et al. (18) identified a 66.7% labor induction rate in cases of brachial plexus injury, demonstrating that labor induction significantly heightened the incidence of injury. We believe that initiating labor induction before adequate cervical ripening may contribute to the development of plexus injury by elevating *in utero* pressure. We also suspect that undetected cephalopelvic disproportion may impact the progress of injury. Therefore, a comprehensive evaluation should be conducted before initiating labor induction to identify potential risk factors that could increase neonatal morbidity. We used oxytocin as an induction agent in 10 women (66.7%) and dinoprostone in 5 women (33.3%). In the study by Louden et al. (19), the use of oxytocin was reported to increase the risk of brachial plexus injury by 2.5 times, and the risk increased by 3.7 times when tachysystole occurred with the use of oxytocin. In contrast, the use of prostaglandins was not associated with an increased risk. These findings suggest that oxytocin use, particularly when complicated by tachysystole, may further elevate the risk of fetal injury. Therefore, a thorough evaluation of the pelvis and cervix should be performed before initiating oxytocin, and careful adjustment of dosage and duration

Table 3. Evaluation of perinatal outcomes

	n=28
USG measurement of fetal FL (mm)	73.55±1.53
Percentiles for FL	
25th percentile	1 (3.6)
50th percentile	10 (35.7)
75th percentile	16 (57.1)
90-95th percentile	1 (3.6)
First minute APGAR	8 (5-9)
Fifth minute APGAR	9 (8-9)
Birth weight (grams)	
3000-3499	10 (35.7)
3500-3999	13 (46.4)
4000 or more	5 (17.9)
Newborn length (cm)	52.57±1.68
Newborn head circumference (cm)	35.11±1.28
Fetal gender	
Female	18 (64.3)
Male	10 (35.7)
Affected side of OBPI	
Right side	22 (78.6)
Left side	6 (21.4)
NICU admission	
Yes	2 (7.1)
No	26 (92.9)
Neonatal complication with OBPI	
None	17 (60.7)
Caput succedaneum	5 (17.9)
Subconjunctival hemorrhage	4 (14.3)
Clavicle Fracture	1 (3.6)
Hematoma in the adrenal area	1 (3.6)
Shoulder dystocia	
Yes	11 (39.3)
No	17 (60.7)

Values are presented as mean ± standard deviation, median (range), and n (%)
USG: Ultrasonography, FL: Femur length, APGAR: Activity pulse grimace appearance respiration, OBPI: Obstetric brachial plexus injury, NICU: Neonatal intensive care unit

during administration is essential. During the study period, a total of 9,930 cesarean deliveries were performed in our clinic, and no cases of brachial plexus injury were detected in the newborns. A study conducted with stratified analysis covering 22 years showed that cesarean section is a protective factor for the development of brachial plexus injury, with the greatest protective effect observed in cases of macrosomic fetuses (20). Cesarean delivery should be considered in the presence of high-risk factors for difficult delivery, such as macrosomia and malpresentation. Most births involving brachial plexus injury (57.1%) occurred during the ante meridian hours. Birth providers working during this time may experience increased sleep deprivation and fatigue, which could contribute to the higher incidence of plexus injury observed in the ante meridian.

Table 4. Clinical outcomes of fetuses with OBPI and their parents' caregiving scores

	n=28
Subgroups of palsy	
Erb paralysis	25 (89.3)
Klumpke paralysis	2 (7.1)
Total paralysis	1 (3.6)
Follow-up period (months)	12 (3-31)
Clinical follow-up results	
Transient injury	24 (85.7)
Permanent injury	4 (14.3)
Zarit scale of caregiver burden	
No to mild burden (0-21 score)	22 (78.6)
Mild to moderate burden (21-40 score)	6 (21.4)
Moderate to severe burden (41-60 score)	0
Severe burden (≥61 score)	0

Values are presented as median (range) and n (%)
OBPI: Obstetric brachial plexus injury

In the present study, 46.4% of fetuses with brachial plexus injury had a birth weight of 3500-3999 g, while 17.9% had a birth weight of 4000 g or more. Previous studies have identified fetal macrosomia as a strong risk factor for brachial plexus injury (9). In a study examining approximately 1 million birth records, a new warning range of 3500-3999 g was determined for the development of plexus injury, and it was reported that the damage increased by 7% for every 50 g increase in fetal weight (21). The important point is that obstetricians should remain vigilant for the possibility of brachial plexus injury when the fetal weight is between 3500 and 3999 g. This range should be carefully considered in the presence of additional risk factors, such as advanced maternal age, GDM, and malpresentation, and considered in labor management.

We found that 64.3% of newborns with brachial plexus injury were female. Previous research has demonstrated that female gender is a risk factor for OBPI (AOR: 1.38). However, some studies have indicated no significant relationship between fetal gender and plexus injury (22). We believe that fetal gender, in isolation, should not be considered a sole risk factor for plexus injury; rather, it should be assessed in conjunction with other coexisting risk factors. Furthermore, we believe that the ethnicity of the study populations may influence these findings. In our study, the right limb was affected in 78.6% of fetuses that developed brachial plexus injury. A recent review indicated that lesions on the right side were more common than on the left (23). Typically, the fetal head enters the pelvis in the left occiput transverse position and undergoes external rotation during the second stage of labor, with the right shoulder positioned near the mother's symphysis pubis. In such cases, downward lateral traction applied to the fetal head by the obstetrician may explain the development of lesions in the right limb.

Table 5. Comparison of maternal and obstetric characteristics between transient and permanent brachial plexus injuries

	Transient injury (n=24)	Permanent injury (n=4)	p
Maternal obesity			
Yes	3 (12.5)	0 (0)	0.497
No	21 (87.5)	4 (100)	
Multiparous			
Yes	15 (62.5)	1 (25)	0.196
No	9 (37.5)	3 (75)	
Induction of labor			
Yes	12 (50)	3 (75)	0.356
No	12 (50)	1 (25)	
Shoulder dystocia			
Yes	7 (29.2)	4 (100)	0.007
No	17 (70.8)	0 (0)	
Macrosomia			
Yes	3 (12.5)	0 (0)	0.497
No	21 (87.5)	4 (100)	
Values are presented n (%)			

In our cohort, clavicle fractures were observed in 3.6% of fetuses with OBPI. Previous research has reported that clavicle fractures are not a risk factor for developing plexus injury (24). However, other studies have indicated that the morphology of clavicular fractures is associated with plexus injury. Specifically, while there is no significant risk between fractures with transverse morphology and plexus injury, a significant correlation was reported between spiral and oblique morphology clavicle fractures and plexus injury (25). Moreover, some studies report that the likelihood of permanent neurological deficit is lower in cases where clavicular fractures accompany plexus injury, and the presence of a clavicular fracture may enhance recovery from palsy (26). We suggest that these differing results across studies are attributable to variations in the fracture mechanisms. For instance, fractures caused by excessive traction applied to the fetal head by the obstetrician may contribute more significantly to plexus injury. In contrast, intentional clavicular fractures during shoulder dystocia may result in less severe plexus injury. Shoulder dystocia occurred during labor in 39.3% of newborns with brachial plexus injury and all newborns with permanent damage developed shoulder dystocia at delivery (p=0.007). The incidence rates of shoulder dystocia and brachial plexus injury vary across different geographies, ranging from 47% to 78%. The presence of shoulder dystocia increases the risk of brachial plexus injury by approximately 100-fold (27). During shoulder dystocia, applying downward lateral traction on the fetal head to deliver the anterior shoulder can stretch and injure the brachial plexus.

Erb's palsy was detected in 89.3% of newborns who developed OBPI. It occurs due to damage to the upper trunk nerves involving C5, C6, and occasionally C7 (Erb's palsy plus). Approximately 85% of brachial plexus cases are classified as Erb's palsy (7). In our cohort, records showed no instances of Erb's palsy plus damage. We suspect that cases of Erb's palsy plus damage were documented as Erb's palsy. The median follow-up period for fetuses who developed brachial plexus injury in our study was 12 months. By the end of this period, 85.7% of cases showed recovery, while 14.3% resulted in permanent injury. According to the literature, the reported rate of permanent injury ranges from 12% to 50% (28). We believe that this wide range is associated with differences in developing healthcare systems across countries. When assessing the caregiving burden of parents of infants with brachial plexus injury, 78.6% reported "no to mild burden", while 21.4% reported a "mild to moderate burden". Given the prolonged recovery and rehabilitation process associated with plexus injuries, parents may face both psychological and financial challenges during this period (29). We hypothesize that the relatively low caregiving burden scores observed in our study were attributable to the free access to healthcare and social support services in our country.

Study limitations

The limitations of our study are its cross-sectional, retrospective and descriptive design. The strengths of our study include reporting the incidence of brachial plexus injury both annually and cumulatively over a six-year period, as well as presenting maternal, perinatal, and neonatal data of affected infants during this timeframe. Additionally, the follow-up of cases for a mean duration of 12 (3-31) months further strengthens our study.

Conclusion

The incidence of OBPI in this single tertiary center retrospective study was 1.01 per thousand births. In the presence of factors that lead to the development of plexus damage, such as shoulder dystocia, the obstetrician's experience is important. Cesarean section may serve as a protective factor against brachial plexus injury. The Erb's palsy subtype was more common, with the right limb being more frequently affected. Newborns with plexus injuries exhibited high recovery rates and, in our cohort, the reported parental caregiving burden was low.

Ethic

Ethics Committee Approval: *This study was approved by the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval number: 2024/48, date: 20.02.2024).*

Informed Consent: *Informed consent was obtained from all participants.*

Footnotes

Author Contributions: *Surgical and Medical Practices: O.A., B.G., N.T., Concept: O.A., Design: O.A., B.G., N.T., Data Collection or Processing: O.A., Analysis or Interpretation: O.A., B.G., N.T., Literature Search: O.A., Writing: O.A.*

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Transplacental cancer transmission: a comprehensive review focusing on mechanisms, challenges, and maternal-fetal outcomes

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Abstract

The phenomenon of transplacental transmission of cancer, where cancer cells pass from a pregnant mother to her fetus is an extremely rare occurrence. This phenomenon has significant implications for maternal and fetal health, challenging our understanding of cancer biology and maternal-fetal interactions. The literature on transplacental cancer transmission is sparse, consisting mainly of case reports, small cohort studies, and reviews. Examples of cancers that have been transmitted in this way include melanoma, choriocarcinoma, leukaemia, and lymphoma. Understanding this phenomenon is important because it has direct clinical implications for managing pregnant women with cancer and the infant, raises questions about the placental barrier and immune interactions between mother and fetus, and offers insights that could influence cancer biology and treatment strategies. This review aims to evaluate existing data, identify and synthesize evidence on transplacental cancer transmission cases, evaluate cancer types involved, their transmission mechanisms, and clinical outcomes for both mothers and infants. A comprehensive electronic search of databases was conducted for relevant case reports and series, using specific keywords related to vertical and transplacental transmission of cancer. The review elucidates comprehensive information from the reports to understand how cancer transmission occurred and was confirmed as vertical transmission, aiming to enhance knowledge in this critical area of maternal-fetal medicine. [J Turk Ger Gynecol Assoc. 2025; 26(3): 212-9]

Keywords: Cancer, choriocarcinoma, melanoma, transplacental transmission, vertical transmission

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Introduction

Transplacental transmission of cancer, also known as vertical transmission, is an exceedingly rare but intriguing phenomenon where cancer cells cross the placental barrier from a pregnant mother to her fetus. Although, about 1 in 1,000 live births involves a mother who has cancer, maternal transmission of cancer to offspring is exceedingly rare, estimated at approximately 1 in every 500,000 infants born to mothers with cancer (1,2). This mode of transmission has profound implications for both maternal and fetal health, challenging our understanding of cancer biology and maternal-fetal interactions. It presents a unique conundrum, combining elements of oncology, immunology, and obstetrics. Given the rarity and complexity of transplacental transmission of cancer, the existing literature is sparse and comprised of case reports, small cohort studies and reviews; types of cancer include melanoma, leukaemia, and lymphoma being transmitted from mother to fetus. Understanding the transplacental transmission of cancer is important for several reasons. Firstly, it has direct clinical implications for the management of pregnant women with cancer, influencing decisions regarding treatment and monitoring. Secondly, it raises fundamental questions about the nature of the placental barrier, the immune interactions

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between mother and fetus, and the unique environment that allows for transmitting malignant cells. Thirdly, insights gained from studying this rare event may have broader implications for cancer biology and treatment along with strategies to prevent metastasis and improve outcomes for patients with cancer. This review sought to critically analyze existing data, identify and consolidate evidence on transplacental cancer transmission, examine the types of cancers involved, their transmission mechanisms, and the clinical impact on both mothers and infants. By consolidating comprehensive data from these rare case scenarios, this review offers a novel perspective on previously overlooked patterns, proposing new insights into transplacental transmission pathways, maternal-fetal interactions, and potential diagnostic as well as therapeutic advances in this rare phenomenon.

Methodology

An electronic search of Scopus, PubMed, Embase and other databases was conducted for case reports and case series of suspected, probable and confirmed mother-to-child transmission or vertical transmission of cancer, published in English from inception until July 2024. The electronic search strategy used keywords such as "vertical transmission" and "transplacental transmission", "mother to child transmission" and "cancer", "carcinoma" and "transplacental transfer", and "metastasis to the fetus" "mother to baby"; "mother and baby". We analysed the titles and abstracts of all case reports identified by the initial search. The reference lists of relevant reports were also explored. Two reviewers double-checked the data to avoid duplication. Case reports with placental metastasis only, without metastasis to the fetus, were excluded. Review articles, original articles, clinical trials, conference abstracts, editorials, poorly described cases, and articles in language other than English language or commentary were also excluded. The article selection and screening process details are presented in the Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart (Figure 1). Of the eligible articles, information pertaining to author and year of publication, age

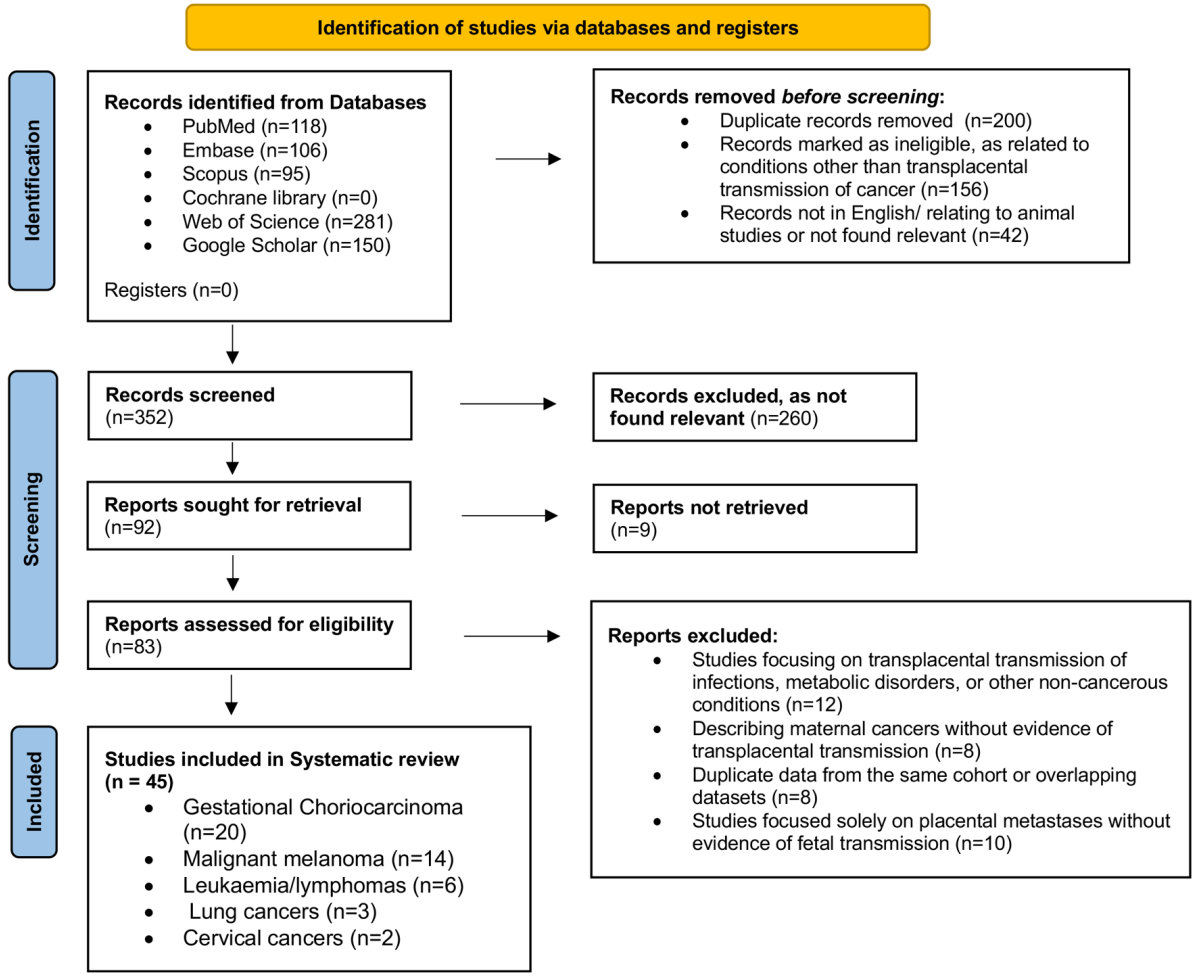

Figure 1. PRISMA flow-chart of study selection

of the patient at the time of presentation, the type of primary cancer in the mother and its stage if available, primary site in the mother, gestational age at the time of delivery, age at diagnosis, presenting clinical features, and sites of metastasis for the baby, and the outcome of the case in the form maternal and fetal/neonatal/infant outcome was extracted. An attempt was made to extract all the possible information mentioned in the report regarding how the cancer transmission occurred and how it was confirmed to be "vertical transmission". By systematically reviewing the literature, we hope to enhance the understanding of transplacental cancer transmission and provide a foundation for informed clinical practice and future research directions in this important area of maternal-fetal medicine.

Overview of published cases of transplacental cancer transmission

A summary of all probable and confirmed cases of transplacental cancer transmission reported in the literature to date are summarised in Table 1: all cases of choriocarcinoma (3-23), Table 2: all cases of malignant melanoma (24-40) and Table 3: other cancers, including leukaemia, lymphomas, lung cancers and cervical cancers (41-51). Choriocarcinoma is the most common tumor showing mother-to-child transmission. In a previous systematic review, conducted by one of the authors of this article, the 12-month overall survival rate for mothers was 71.8%±10.7%, while for infants, it was 22.2%±9.8% (52). The median time to diagnose gestational trophoblastic neoplasia in mothers was six weeks post-partum. For infants, the median age at presentation was 1.75 weeks [interquartile range (IQR): 0.1 to 6.75 weeks], and the median age at diagnosis was 5.00 weeks (IQR: 3.55 to 8 weeks). However, the diagnosis of vertical transmission was not confirmed in most cases (16/20). It was not clear whether the infant's tumor was primary or secondary to maternal choriocarcinoma. Another diagnostic dilemma with choriocarcinoma is whether it has arisen from the present pregnancy or hydatiform mole in a previous pregnancy or from previous abortions where histopathology was not done, as they could have been molar pregnancy of choriocarcinoma, and this is usually not clear (52).

Malignant melanoma was found to be the second most common tumor, showing transplacental transmission after gestational choriocarcinoma. After analyzing the existing literature, we found that the tumor might have a higher incidence in male fetuses, with a male-to-female ratio of 2:1. However, in two cases where the tumor metastasis led to intrauterine fetal demise, the sex was not mentioned. All infants presented during infancy with cutaneous metastasis. The mastoid cavity and external auditory meatus were other favoured sites, followed by brain, lung, liver, testicles and adrenal glands. Interestingly, in two cases, auto-regression of the tumour was noted (28,32). In 4/14 cases, vertical transmission was confirmed because the placenta was grossly and microscopically involved. In 5/14 cases, karyotypically female cells in a male baby were presumed to be of maternal origin, or genetically identical mutations in both tumours were confirmatory. The prognosis was very poor, both for the mother and the baby. Most (9/14, 64.3%) of the babies died, while in one case, the details were not available. For mothers, if vertical transmission had occurred, the result was invariably fatal when outcome was reported; 13/14 mothers died, while in one patient, the details were not available.

There are three cases of cervical cancer reported to be transmitted vertically (47,48). In all three cases, the authors stressed mother-to-infant vaginal transmission through aspiration of tumour-contaminated vaginal fluids during birth. In the case described by Herskovic et al. (47), the authors acknowledged that the spread could have been hematogenous transplacental or through direct inoculation or transbronchial spread. In the cases reported by Arakawa et al. (48), the transmission was evidenced by the fact that the tumors in both male children lacked the Y chromosome and shared multiple somatic mutations, an human papilloma virus genome, and single nuclear polymorphic (SNP) alleles with their mothers' tumors. In addition, the peri-bronchial growth pattern of the tumors in both children suggested that they originated from mother-to-infant transmission via aspiration of tumor-contaminated vaginal fluids during birth. Maternal tumor cells were likely present in the amniotic fluid, cervical secretions, or blood and were aspirated by the infants during vaginal delivery.

We found six reported cases of haemato-lymphoid malignancies that have been reported to be transmitted from mother to child trans-placentally (41-46). Transplacental transmission of cancer appears to have a predisposition for male fetuses. In cases of leukaemia and lymphoma, 5 out of 6 reported instances involved male fetuses, with the remaining one case involving a female fetus (46). Similarly, in lung cancer, 2 out of 3 cases involved male fetuses (with the sex of the baby in the third case not reported). For cervical cancer also, 2 out of 3 cases, involved male fetuses (with the sex of the baby in the third case not reported). The confirmation in these cases (where done) is either by gross/microscopic involvement of the placenta, of the finding of XX genotype in cancer cells of the male fetus, which is presumed to be of maternal origin or by identical mutations found in maternal and fetal tumors.

Table 1. A summary of all cases of gestational choriocarcinoma, reported in literature with suspected or confirmed, vertical transmission

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome of the baby	Outcome of the mother	Remarks
Mercer et al. (3)	NM/ Choriocarcinoma/ Uterus (a blackish-red nodule 1.5 X 1.5 cm, located in the fundus)	VD/Full-term	NM/3 months	Small red nodule in the upper anterior alveolar ridge	Upper maxilla, nasal fossa and later head and neck	Transplacental ?	Not confirmed	Not done	Died at 6 months of age d/t extensive invasion of the tumor about the head and face.	Death at 8 months pp due to widely metastatic disease.	Whether the tumor of the alveolar ridge of the infant represented a primary or a secondary metastasis is unknown.
Brooks and Nolting (4)	NM/ Choriocarcinoma/ Diagnosed with metastatic disease after child's confirmation.	VD/35 weeks	Female/11 days	Right-sided facial mass, Recurrence of facial mass after resection	Lung	Transplacental ?	Not confirmed	Not done	Survived	Alive and Healthy	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Hanson et al. (5)	NM/ Choriocarcinoma/ Diagnosed with metastatic disease after child's confirmation.	NM	Male/6 weeks	Fever, pallor, and fatigue, Recurrent severe anaemia, hepatomegaly	Liver	Transplacental ?	Not confirmed	Not done	Survived	Survived	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Sashi et al. (6)	NM/ Choriocarcinoma/ Diagnosed with metastatic disease after child's confirmation.	NM/full term	Female/At birth	Anaemia, abdominal distension, Tachycardia, cyanosis, liver tumours	Liver, lung, brain	Transplacental ?	Not confirmed	Not done	Died at 38 days d/t metastatic disease.	Survived till 14 months from diagnosis and later	In this case there were two possible primary sites: the placenta of this pregnancy and the hydatidiform mole occurring 2 years before.
Andreitchouk et al. (7)	36/ Choriocarcinoma WHO score 13/ Uterus with widespread metastasis diagnosed after confirmation in child	CS (CPD)/ full-term	Female/At birth	Severe anaemia Hepatomegaly	Liver, lung, brain.	Transplacental ?	Not confirmed	Placenta grossly normal. HPE not done	Died at 38 days of life d/t metastatic disease.	Remission	Origin could have been from hydatiform mole 2 years before this pregnancy. Feto-maternal haemorrhage was noted.

Table 1. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome of the baby	Outcome of the mother	Remarks
Avril et al. (8)	21/ choriocarcinoma/ placenta with lung metastasis	VD/ full-term	Female/At birth	Cutaneous lesions Disseminated cutaneous tumours, hepatomegaly, lung rales	Skin, lung, bone, pelvis	Transplacental	Confirmed because placenta was involved pathologically	An abnormal 5 cm wide white growth on the uterine surface, pathologically confirmed as choriocarcinoma	Died at day 24 of life d/t lung haemorrhage	Alive at 14 months No further details available	None
Bolze et al. (9)	35/ Choriocarcinoma FIGO Stage 4 Score 14/ Uterus	NM/NM	Male/ 5 month	Dyspnea and anaemia, Liver mass, mediastinal lymphadenopathy.	Liver, lung, mediastinal lymph nodes	Transplacental confirmed	Genotyping	Placenta grossly normal. HPE not done	Died at 11 months of age	Normal at 3 years f/u.	None
Flam et al. (10)	30/ choriocarcinoma/ uterus	VD/ full-term	Female/ 24 hours of life	Anaemia Liver tumour	Liver	Transplacental?	Not confirmed	Placenta grossly normal. HPE not done	Died at 20 days of life (sudden death at home)	Alive at 7 years	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Rzanny-Owczarzak et al. (11)	NM/ choriocarcinoma/ uterus	CS (NPOL)/ full-term	Male/ 1 month	Hematemesis Liver tumour	Lung, liver, intestine, lymph nodes	Transplacental?	Not confirmed	Not mentioned	Died at 1.5 months d/t MODS	Alive and pregnant at 1 year	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Liu and Guo (12)	35/ Choriocarcinoma stage IIIa (FIGO score 4) / Uterus, metastatic to lungs.	VD/ full-term	Male/ Day 13 of life	Unexplained melena, Jejunal mass	Lung, jejunum,	Transplacental?	Not confirmed	Not mentioned	Survived	Normal at 1 year f/u	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Tsukamoto et al. (13)	24/ choriocarcinoma/ uterus	VD of dead baby/ full-term	Male/ Intrauterine fetal demise	Unexplained intrauterine fetal death Metastatic liver disease	Liver, lungs, hilar lymph nodes, diaphragm, and subcutaneous tissue of the head	Transplacental?	Not confirmed	Placenta was enlarged but grossly normal, sent for HPE but found normal	Intrauterine fetal death	Asymptomatic at 9 months f/u	Not clear whether the infant's tumor was primary, or secondary to maternal CC

Table 1. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome of the baby	Outcome of the mother	Remarks
Buckell and Owen (14)	25/ choriocarcinoma/ uterus	NM/ full-term	Male/ 7 weeks	Vomiting, abdominal distension, Anaemia, epigastric mass	Liver, ribs and nodes	Transplacental?	Not confirmed	Not mentioned	Died at 52 days of life	Alive at 13 months pp	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Kruseman et al. (15)	20/ choriocarcinoma/ uterus and vagina	VD of dead baby/ full-term	Female/ Intrauterine fetal death	Still birth, polyhydramnios, Tumour in left kidney 1.2x1.8 cm	Kidney	Transplacental ?	Both tumours were similar on Immuno-histochemistry.	Not mentioned	Intrauterine fetal death	Alive at 6 months	Massive Feto-maternal haemorrhage. Not clear whether the infant's tumor was primary, or secondary to maternal CC
Mosayebi et al. (16)	22/ choriocarcinoma	CS (morbid maternal condition)/ 31 weeks	Female/ 6 weeks	Recurrent vomiting and poor feeding, Sick child, decreased neonatal reflexes, systolic murmur, bilateral megalo-cornea and leukocoria	Brain, lung, liver and eye	Transplacental?	Not confirmed	Not done	Died	Died at 30 days pp	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Mcnally et al (17); Heath and Tiedemann (18)	35/ choriocarcinoma/ Uterus and placenta	VD/ full term	Male/ 3 months	Solitary liver nodule	Liver	Transplacental	Confirmed by HPE of placenta	Placenta involved grossly and microscopically (Villous invasion present)	Alive and Healthy at 3 years	Alive and healthy at 36 months, following multiple courses of chemotherapy and related complications	h/o hydatiform mole, before this pregnancy, which went on to develop CC
Aozasa et al. (19)	NM/ choriocarcinoma not confirmed on HPE/ Uterus	VD/ full-term	Female/ 2 months	Weakness of feeding and oedema in the right inguinal and labial region, Hepatomegaly, abdominal distension, thrombocytopenia,	Liver, lung	Transplacental?	Not confirmed	No comment on placental examination	Died	Died at 5 months pp	Not clear whether the infant's tumor was primary, or secondary to maternal CC

Table 1. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome of the baby	Outcome of the mother	Remarks
Getrajdman et al. (20)	33/ choriocarcinoma	VD/ 37 weeks	Male/At birth	Pallor Hepatomegaly and anaemia	Liver, lung, eyes	Transplacental?	Not confirmed	No comment on placental examination	Survived and disease free at 2 years	Alive and Healthy at 2 years	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Kishkurno et al. (21)	36/ choriocarcinoma	CS (CPD)/ full-term	Female	Anaemia, hepatomegaly	Liver, brain, lungs	Transplacental?	Not confirmed	Placenta grossly normal. HPE not done	Died at 38 days of life d/t widespread metastasis	Alive and healthy	Origin could have been from hydatiform mole 2 years before this pregnancy. Feto-maternal haemorrhage was noted
Picton et al. (22)	24/ choriocarcinoma high risk with prognostic score 17/ Diagnosed with metastatic disease after child's confirmation	CS (fetal distress)/40 weeks	Male/Day 22 of life	Feeding difficulty, poor weight gain, anaemia, vomiting Failure to thrive, hepatosplenomegaly	Brain, liver, lung	Transplacental??	Not confirmed	On gross examination, membranes appeared ragged, but HPE not done.	Died at 1 month d/t widespread metastasis.	Alive and healthy at 11 months	Feto-maternal haemorrhage was noted
Monclair et al. (23)	32/PSTT high risk WHO prognostic score 9	NM/ 37 weeks	Male/4 months	General malaise, common cold Hepatomegaly, dyspnoea, tachycardia, pneumothorax	Liver, lung, mesentery	Transplacental??	Not confirmed. Both tumours were similar on Histology and Immunohistochemistry	Placenta was grossly normal, but histopathology was not done	Died at 5 months d/t MODS	Alive and Healthy at 26 months	Not clear whether the infant's tumor was primary, or secondary to maternal PSTT

CC: Choriocarcinoma, CPD: Cephalo-pelvic disproportion, CS: Caesarean section, CT: Computer tomography, d/t: Due to, f/b: Followed by, f/u: Follow-up, HPE: Histopathological examination, IUFD: Intra-uterine fetal death, LSCS: Lower segment caesarean section, NAD: No abnormality detected, NM: Not mentioned, NPOL: Non-progress of labour, MODS: Multi-organ dysfunction syndrome, pp: Post-partum, PSTT: Placental site trophoblastic tumor, VD: Vaginal delivery, WHO: World Health Organization

Table 2. A summary of all cases of Malignant Melanoma, reported in literature with suspected or confirmed, vertical transmission

Author and Year of publication	Age/type of cancer/ primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Weber et al. (24), Holland (25)	27/melanoma/ skin (left thigh)	CS (morbid maternal condition)/38 weeks	Male/8 months	Abdominal distension, cachexia, hepato-splenomegaly,	Subcutaneous nodules	Transplacental	Histopathology of placenta.	Placenta involved, Gross and Microscopic (villous invasion present)	Death at 10 months of age	Died at 3 months	None
Gottron and Gertler (26)	25/melanoma/ skin (back)	NM/Term	Male/5 months	NM	NM	Transplacental	Not confirmed	Microscopic examination not done (not known)	Death at 14 days of life	Died at 2 months	None
Aronsson (27); Cavell (28)	NM/melanoma/ not known	VD/ 32 weeks	Female/2.5 months	Tumor-like masses in her right thigh and right lower leg	Skin	Transplacental likely.	Melanin + ve pigments in the tumor of the infant and the presence of metastasizing malignant melanoma in the mother	Placental microscopic examination was not done (not known)	Alive and Healthy at 2 years	4 days, death due to sepsis	Spontaneous regression occurred
Trumble et al. (29)	NM/melanoma/ skin	NM/ term	Male/7 months	2-week h/o bulging fontanel, diminished oral intake, and lethargy	Posterior fossa	Transplacental	Sex Chromosome FISH	NM	Died of recurrence at 18 months	Died, but duration not mentioned	Karyotype analysis was done to confirm maternal origin of cancer
Brodsky et al. (30)	28/melanoma/ skin (mid-interscapular region)	CS (failed induction)/37 weeks	Male/day 11 of life	pin point brown lesion on anterior chest wall, that progressed rapidly to involve skin of the left shoulder and posterior chest wall	Skin	Transplacental	HPE of placenta	Malignant cells found in the cord blood. (villous invasion present).	Died at 48 days of age, MODS	Sudden death at 17 days post-partum	None
Raso et al. (31)	NR/melanoma/ not reported	NM/NM	Male/6 months	Tumor swelling in temporal region	Middle ear, temporal bone	Transplacental	Quantitative PCR	NAD	Alive and Healthy at 12 years	Died few weeks after delivery	None
Valenzano Menada et al. (32)	28/melanoma/ skin (right gluteus), f/b multiple bilateral breast masses and a growing right inguinal lymph node	CS (morbid maternal condition)/ 31 weeks	Male/3 months	Restlessness and peripheral defect of the left facial nerve	Left mastoid	Transplacental	Sex Chromosome FISH	Placenta normal grossly and microscopically (absent)	Alive and healthy at 2 years	Died at 2 weeks post-partum d/t liver failure.	Spontaneous regression
Pourtsidis et al. (33); Chrysouli et al. (34)	31/melanoma/ not mentioned	CS/33 weeks	Female/8 months	Swelling and erythema of the left cheek and the mastoid region, f/b a 4-day otorrhea and fever	Mastoid cavity	Transplacental	Real Time PCR and High resolution melt analysis	Placental microscopic examination was not done	Alive and healthy at 16 months	Died at 3 months post-partum.	None

Table 2. Continued

Author and Year of publication	Age/type of cancer/ primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
De Carolis et al. (35)	31/melanoma/ left ovary with positive peritoneal fluid cytology associated with bilateral breast masses.	CS/27 weeks	Male/4 months	Epileptic seizure. A brain CT scan documented the presence of metastatic lesions	Brain	Transplacental?	Placenta was involved pathologically	Placenta involved, Gross and Microscopic (Villous invasion present)	Died at 5 months due to metastasis to brain	Died at 12 weeks post-partum	Autopsy of baby not performed. HPE of baby's tumors not done. Baby has brain tumors, but not known, what they were ??
Canu and Dutriaux (36)	39/melanoma/ skin (left arm)	CS/IUFD	NR/ intrauterine fetal death	Ultrasound at 32 weeks, suggested IUFD of one twin	Skin (about 20 subcutaneous nodules, six of which were pigmented)	Transplacental	Not confirmed	Not known	Intrauterine fetal death	Not mentioned	IUFD d/t feto-maternal haemorrhage, most likely secondary to a breach caused by a placental metastasis
Naidu et al. (37)	NR/melanom/ skin (face)	CS (prev. LSCS)/ full term	Female/3 months	6-week h/o multiple bluish-black cutaneous lesions on scalp and buttocks	skin, brain (multiple), lung and liver	Transplacental	Both the mother and the infant's melanoma tested positive for the B-Raf proto-oncogene (BRAF) mutation.	Placenta involved, Gross and Microscopic (villous invasion not mentioned)	Died at 2 years of age	Died at 8 months d/t widespread metastasis.	None
Dargeon et al. (38)	28/melanoma/ skin (right leg)	CS/8 months	Male/9 months	Left facial palsy	Left EAC, mastoid, left preauricular lymph node, liver, subpleural, right adrenal, left testicle	Transplacental?	Not confirmed	Microscopic examination not done (not known)	Died at 10.5 months.	Died at 4 days post-partum	Post-mortem brain examination not performed
Lo et al. (39)	33/melanoma/ not reported	NM/NM	Female/5 months	Skin lesion on forehead	Skin	Transplacental?	Not confirmed	NM	Died of disease at 28 months	Died 10 months after delivery	None
Ferreira et al. (40)	33/melanoma breslow 10.7 mm/left shoulder	CS/full-term	NM/ IUFD	Multiple skin lesions	Skin	Transplacental	Placenta was involved pathologically	Placenta involved, Gross and Microscopic (villous invasion present)	NM	Died after 2 days of delivery	None

CS: Caesarean section, CT: Computer tomography, d/t: Due to, EAC: External auditory canal, FISH: Fluorescent *in-situ* hybridisation, f/b: Followed by, h/o: History of, HPE: Histopathological examination, IUFD: Intra-uterine fetal death, LSCS: Lower segment caesarean section, NAD: No abnormality detected, NM: Not mentioned, PCR: Polymerase chain reaction, VD: Vaginal delivery, NR: Non-representative

Table 3. A summary of all cases of other cancers (leukaemia, lymphoma, lung cancer and cervical cancer), reported in literature with suspected or confirmed, vertical transmission

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/GA at birth	Child's sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Cramblett et al. (41)	32/ALL	VD/full term	Male/9 months	Irritable, anorexic for a few days, easy bruisability, bleeding gums, petechiae, ecchymosis and hepato-splenomegaly	Widespread	Transplacental ?	Not confirmed	Not done, because not suspected (not known)	Details not available, At last follow up, mentioned to be in partial remission	Died of disease	Transplacental transmission not confirmed
Osada et al. (42)	32/AML M5a/ presented with continuous vaginal bleeding after delivery	VD/full term	Male/20 months	1 week h/o un-explained fever, exophthalmos, gingival swelling, and pronounced hepatosplenomegaly.	NM	Transplacental transmission probable	Karyotype and Immunohistochemistry Immune adherence assay (no serological reaction between infant serum and maternal & self-leukemic cells)	Not done, because not suspected (not known)	Alive and in remission at 2 years	Alive and in remission at 3.5 years after chemotherapy and bone marrow transplantation.	karyotype of the mother's marrow cells at diagnosis was 47,XX,+8 in 55%, 47,XX,+8,t(11;12)(q23;q22) in 30%,and 46,XX in 15%.
Catlin et al. (43)	15/NK cell lymphoma/ bilateral nodular masses in the mesosalpinx	CS (fetal distress)/33 weeks	Male/4 weeks	pyrexia of unknown origin, and hepato-splenomegaly.	NM	Transplacental	Karyotype and immuno-histochemistry	Placenta involved microscopically (villous invasion present)	Died of disease at day 59 of life	Died at 20 days after delivery	The karyotype of this boy's lymphoma was female and carried the same translocation as his mother's tumor cells.
Maruko et al. (44)	29/NHL	CS (fetal distress)/ 29 weeks	Male/8 months	Till 8 months asymptomatic, developed high fever	NM	Transplacental	FISH and Immuno-histochemistry	Placenta involved, Gross and Microscopic (villous invasion present)	Died at 9 months.	Died at 5 months post-partum	None
Yagasaki et al. (45)	32/EBV-related NK/T-cell leukaemia,	CS (fetal distress)/ 30 weeks	Male/8 months	Enlarged Scrotum, d/t a testicular tumor	NM	Transplacental ?	FISH and microsatellite analysis	Not mentioned, (not known)	Not clearly mentioned. Received Multiagent chemotherapy and cord blood transplantation	Died at 25 days post-partum d/t of hepatic failure and DIC	None
Isoda et al. (46)	28/B-cell precursor Ph + ALL	VD/40 weeks	Female/11 months	Right cheek swelling	NM	Transplacental	Loss of heterozygosity analysis, STR microsatellite analysis of the DNA	NM	NM	NM	None

Table 3. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/GA at birth	Child's sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Herskovic et al. (47)	NM/ neuroendocrine cervical cancer	Induced VD/27 weeks	NR/8 months	3 month history of persistent and occasionally bloody bilateral otorrhea	lobulated, enhancing, solid lesions of the b/l petro-mastoid temporal bones	Transplacental ??; Could be by direct inoculation/ transbronchial ??	Not confirmed	Not done. (not known)	Died at 3 years and 4 months age	Died 3 days after delivery due to metastatic disease	Could have been two separate tumours with similar histopathology
Arakawa et al. (48)	35/poorly differentiated SCC of cervix with focal neuroendocrine differentiation admixed with a minor component of adenocarcinoma	VD/39 weeks	Male/23 months	2-week history of a productive cough. Lung biopsy revealed neuroendocrine carcinoma with focal glandular differentiation	Lung f/b multiple	Aspiration of tumour cells into the lung	NGS - Both tumors had the same pathogenic mutations FISH - Tumor in the boy lacked Y chromosome. Both tumors – HPV-18 +	Not done. (not known)	Child survived	Died at 3.5 years d/t disease progression	Some tumor nodules showed Spontaneous Regression.
Arakawa et al. (48)	NM/ adenocarcinoma cervix	VD/38 weeks	Male/6 years	Chest pain on the left side. CT revealed a mass at hilar region of the left lung; On HPE- mucinous adenocarcinoma	Lung f/b multiple	Mother-to-infant vaginal transmission through aspiration of tumor-contaminated vaginal fluids during birth.	NGS and FISH WES - Additional 14 somatic mutations that were present in tumors from both the mother and the child. Both tumors – HPV-16 +	Not done. (not known)	Child survived	Died after 2 years of Radical hysterectomy	NGS- Both tumors had the same KRAS (c.G35A:p. G12D) and STK11 (c.464+1G→A) mutations.
Tolar et al. (49)	37/small-cell carcinoma of the lung	CS/33 weeks	Male/5 months	Detected on imaging	Liver and right lung	Transplacental	Placenta infiltrated with small-cell carcinoma Karyotype and FISH	Placenta involved microscopically (villous invasion not mentioned)	Child survived	Died at 5 months d/t metastatic disease.	None
Walker et al. (50)	45/poorly differentiated carcinoma of Lung Stage 4	CS (morbid maternal condition)/32 weeks	Male/2 weeks	Four rapidly growing scalp nodules	Scalp	Transplacental ?; direct implantation ?	Not confirmed	Not done. (not known)	Child survived	Died.	None
Teksam et al. (51)	37/small-cell carcinoma of the lung	CS (fetal distress)/ 33 weeks	NM/5 months	lung nodules on imaging, hypermetabolic on PET scan	Lung, liver, brain	Transplacental	Not confirmed, assumed because placenta was involved	Placenta involved microscopically (villous invasion not mentioned)	Died at 23 months	Died at 5 months d/t metastatic disease.	None

AML: Acute myelogenous leukemia, b/l: Bilateral, CS: Caesarean section, CT: Computer tomography, DIC: Disseminated intravascular coagulation, d/t: Due to, EBV: Epstein barr virus, FISH: Fluorescent *in-situ* hybridisation; f/b: Followed by, HPE: Histopathological examination, HPV: Human papilloma virus, NGS: Next generation sequencing, NHL: Non-hodgkin lymphoma, NK: Natural killer, NM: Not mentioned, SCC: Squamous cell carcinoma, STR: Short tandem repeat, VD: Vaginal delivery, WES: Whole exome sequencing

Mechanisms of transplacental cancer transmission, engraftment and survival

Unlike vertical transmission of infectious agents, cancer cells typically cannot cross the placental barrier due to robust immune surveillance and the placental membrane's selective permeability (Figure 2). However, certain conditions can allow this rare transmission, leading to significant clinical and research implications. Several hypotheses explain how cancer cells might breach the placental barrier and establish themselves in the fetus (Figure 3) including the following.

Immune tolerance

In pregnancy, immune tolerance, the immune system's ability to recognize and not attack the own body's cells, is critical (53). The mother's immune system must tolerate the fetus, which expresses maternal and paternal antigens, to avoid attacking it as foreign tissue. This tolerance is mediated by

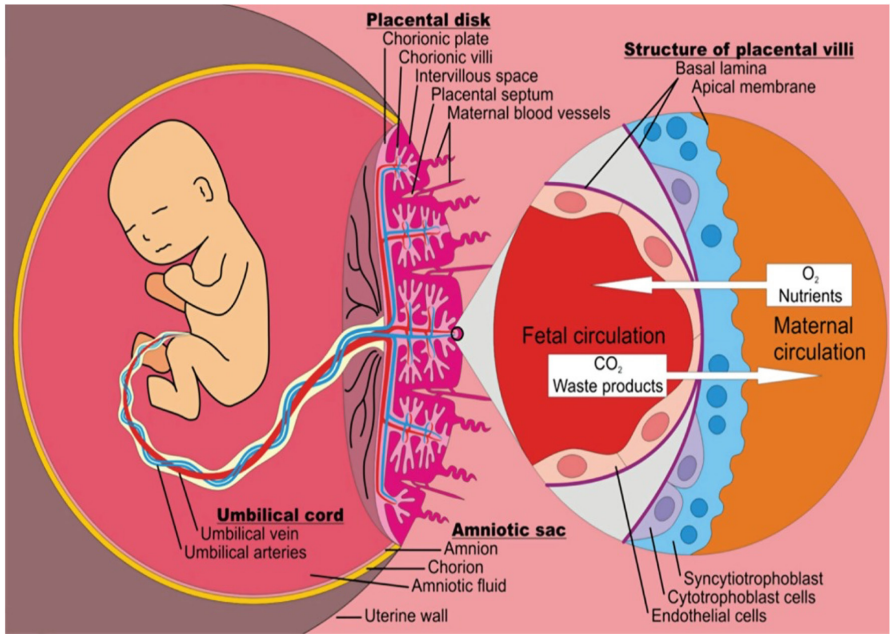

Figure 2. Diagrammatic illustration of the placental membrane that separates fetal and maternal circulations in the human placenta. (Image courtesy of Prof. Christiane Albrecht, University of Bern. All rights and permissions to use this figure are owned by her. Reproduced with permission)

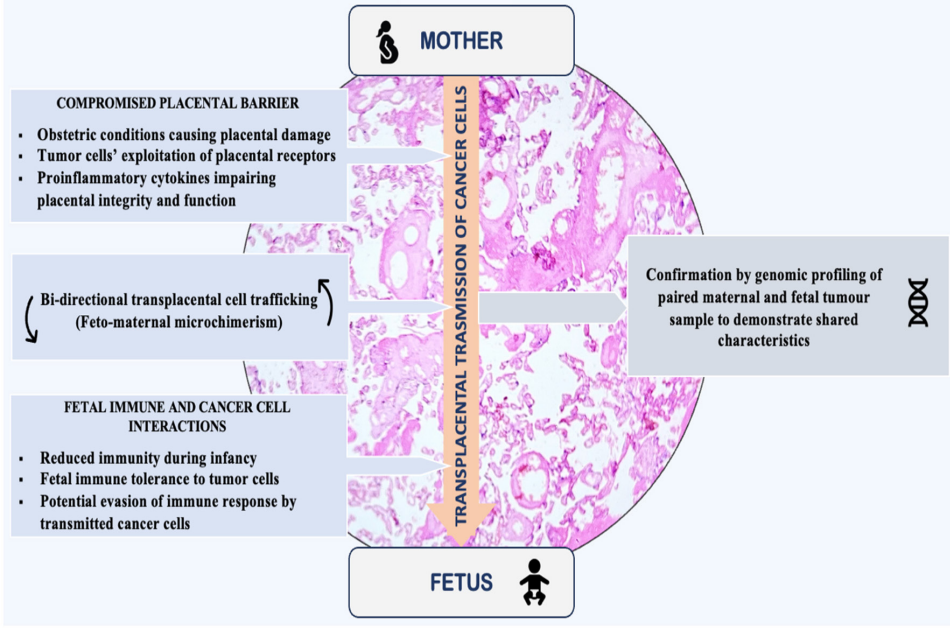

Figure 3. Various mechanisms of vertical transmission of cancer

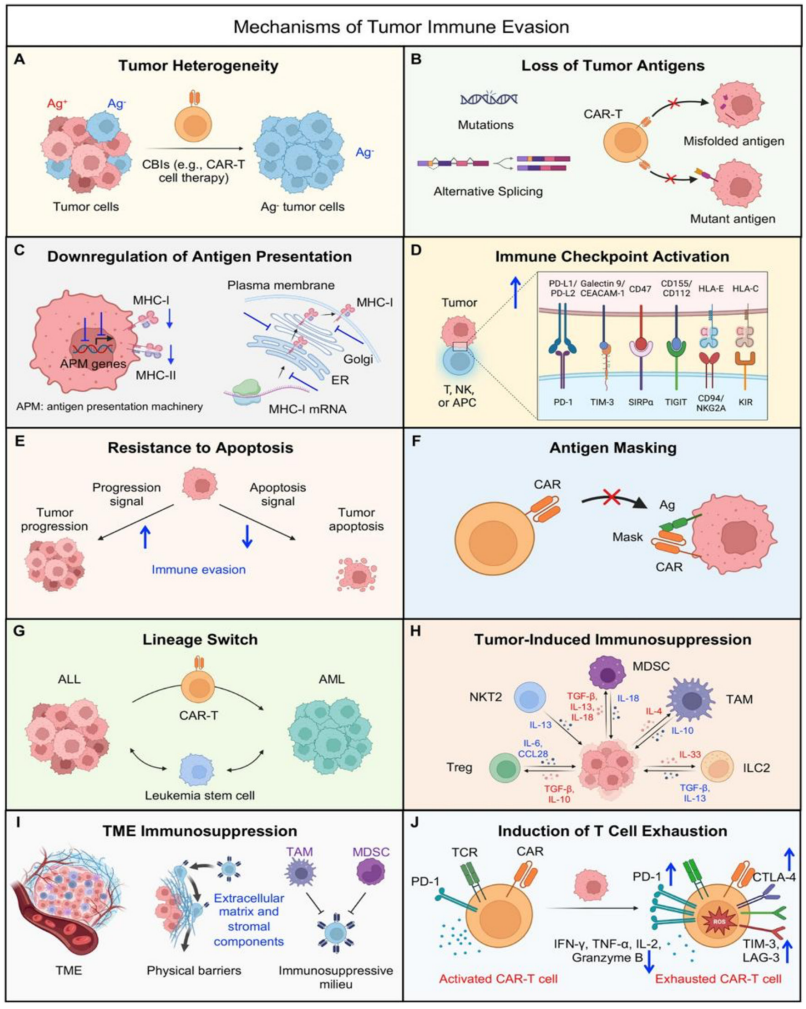

Figure 4. Mechanisms of tumor immune evasion. Tumor cells employ a diverse array of immune evasion mechanisms that curtail the effectiveness of cell-based immunotherapies, such as CAR-T cell therapies. These multifaceted strategies encompass tumor heterogeneity (A), tumor antigen loss (B), antigen presentation downregulation (C), immune checkpoint activation (D), apoptosis resistance (E), antigen masking (F), tumor lineage switch (G), tumor-induced immunosuppression (H), tumor microenvironment (TME) immunosuppression (I), and induction of T cell exhaustion (J) [Reproduced from Li YR, Halladay T, Yang L. Immune evasion in cell-based immunotherapy: unraveling challenges and novel strategies. J Biomed Sci. 2024;31(1):5. doi: 10.1186/s12929-024-00998-8]

various mechanisms, including the action of regulatory T cells, placental hormones, and other immunomodulatory factors that help maintain a healthy pregnancy (54).

Vertical cancer cell transmission occurs during the perinatal period, a time when the fetus is still developing immunity. Thymic development begins around week 8 of human gestation, and initial fetal T cells populate the periphery by weeks 12-14 of gestation (55). If cancer cells are transmitted before this period, they may not be recognized as foreign antigens, potentially evading an immune response, resulting in their engraftment or growth. Moreover, maintaining pregnancy requires tolerance to self-in and non-inherited maternal antigens, primarily regulated by regulatory T cells. Intrauterine hypoxia or placental hormones may influence maternal tolerance by modulating T cell function. Taken together, fetal immune immaturity/tolerance could play a role in facilitating the engraftment and survival of maternal-derived cancer cells within the body. However, the specific mechanistic evidence for fetal cancer immune tolerance remains to be demonstrated conclusively (56-60).

Bi-directional transplacental cell trafficking (feto-maternal micro-chimerism)

It is well-documented that normal blood cells migrate between mother and fetus and *vice versa*, leading to micro chimerism. Micro-chimerism refers to a small population of cells originating

from another individual, making them genetically distinct from the host individual's cells (61,62). During pregnancy, there are two types of feto-maternal micro-chimerism: fetal micro-chimerism (FMc) and maternal micro-chimerism (MMc). FMc occurs when fetal cells persist in maternal tissues, while MMc involves the presence and maintenance of maternal cells in fetal tissues (63-65). It is, therefore, quite plausible that maternal cancer cells can sometimes take advantage of this mechanism of micro chimerism, leading to carcinogenesis in the infant (1).

Immune evasion: How cancer cells escape immunity

Cancer cells can escape the immune system through various mechanisms, enabling them to survive, proliferate, and spread within the body (Figure 4) (66). Tumour cells gradually develop mechanisms to evade immune surveillance, a process known as "cancer immunoediting," to avoid elimination by immune cells with antitumor properties. Cancer cells can exploit immune checkpoints, regulatory pathways in the immune system that prevent excessive immune responses. For instance, they may overexpress proteins like Programmed Death-Ligand 1 (PD-L1), which binds to PD-1 receptors on T cells, leading to T cell inactivation and immune evasion (67,68). Tumor microenvironment might further dampen the immune response by recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells that inhibit other immune cells and elaboration of immunosuppressive cytokines like transforming growth factor-beta and interleukin 10 (IL-10).

Tumor cells can downregulate the expression of major histocompatibility complex molecules on their surface, essential for presenting tumor antigens to T cells (69). This prevents the immune system from recognizing and attacking the cancer cells. Immune evasion through the loss of heterozygosity of *HLA* genes has also been proposed (70). Loss or mutation of molecules involved in the antigen-processing machinery can also impair antigen presentation. Cancer cells can develop resistance to apoptosis, which allows them to survive despite immune attacks (71). Cancer cells can secrete various substances that inhibit immune cell function, such as indoleamine 2,3-dioxygenase, which depletes tryptophan and suppresses T cell activity.

Placental microscopic trauma

Trophoblasts, chorionic villi, and capillary endothelium separate the fetal and maternal circulations (Figure 2). Along with the fetal immune system, the placental barrier prevents the spread and allografting of maternal tumors into the fetus. Despite this protection, the transmission of neoplastic and non-neoplastic maternal cells to the fetus does occur during pregnancy. Suppose the separation between the fetal and maternal blood systems is breached, maternal intravascular tumour cells can cross the placenta and reach the fetal liver through the umbilical vein or the fetal lungs via the ductus venosus (49).

Several obstetric conditions can cause microscopic damage to the placenta, affecting its structure and function. Preeclampsia and placental fetal growth restriction can lead to placental infarcts, intervillous fibrin deposition, and increased syncytial knots, resulting in reduced placental perfusion and placental insufficiency. Gestational diabetes leads to villous immaturity, and villous hyperplasia. There can also be increased deposition of glycogen in the placental tissue. Placental abruption can cause haemorrhage into the placental tissue, leading to infarcts, necrosis, and fibrin deposition. Maternal infections, such as chorioamnionitis, may cause inflammatory changes in the placenta, including villitis and funisitis, leading to damage and sometimes necrosis of the placental tissue. Each of these conditions may compromise placental ability to effectively control cell and nutrient traffic across the placental membrane, potentially leading to adverse pregnancy outcomes (49,50).

Placental receptor similarity and reduced placental function

Tumor cells may exploit receptors on placental cells to gain entry into fetal circulation, mimicking the way nutrients and other substances pass through. Also, given the similarities between tumor cells and trophoblastic cells in biological processes, there is substantial evidence that maternal tumour-induced effects could impact placental function (72). Studies have indicated that the presence of maternal cancer or certain tumor factors, such as proinflammatory cytokines IL-6, interferon-gamma (IFN-γ), and tumour necrosis factor, can impair the placental integrity and function (73,74). These factors may play a role in the vertical transfer of cancer clones. However, more research is needed on how the damage caused by cancer cells in the placenta facilitates transplacental cancer spread.

Diagnostic confirmation of vertical transmission

Modern genetic tools, such as DNA sequencing and genomic profiling, can compare the genetic material of maternal and fetal tumors, providing concrete evidence of the origin of the cancer. Next-generation sequencing (NGS) can be used to look for mutations in the tumor that are present in the maternal DNA but absent in the patient's germline DNA, which can help determine if the cancer was inherited from the mother. Since mitochondrial DNA (mtDNA) is inherited maternally, analyzing mtDNA from the tumor and comparing it to the maternal mtDNA can provide additional clues. SNP arrays can be used to compare genetic variations between the tumor, patient's germline or maternal DNA, which can further help identify the source of the cancer (75-77).

Most of the studies have used karyotyping or fluorescent *in situ* hybridisation (FISH) techniques, as the absence of Y

chromosome in the cancer tissue, in a male fetus, provides indirect evidence that the tumor originated from the mother. Involvement of placenta by the tumor, on gross and microscopic examination, particularly the presence of villous invasion, also implies that the transmission occurred through the placenta. Arakawa et al. (48) recently reported two intriguing cases of perinatal transmission of maternal cervical cancer to the infant, subsequently developing into lung cancer. FISH analysis revealed the absence of the Y chromosome in tumor in the male babies and upon sequencing, both the tumors in the mothers and babies showed shared genomic tumor characteristics, which substantiates mother-to-infant vaginal transmission through aspiration of tumor cell-contaminated vaginal fluids during birth.

Treatment considerations: Why is an understanding of transplacental cancer transmission essential?

Clinicians must distinguish whether the tumor in the newborn is a primary disease or a metastasis from the mother as treatment protocols differ drastically between congenital cancers and those acquired through transmission. Vertical transmission of metastases could be viewed as a "haploidentical transplant" (78). In this scenario, the newborn's already functional immune system might reject non-inherited maternal antigens. Consequently, administering modified or reduced therapeutic regimens could be justified, allowing the newborn's immune system time to develop effective responses. The possibility of transplacental cancer transmission also brings forth ethical dilemmas. Decisions regarding the continuation of pregnancy, the timing of delivery, and the treatment options for both mother and child are complex and emotionally charged. Counselling and psychological support for affected families are critical components of care.

Due to the rarity of infant melanoma, infants and children have not been included in the majority of clinical trials for treatment, resulting in a lack of specialized treatment standards for this population. Consequently, current treatment strategies for melanoma in this age group are derived from adult treatment protocols. Surgery remains the primary treatment for melanoma in both children and adults. For pediatric patients with more advanced disease, biologic therapies are more commonly used than chemotherapy or radiation therapy (79). Since *BRAF* mutations are present in approximately 50% of melanoma patients, BRAF inhibitors like Vemurafenib and Dabrafenib, and other specific inhibitors like Trametinib, which targets other components of the MAPK signal transduction pathway, such as MEK1 and MEK2, provide an effective therapeutic option for patients with this mutation. Another treatment approach involves modulating the host's immune system to target melanoma. Immunotherapy drugs, such as Ipilimumab, use monoclonal antibodies to suppress CTLA-4, enhancing the immune system's response to tumor cells. Agents like IL-2 activate the immune system to attack malignant cells. High-dose interferon alfa-2b has shown promising results in children with melanoma with an acceptable risk-benefit profile. In addition, anti-PD1 antibodies, such as Pembrolizumab and Nivolumab, have the potential to improve prognosis with long-lasting effects (80,81). One such case with successful treatment with nivolumab therapy has been reported by Arakawa et al (48).

As with other germ cell tumors, the management of choriocarcinoma in infants and children involves a comprehensive approach with multi-agent neoadjuvant chemotherapy, reassessment after 2-4 cycles, surgical removal of persistent disease, and adjuvant chemotherapy. This complex therapy aims to control the metastatic nature of the disease and prevent relapse. Upfront chemotherapy is particularly crucial for children with multi-systemic involvement who are not candidates for immediate surgery. The excellent survival rates observed in this review reinforce the effectiveness of these treatment principles, which are well-established and readily available (82,83). In most current protocols, treatment is stratified based on an initial risk assessment that includes age, site, histology, stage, completeness of resection, and tumor markers alpha1-fetoprotein and human chorionic gonadotropin (β-HCG). Using these modern protocols, overall cure rates exceed 80%. Moreover, previously high-risk groups can now expect a favourable prognosis with risk-adapted treatment, while an increasing number of low-risk patients are managed expectantly or with significantly reduced chemotherapy (82).

Conclusion

Transplacental transmission of cancer, while rare, poses significant medical and ethical challenges. It underscores the complexity of the placental barrier and the interactions between maternal and fetal health. Advances in genetic diagnostics and a deeper understanding of immune mechanisms hold promise for better management and outcomes for both mothers and their children. NGS of paired tumors (both mother and baby) and normal tissue samples might be a valuable method for diagnosing cancer transmitted from mothers to infants and for understanding how common this transmission is. Furthermore, analysing the HLA haplotype of cancer cells and peripheral normal lymphocytes may offer insights into the risk of maternal-to-fetus transmission. Continued research and interdisciplinary collaboration are essential in unravelling the mysteries of this unique cancer transmission pathway.

Footnotes

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The future of research on vulvar intraepithelial neoplasia: towards precision diagnostics and risk stratification

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Abstract

Vulvar intraepithelial neoplasia (VIN) represents a heterogeneous group of premalignant lesions arising through distinct human papillomavirus (HPV)-associated and HPV-independent pathways. Despite well-characterized differences in etiology, prognosis, and progression risk, current management remains largely uniform and predominantly surgical. This one-size-fits-all approach neglects opportunities for individualized care and exposes patients, particularly younger women and those with multifocal disease, to potentially avoidable psychosexual morbidity. Recent advances in molecular pathology, including immunohistochemistry, genomic profiling, DNA methylation analysis, and copy number alteration detection, offer promising avenues for refining diagnostic precision and enabling risk stratification. Integration of markers such as $p16^{INK4a}$, p53, and emerging methylation panels into diagnostic workflows may improve differentiation between lesion subtypes, guide surveillance, and identify candidates for conservative therapy. Moreover, the unique pathogenesis of vulvar high-grade squamous intraepithelial neoplasia, which diverges from squamocolumnar junction (SCJ)-driven models seen in other HPV-associated cancers, highlights the need for focused research on host-virus interactions and early oncogenic events in non-SCJ epithelium. Future directions include non-invasive sampling methods, molecularly-guided surveillance protocols, therapeutic HPV vaccines, and combined immunomodulatory treatments to reduce the burden of excisional therapy. Establishing precision-based approaches for VIN could not only preserve vulvar integrity and function but also improve oncological outcomes through targeted prevention and early intervention strategies. [J Turk Ger Gynecol Assoc.2025; 26(3): 230-4]

Keywords: Vulvar intraepithelial neoplasia, vulvar squamous cell carcinoma, HPV, p16, p53, DNA methylation, prevention

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Introduction

The current landscape of vulvar intraepithelial neoplasia and its limitations

Recent years have witnessed a growing emphasis on precision medicine approaches in gynaecologic oncology, including vulvar intraepithelial neoplasia (VIN). VIN encompasses a spectrum of preinvasive lesions of the vulvar epithelium, with human papillomavirus (HPV)-associated and HPV-independent lesions reflecting two distinct oncogenic pathways (1). HPV-related vulvar high-grade squamous intraepithelial neoplasia (vHSIL) is commonly diagnosed in younger women and has

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a more favorable prognosis, with a relatively low 10-year cumulative risk of invasive cancer, estimated at approximately 10% (2). In contrast, HPV-independent VIN, which often arises in the context of chronic dermatoses, such as lichen sclerosus (LS), is associated with a higher neoplastic progression rate of up to 50% and tends to affect older women (3).

Despite this evidence of difference, the clinical management of VIN is largely uniform, with excisional surgery being the mainstay of treatment regardless of individualized cancer risk (4). This approach, while effective in removing dysplastic tissue, carries significant psychosexual and anatomical consequences, especially for younger patients or those with multifocal disease (5). Moreover, the diagnosis of HPV-independent VIN remains challenging, given its subtle histological presentation and overlap with benign inflammatory dermatoses (6). Thus, a critical gap persists in our ability to identify patients at high risk for progression and those who could benefit from conservative or surveillance strategies.

The future of VIN research lies in refining diagnosis precision, integrating histopathological features with molecular biomarkers, with the aim of improving diagnostic accuracy, stratifying risk, and guiding individualized surveillance and treatment strategies. This would ultimately facilitate personalized treatment paradigms.

Biomarker-driven diagnostics and prognostics

A giant step towards addressing this gap would be the integration of objective molecular biomarkers into both diagnostic and prognostic algorithms. Advances in molecular pathology have opened new frontiers in the diagnosis and classification of VIN, offering tools that enhance histological interpretation and provide insight into the biological behavior of preinvasive lesions. The integration of immunohistochemical (IHC) and genomic markers into routine diagnostic workflows promises to improve the accuracy and reproducibility of VIN classification and identify the lesions with a higher risk of malignant transformation (7).

The IHC markers $p16^{INK4a}$ and p53 are central to the distinction between HPV-related and HPV-independent pathways:

- p16 overexpression is a surrogate marker of high-risk HPV oncogenic activity. It is consistently positive in HSIL and facilitates its recognition, especially in morphologically ambiguous cases (8).
- p53 expression patterns, on the other hand, are particularly valuable in identifying HPV-independent VIN. Aberrant p53 staining is frequently associated with mutations in the *TP53* gene and correlate with HPV-negative carcinogenic pathways (7). In LS lesions, mutant p53 staining has been significantly associated with progression to vulvar squamous cell carcinoma (VSCC), with odds ratios exceeding 30, suggesting a pivotal role for *TP53* dysfunction in HPV-independent carcinogenesis (9).

Despite their usefulness, both markers have limitations in sensitivity and specificity, and interpretation can vary among pathologists. Beyond p16 and p53, several additional biomarkers are being explored:

- Ki-67, a proliferation marker, is typically elevated in VIN, but lacks the discriminatory power needed for subtype differentiation (10).
- CK17, SOX2 and GATA3 can be useful in the diagnosis of HPV-independent VIN, p53 wild-type lesion and its distinction from hyperplastic non-neoplastic vulvar lesions (11).

Emerging next-generation sequencing studies have begun to elucidate the genomic alterations that differentiate HSIL, HPV-independent VIN, and invasive VSCC (12). These include mutations in *NOTCH1*, *TP53*, *CDKN2A*, and others, with HPV-independent VIN lesions showing higher molecular instability (13).

Recent studies have identified DNA methylation signatures as promising tools for both diagnostic and prognostic applications in VIN. A panel including *ZNF582, SST,* and *miR124-2* has shown robust performance in detecting VIN, including the HPV-independent subtype, with area under the curve values approaching 0.90 in large validation cohorts (7). These markers not only differentiate VIN from benign dermatoses, like LS, but also correlate with an increased risk of malignant transformation.

Emerging evidence demonstrates that copy number alterations (CNAs) co-occur with elevated DNA methylation levels and are associated with increased severity of disease. A study using modified fast aneuploidy screening sequencing (mFAST-SeqS) identified gains in chromosomal arms (e.g., 1pq, 3q, 9q) and losses (e.g., 2q, 4q) as potential markers of progression risk in HPV-associated VIN (14). A significant positive correlation between aneuploidy scores and methylation burden suggests a synergistic model of genetic and epigenetic dysregulation in VIN pathogenesis (14).

Pathogenesis of HPV-associated vulvar high-grade squamous intraepithelial lesion

In the cervix, anus and oropharynx, high-risk HPV (hr-HPV) preferentially infects multipotent reserve cells that lie immediately beneath the columnar epithelium of the squamocolumnar junction (SCJ). These reserve cells, which retain an embryonic immunophenotype (CK7-positive/p63-negative), appear exquisitely vulnerable to viral oncoprotein-driven deregulation and give rise to most high-grade squamous intraepithelial lesions and carcinomas in those organs (15).

By contrast, the vulva lacks a discrete SCJ, indicating that hr-HPV-driven carcinogenesis in the vulva must originate in non-SCJ basal keratinocytes, possibly in the hair-bearing labial skin or its associated appendages and, at the level of the vulvar vestibule, micro abrasions or epithelial disruptions may enable HPV to access basal cells in an otherwise intact stratified squamous epithelium (16). The absence of a privileged SCJ-derived stem-cell niche may explain the substantially lower incidence of vulvar neoplasm compared to cervical cancer, despite comparable HPV exposure. Research should explore putative different host-virus interactions, immune surveillance pressures and micro-environmental cues that govern malignant progression in the vulva.

Current molecular work is directed at identifying the earliest driver events in vHSIL (e.g., E6/E7-mediated $p16^{INK4a}$ up-regulation, APOBEC mutational signatures, and field changes in the vestibular epithelium). Clarifying this pathway is expected to uncover targetable vulnerabilities, such as epigenetic modifiers or immune checkpoints, and to refine risk stratification algorithms for lesions that may otherwise remain indolent.

Prevention and treatment strategies

Standard of care

All guideline-issuing bodies agree that every histologically confirmed VIN warrants treatment because of the possible progression to invasive carcinoma if left untreated. Wide local excision with free macroscopic margins remains the reference therapy and is recommended whenever invasion cannot be excluded clinically or histologically (17). Excision provides a specimen for margin assessment but is intrinsically disfiguring and may compromise sexual function.

For cases of multifocal, HPV-associated, HSIL cosmetic outcome is paramount, laser or radio-frequency ablation that destroys the full epithelial thickness is an accepted alternative when stromal invasion is excluded with adequate biopsies. Topical 5% imiquimod three times weekly for 12-20 weeks yields complete histologic regression in 35%-60% of selected cases, with durability linked to clearance of oncogenic HPV DNA (18).

As mutilating surgery is still the price of cure for many women, translational research should prioritize:

1. Combined modality regimens (e.g., fractional ablation plus topical or intralesional immunomodulators) aimed at maximizing viral clearance while preserving anatomy;
2. Therapeutic HPV vaccines that expand lesion-specific tissue-resident memory T cells; and
3. Molecularly-guided surveillance using viral or host methylation markers to individualize follow-up intensity and trigger pre-emptive therapy only for lesions with a high progression signature.

Future research should also aim to explore non-invasive treatment approaches for HPV-independent VIN, recognizing its significantly higher propensity for rapid progression to invasive carcinoma compared to HPV-associated vHSIL. Notably, the molecular and genetic landscape of dVIN closely mirrors that of invasive squamous cell carcinoma, underscoring its biological aggressiveness and the urgency for early, effective, and potentially conservative therapeutic interventions.

Collectively, these strategies aspire to reduce treatment morbidity without sacrificing oncological safety, a goal that can only be met if the unique vulvar pathogenetic cascade is fully elucidated.

Clinical implications and future research directions

VIN lies at the crossroads of gynecology, dermatology, pathology, virology, and oncology. Strengthening interdisciplinary collaboration is therefore paramount for both research and especially in patient care pathways.

Current surveillance protocols for VIN are largely empirical and not risk-adapted (4). By integrating methylation testing, CNA profiling, and p53 IHC, clinicians could stratify patients into low-, intermediate-, and high-risk categories. This would facilitate tailored and more judicious use of surgical intervention, earlier detection of progression and different follow-up intervals.

Translating molecular diagnostics into clinical practice requires accessible and acceptable testing modalities. In analogy to cervical and anal cancer screening, methylation-based assays could be adapted for non-invasive sampling, such as vulvar swabs or self-collection devices. This would be especially valuable in the context of immunocompromised women, women with other lower genital tract HPV lesions or long-term monitoring of patients with LS.

Raising awareness of vulvar health is a key factor for improving women's cancer prevention strategies. Despite being a critical part of the lower genital tract, the vulva is often overlooked during routine gynecologic care (19). Evidence has highlighted that incorporating vulvar inspection into cervical cancer screening may facilitate earlier detection of vulvar precancerous lesions and malignancies, leading to improved patient outcomes (20).

Public health campaigns should focus on educating both healthcare providers and the general population about the importance of vulvar examination. Routine inspection of the vulva, combined with appropriate patient education on recognizing symptoms, such as persistent itching, lesions, or pain, can significantly reduce diagnostic delays.

Clear, evidence-based public health messages and multidisciplinary collaborations are needed to normalize discussions around vulvar health, reduce stigma, and empower women to seek timely medical advice. By integrating vulvar

inspection into established cancer screening programs, we could take an important step forward in comprehensive women's health care.

Conclusion

The future of research on VIN is moving towards an integrated molecular framework that transcends traditional morphology. By leveraging advances in DNA methylation profiling, genomic instability assessment, and IHC markers, we are approaching an era of precision gynecologic oncology, in which risk-adapted strategies can improve outcomes while preserving quality of life.

Elucidating the distinct, non-SCJ pathway by which high-risk HPV drives vHSIL is essential, as it will clarify early oncogenic events and identify molecular or immunologic targets for management. While wide local excision remains the oncologic standard for non-HPV-associated VIN, future combined therapeutic vaccines, topical immunomodulators and biomarker-guided surveillance should be researched in order to reduce mutilation while maintaining cure rates. Raising awareness about VIN remains a critical public health priority. Many cases are undiagnosed because of non-specific symptoms, individual patient stigma, or lack of routine vulvar examination in gynecologic care. Educational campaigns targeting both healthcare professionals and patients will be important for promoting and improving early detection.

Footnotes

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What is your diagnosis?

A 34-year-old woman, P2L2, presented to the outpatient department with a one-month history of abdominal distension. It was sudden in onset, progressive, and associated with abdominal pain and heaviness, accompanied by backache. She reported irregular and frequent menstrual cycles for two years. A history of loss of appetite and constipation was also present. Abdominal examination revealed a grossly distended abdomen with a huge abdominopelvic mass corresponding to 30 weeks' size involving all quadrants of the abdomen, with no shifting dullness and fluid thrill. External genitalia, cervix and vagina appeared healthy. The same abdominopelvic mass was felt on vaginal examination with bilateral fornical and pouch of Douglas fullness; uterus could not be palpated separately. Ultrasound was suggestive of a large (26x25.3x14.7 cm) cystic lesion with septations and Doppler color flow, but the bilateral ovaries and uterus were not defined separately. Among tumor markers, CA-125 (339 U/mL) and lactate dehydrogenase (LDH) (1650 U/L) values were raised while carcinoembryonic antigen, alpha-fetoprotein (AFP), beta-hCG and CA19-9 levels were within normal limits. A contrast-enhanced magnetic resonance imaging study was ordered for mass characterization and reported a 28x25x18 cm large solid cystic mass in the right adnexa with solid areas, apparently a right ovarian neoplastic mass. In view of a high suspicion of ovarian malignancy, staging laparotomy was planned after thorough counseling of the patient and her husband. She had no desire for future fertility and was keen to undergo definitive surgery in a single session. A prior written consent was obtained for staging laparotomy, along with hysterectomy and contralateral oophorectomy, if intraoperative frozen section suggests epithelial ovarian malignancy.

Intraoperatively, straw-coloured ascites (≃800 cc) was noted. An approximately 30x30 cm large solid cystic mass was seen arising from the right ovary with an intact capsule and no surface excrescences. The mass was dissected from all attachements. It weight 5.8 kg (Figure 1A). The cut specimen contained 2.5 litres of hemorrhagic fluid with multiloculated cystic, solid and necrotic areas (Figure 1B). The frozen section was suggestive of serous cystadenocarcinoma. Therefore, complete cytoreductive surgery was performed (total abdominal hysterectomy, left salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, and gastric arcade sparing omentectomy).

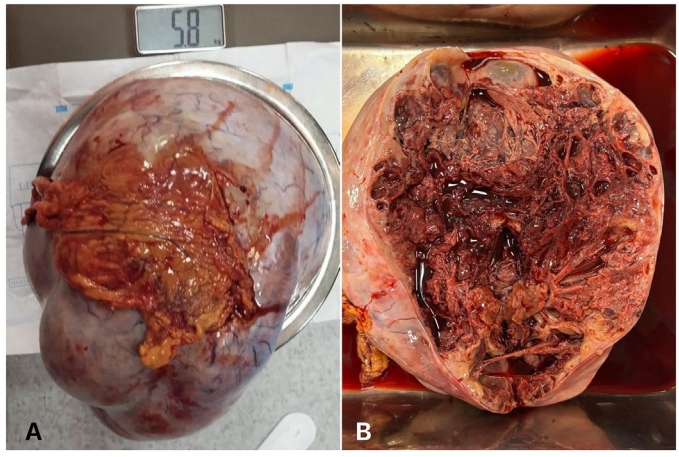

Figure 1. (A) Right ovarian mass weighing 5.8 kg; (B) The cut specimen containing 2.5 litres of hemorrhagic fluid with multiloculated cystic, solid and necrotic areas

Answer

The final histopathology report revealed the diagnosis of a Sertoli Leydig cell tumor (SLCT) FIGO stage 1A with calretinin focal positive, CD 56 focal positive, vimentin positive and PR focal positive (Figure 2).

Inhibin A and B levels were ordered after the final diagnosis, which were within normal limit (0.8 ng/L and <10 pg/L, respectively). A medical oncology opinion was sought, and she was planned for three monthly follow-ups with CA-125 measurements.

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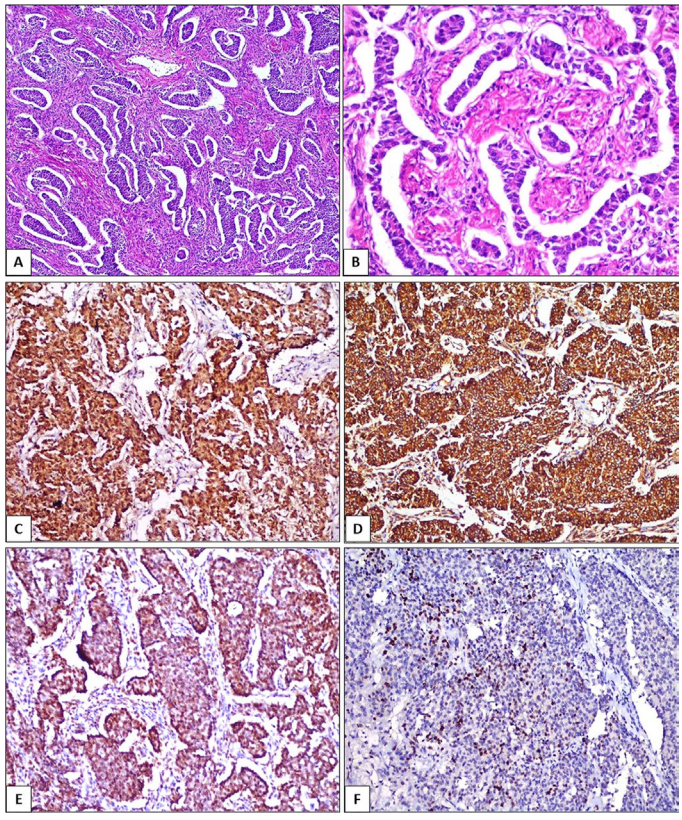

Figure 2. (A) Haematoxylin and eosin stained section shows Sertoli cells arranged in nests and tubules without significant nuclear atypia. Delicate fibrous stroma contains Leydig cells singly (Ax100); (B) Higher magnification shows irregular solid tubules, nests of Sertoli cells with mild cytological atypia and plump eo-sinophilic Leydig cells in within stroma (Bx200); (C) Immunohistochemistry (IHC) demonstrating positivity for Vimentin; (D) Immunopositive for calretinin; (E) Weak minimal positivity for WT-1; (F) IHC for Ki-67 shows mild mitotic activity

Postoperative CA-125 values were 9 U /mL and 5.50 U/mL at 3 months and 6 months, respectively. Currently, she is asymptomatic with no signs of radiological or biochemical recurrence.

SLCTs are a rare group of ovarian malignancies that contribute to <0.5% of all ovarian neoplasms (1). It occurs mostly in prepubertally or within the first three decades of life (2,3). It is the most common virilizing ovarian tumor. These tumors frequently produce sex steroid hormones, mostly androgens. Therefore, most of the patients present with overt virilization (amenorrhea, hirsutism, acne, hoarseness of voice, clitoromegaly, labial hypertrophy and psycho-sexual behavioral changes) (2-5). Rarely, patients may present with features of hyperestrogenism, i.e. precocious pseudopuberty, menometrorrhagia and postmenopausal bleeding (6). In the absence of hormonal manifestations, patients may present with non-specific mass symptoms like abdominal distension, pain, and heaviness (7). Hence, preoperative diagnosis may be challenging. The present case also had an atypical presentation with complaints of abdominal distension, pain and frequent menstrual cycles. The majority of SLCTs are unilateral and classified as stage I. In the literature, the largest size of SLCT documented was 24 cm, with an average size being 12-14 cm (7,8), whereas the mass in the present case was 30 cm and weighed 5.8 kg.

Grossly, SLCTs show solid, fleshy, yellow, and lobulated cut surfaces with focal cyst formation. Histologically, SLCTs are classified into five sub-types: well-differentiated, moderately-differentiated, poorly-differentiated, retiform, and those with heterologous elements (1). The degree of differentiation is based on Sertoli tubular differentiation, the proportion of Leydig cell component, and the quantity of primitive gonadal stroma. Sertoli and Leydig cells of SLCTs express inhibin, calretinin, SF1, and CD5. Molecular types of SLCT are: (a) DICER1- mutant; (b) FOXL2 c.402C>G (p.Cys134Trp)-mutant; and (c) DICER1/FOXL2-wildtype (9).

Inhibin-B is the most commonly used biomarker for the diagnosis of SLCTs. However, CA-125 has also been reported to be elevated in 42% of cases of sexcord stromal tumors and has a prognostic role in such cases. Patients with raised CA-125 had worse overall survival than those with normal values (10). Our patient had raised CA-125 and LDH levels with normal AFP, inhibin A and B levels. There are no specific imaging findings pertaining to SLCTs.

Surgery is the mainstay of treatment. Since the majority of these tumors are unilateral and affect young women, a fertility-sparing surgical approach is appropriate. For women with bilateral disease, advanced stage, or postmenopausal status, a complete cytoreductive procedure, including total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed (11). Lymphadenectomy may be omitted as these tumors rarely spread to lymph nodes (12). Complete cytoreductive surgery was performed in the present case as the frozen section was suggestive of serous cystadenocarcinoma and the patient was keen to undergo definitive surgery in a single operating session. The role of frozen section is limited in the accurate diagnosis of rare ovarian tumors, such as sex cord stromal tumors and germ cell tumors, as they can mimic epithelial ovarian tumors, which was what happened in our case (13).

The scarcity of data limits the understanding of the prognostic factors of the disease and the role of adjuvant therapy. However, the grade and stage of the disease seem to be important prognostic factors. Sigismondi et al. (14) reported an excellent five-year survival rate of 100% in grade 1 tumors, while it fell to 77.8% in grade 2 and 3 tumors. They also documented a high five-year survival rate of 92.3% when tumors were localized

to the ovary, but once they become metastatic, the prognosis worsens significantly, with a five-year survival of only 33.3%. This tumor type has a relapse rate of 0 to 33.3% and 95% of them relapse within 5 years. The prognosis is extremely poor in recurrent disease, with a salvage rate of less than 20% (15).

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Is HRT a trigger for cancer in postmenopausal patients with a history of endometriosis?

Dear Editor,

We read the article entitled "management of menopause in women with a history of endometriosis" by Akgün et al. (1) with a great deal of interest. The authors discussed the hormone replacement therapy (HRT) options, indications, and contraindications in postmenopausal patients with endometriosis. Furthermore, a recently published prospective cohort study examined the relationship between endometriosis and fibroids and the risk of premature mortality, highlighting the importance for primary care providers to consider these gynecological disorders in their assessment of women's health (2). Barnard et al. (3) investigated the relationship between endometriosis typology and ovarian cancer risk. Ovarian cancer risk was highest in women with deep infiltrating endometriosis and/or ovarian endometriomas for all ovarian cancers. These authors recommended counseling regarding ovarian cancer risk and prevention (3).

As mentioned by Akgün et al. (1), endometriosis is a hormone-dependent condition and residual or recurrent endometriotic lesions might still be found in menopause. In this scenario, we would like to ask whether HRT might increase the risk of malignancy. A recent meta-analysis reported that the risk of ovarian malignancy, especially for serous histological type, increased with prolonged exposure time, especially when estrogen replacement therapy (ERT) exceeded 10 years. In the same meta-analysis, it was recommended that long-time users should consider continuous estrogen-progesterone replacement therapy (EPRT) as a safer alternative (4).

Moreover, Lee et al. (5) analyzed a database of ten cancers (cervical, uterine, ovarian, breast, colon, stomach, liver, lung, pancreas, and thyroid) and showed that HRT was a significant risk factor for uterine cancer, but decreased the risk of liver and thyroid cancer while ERT decreased the risks of breast and lung cancers significantly. In the same study, tibolone was not associated with the risk of any of the cancers assessed. Finally, the same group of researchers clarified in another meta-analysis that, although the use of ERT was found to be a significant risk factor for ovarian cancer, after adjusting for co-variables, HRT use, duration of HRT, EPRT and tibolone were not found to be associated with increased risk of developing ovarian cancer (6). The practical implications for clinical decision-making and a clearer differentiation of risks associated with ERT, EPRT, and tibolone would further enhance its impact.

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Author's Response

Dear Editor,

We thank Iavazzo and Gkegkes for their interest in our review on "management of menopause in women with a history of endometriosis" and reiterating the messages in it (1). As Iavazzo and Gkegkes highlight, the messages in our review have been further supported by additional epidemiological evidence since the preparation of our review. Wang et al. (2) analysed the risk of premature mortality in women with a history of laparoscopically confirmed endometriosis based on data from Nurses' Health Study II and found that laparoscopically confirmed endometriosis was associated with an increased risk of premature deaths (deaths before age 70 years), mainly driven by increased gynaecological malignancies, along with non-malignant mortality caused by respiratory disorders, senility and ill-defined diseases and diseases of the central nervous system and sense organs. These findings add a new dimension to our messages that women with endometriosis are at greater risk of cardiovascular disease, hypercholesterolemia and osteoporosis. They support our main conclusion that hormone replacement therapy (HRT) should be recommended to women who have a history of endometriosis, when they become menopausal at an early age, at least until the age of natural menopause (1). This approach is likely to improve their quality of life and may reduce the increased morbidity and mortality that the new data show in this group of women.

The article by Xiang et al. (3) is suggestive of increased risk of ovarian cancer in users of HRT who have a history of endometriosis, although more recent studies indicate the risk is minimal. The article by Lee et al. (4) is suggestive of an increase in the risk of uterine cancer but not ovarian cancer, and a decrease in the risks of liver and thyroid cancers in estrogen/progesterone users and in the risk of breast cancer in estrogen-only users. These studies indicate that there are still methodological challenges in analysing the risk of cancer in HRT users and demonstrate that further research is needed with a more robust design.

We reiterate our assertion that combined HRT with estrogen and progesterone, or tibolone should be used in women with a history of endometriosis, even after a hysterectomy, as this approach may reduce the risk of malignant transformation and disease reactivation. Future research may shed some light on the potential benefits and risks of HRT in the long-term. It is necessary to determine whether HRT contributes to the increased premature mortality due to increased gynaecological malignancies.

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Conservative management of idiopathic gross hematuria post-cesarean delivery

To the Editor,

We present a very strange case of idiopathic, gross hematuria after cesarean section where all potential causes were ruled out but the patient continued to have hematuria, which eventually was controlled with multiple irrigations of the bladder.

A 30-year-old G4P1L0A2 with a diagnosis of placenta previa presented at 28 weeks with her first episode of antepartum hemorrhage. The bleeding was minimal, bright red in color and painless. She had a history of one lower segment cesarean section (LSCS), two surgical evacuations and one hysteroscopic septal resection, which was diagnosed during cesarean section. Her previous cesarean section was an uncomplicated, term elective section for breech presentation. The patient was given conservative management as the bleeding stopped spontaneously. Since she had high risk factors for adherent placenta, Doppler ultrasound was done to rule out the same during the presentation being described herein. It was inconclusive and hence magnetic resonance imaging was done which ruled out adherent placenta. She had preterm labor after two days of admission and underwent an emergency cesarean section. There was complete placenta previa and she had a postpartum hemorrhage which was managed with stepwise devascularization along with intrauterine Foleys bulb placement in the lower uterine segment, inflated with 40 cc saline. She had an intraoperative blood loss of 1.6 liters and received three units of packed red blood cell and three units of fresh frozen plasma. She also had gross hematuria intraoperatively. The bladder integrity was checked by retrograde filling with saline followed by bladder irrigation with 1.5 liters saline. She continued to have hematuria in the postoperative period (Figure 1). There was no past history of similar episode or any renal disease. She did not have any history of easy bruising, gum bleeding or previous blood transfusions. She had a hemoglobin of 11.5 g/dL, platelet count of 2.5 lakh/dL, an international normalized ratio of 1.0 and a partial thromboplastin time of 22 seconds (normal 26 seconds), a bleeding time of one minute and clotting time of three minutes. She also had normal renal and liver function tests. On the second postoperative day, ultrasound showed clots in the bladder for which tranexamic acid was administered, together with multiple bladder irrigations. She continued to have hematuria for which a cystoscopy was done and the clots were removed. There were no abnormal vessels nor any lesion or stitch in the bladder mucosa. The ureteric orifices were also normal. The bladder irrigation was continued and the hematuria gradually subsided over the next seven days. The catheter was removed and she was discharged in good health.

Figure 1. Gross hematuria in the postoperative period

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A similar case was reported by Mujini et al. (1), where LSCS was done for placenta previa and the patient had a similar presentation and was managed conservatively with bladder irrigation and blood transfusion. In a series of three cases reported by Chauhan et al. (2), gross hematuria in the puerperium can occur even after vaginal delivery. However, the first and foremost cause to be ruled out is bladder injury. Once ruled out, conservative management can be safely administered and should include repeated bladder irrigation.

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Mobilization and protection of the ureter during laparoscopic total hysterectomy for cervical fibroids

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Abstract

Cervical fibroids (CFs) grow in the narrowest part of the uterus, which is adjacent to the ureter, uterine vessels and their branches. The ureter is at risk of being divided, thermally injured, and/or misligated when handling the vessels during total laparoscopic hysterectomy (TLH) to treat CFs We present a series of videos to detail the methods and skills required to perform blunt ureterolysis and handle the uterine vessels during TLH for CFs. This video contains three cases of CFs that underwent TLH. In Case 1, the surgeon did not separate the ureter in advance and mistook the ureter for a vessel during coagulating the vessels with bipolar forceps, which resulted in thermal injury to the ureter. Therefore, a ureteral stent was placed under cystoscopy, which was removed three months after the operation. In both Cases 2, 3, the surgeon used a curved vascular clamp to bluntly separate and fully expose the pelvic part of the ureter and then coagulated and divided the vessels. The separation started when the ureter traced the base of the posterior lobe of the broad ligament until it entered below the uterine artery. The uterine artery dissection site differed in Cases 2 and 3, with Case 2 being at the origin of the internal iliac artery and Case 3 in an area close to the CF, depending on the space between the CF and uterine artery. After six months of follow-up, all three patients were free of pyelonephrosis and ureteral dilatation, and no ureterovaginal fistulae occurred. Blunt ureterolysis procedure can effectively avoid ureter injury in TLH for CFs. [J Turk Ger Gynecol Assoc. 2025; 26(3): 242-5]

Keywords: Blunt ureterolysis, fibroids, Laparoscopic hysterectomy, ureteral injuries, urology

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Introduction

Cervical fibroids (CFs), with an incidence of 0.6% to 10%, grow in the narrowest part of the uterus, adjacent to the ureter, uterine vessels and their branches (1,2). Total laparoscopic hysterectomy (TLH) for CFs is challenging because CFs displaced the ureter from its anatomical positions, thus changing its alignment and the positions of associated structures. The ureter is at risk of being divided, thermally injured, and/or mis-ligated when handling the vessels during hysterectomy due to CFs, especially when the fibroids are large (3-6). In a Cochrane review, TLH was associated with a higher risk of genitourinary injury (bladder injury and ureteric injury combined) than abdominal hysterectomy [odds ratio: 2.44, 95% confidence interval: 1.24-4.80] (7). Therefore, we present tips and tricks for release and protection of the ureter during laparoscopic TLH for CFs, with the aim of avoiding ureteral injury.

Material and Methods

Management of uterine vessels is a crucial step in TLH for CFs. In this procedure, the ureter adjacent to the uterine vessels is separated and exposed in advance using blunt dissection technique for ureterolysis methods, and then the uterine arteries are electrocoagulated and disconnected, thus avoiding damage to the ureter. We present a series of videos to detail the methods and skills required to perform safe and effective blunt ureterolysis and handle the uterine vessels during TLH for CFs.

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Results

To demonstrate the process of blunt ureterolysis, the video contains three example cases of CFs undergoing TLH, which varied in their management of the parametrium. The process of blunt ureterolysis required fully exposing the pelvic segment of the ureter, starting from the base of the posterior lobe of the broad ligament where the ureter travels until it enters beneath the uterine artery, without opening the ureteral tunnel. All three patients had their urinary catheters extubated on the 2nd day postoperatively and were discharged on the 4th day after surgery.

The first video shows a 43-year-old woman with a body mass index (BMI) of 27.5 kg/m^2 undergoing TLH and bilateral salpingectomy. Intraoperative exploration revealed an enlarged uterus, equivalent to 4 months' gestation, and a fibroid on the right anterior wall of the cervix, about 11 cm in size, protruding into the broad ligament, with the right ureter and its adjacent uterine vessels in close proximity to the fibroid. When we coagulated the vessels with a bipolar forceps, there was thermal injury to the right ureter because of the large CF that displaced the ureter in close proximity to the blood vessel, and the two were strikingly similar in appearance (Figure 1). Afterwards, the alignment and peristalsis of the ureter were examined. We found part of the ureter close to the right parametrial vessels had turned light burnt yellow in appearance due to thermal injury. Therefore, a ureteral stent was placed under cystoscopy, which was removed three months after the operation. The occurrence of ureter injury in this patient was considered to be related to her increased BMI, large CF causing displacement of the ureter and narrowing of the paracervical space, and the surgeon's lack of prior separation and exposure of the ureter.

The second video presents a 47-year-old woman who underwent TLH and bilateral salpingectomy for CFs. During the operation, a slightly enlarged uterus was observed, and there was a fibroid of about 8 cm in diameter with abundant blood vessels protruding from the right side of the cervix. Only a small part of the fibroid was located in the cervix, and most of it was located in the right broad ligament; these CFs are also termed "broad ligament fibroids" (Figure 2). Although this fibroid was very close to the ureter, we bluntly separated and exposed the ureter beforehand until the ureter was freed from the fibroid, thus avoiding damage to the ureter. The right uterine artery was cut-off after being clamped with titanium clips at the beginning of the internal iliac artery, and then the fibroid was lifted medially. The deep uterine vein was exposed and cut-off after being clamped, all of which were done to avoid intraoperative hemorrhage. After completing these important

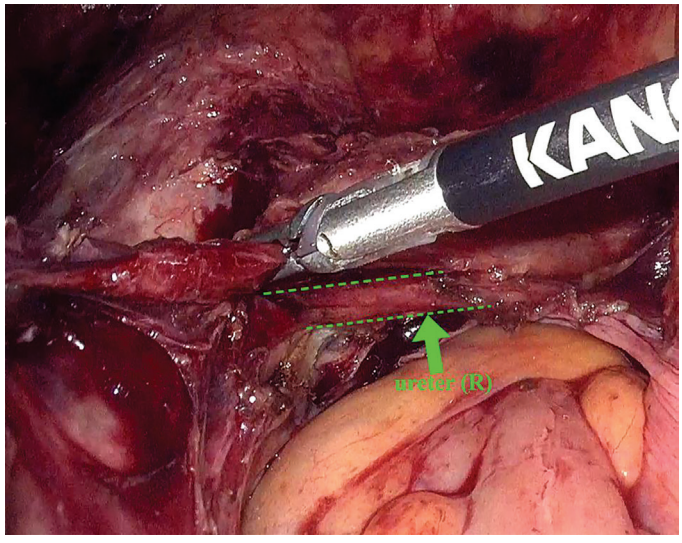

Figure 1. Distribution of the right ureter and uterine vessels

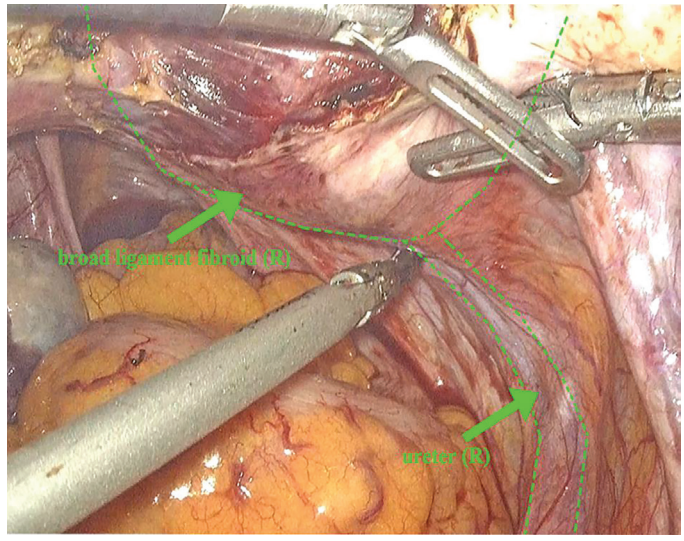

Figure 2. The cervical fibroid compressed the right ureter

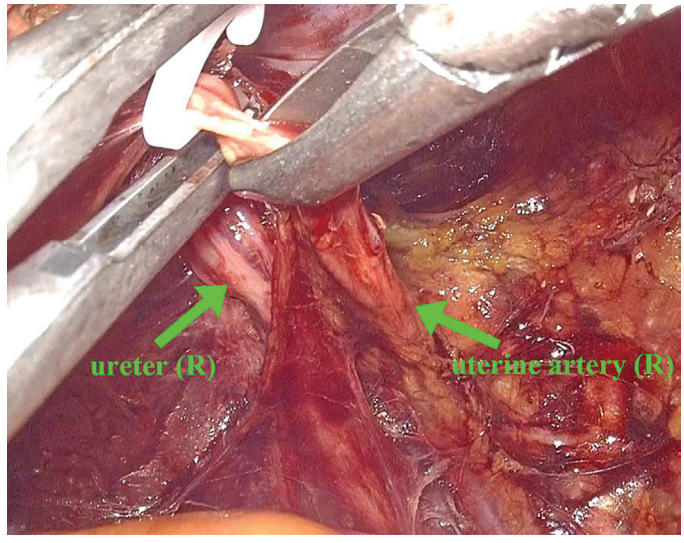

Figure 3. The right uterine artery and the right ureter are identified by blunt ureterolysis

Table 1. Clinical characteristics and operative details

Patient	Age at diagnosis (years)	Manopausal status	BMI (kg/m²)	Operation	Fibroid size (cm)	Operation time (mins)	Blood loss (mL)	Blood transfusion (mL)	Indwelling urinary catheter time (days)	Hospital stay (days)	Postoperative ureteral stenosis	Postoperative pyelonephrosis	Postoperative ureterovaginal fistulae
1	43	Premenopausal	27.5	TLH + BS	11	209	100	No	2	7	No	No	No
2	47	Premenopausal	20.2	TLH + BS	8	310	150	No	2	8	No	No	No
3	54	Postmenopausal	21.0	TLH + BSO	10	126	100	No	2	7	No	No	No

BMI: Body mass index, TLH + BS: Total laparoscopic hysterectomy and bilateral salpingectomy, TLH + BSO: Total laparoscopic hysterectomy and bilateral salpingo-oophorectomy.

steps, the hysterectomy was then performed with ease. For this patient, the uterine artery was dissected at the beginning of the internal iliac artery to minimize bleeding, as there was a rich blood supply to the CF demonstrated in the preoperative magnetic resonance imaging.

The third video shows a 54-year-old postmenopausal woman undergoing TLH and bilateral salpingo-oophorectomy. Intraoperative exploration revealed a normal-sized uterus with a fibroid on the right wall of the cervix, approximately 10 cm in size. During exposure of the right uterine vessels, the right ureter was noted to be in close proximity to the fibroid. The right ureter was bluntly separated and pushed outward until it went below the uterine artery, and then the uterine vessels were sufficiently exposed, clamped, coagulated and severed on the medial side of the ureter (Figure 3). In Cases 2, 3, we avoided ureter injury by isolating and pushing the ureter in advance, subsequently exposing the uterine vessels and clamping and severing them during TLH for large CFs.

After six months of follow-up, none of the three patients developed pyelonephritis, ureteral dilation or ureterovaginal fistulae (Table 1).

Conclusion

This blunt ureterolysis technique can effectively avoid ureter injury in TLH for CFs. We believe it will be of interest to our colleagues in training and in practice. Informed consent was obtained from the patients prior to the utilization of clinical data and surgery video in the study.

Video 1. https://youtu.be/GZfBK1MilBk

https://www.doi.org/10.4274/jtgga.galenos.2025.2024-11-1.video1

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Informed Consent: *Informed consent was obtained from the patients prior to the utilization of clinical data and surgery video in the study.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website: https://www.emedevents.com/obstetrics-and-gynecology)

September 14-17, 2025	35th ISUOG World Congess, Cancun, Mexico
October 25-29, 2025	American Society for Reproductive Medicine (ASRM) 81st Annual Meeting, Texas, USA
October 19-22, 2025	ESGE 34th Annual Congress, İstanbul, Türkiye
November 08-11, 2025	The 54th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Vancouver, BC, Canada
November 27-29, 2025	The 33rd World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Rome, Italy

CONGRESS CALENDER

NATIONAL MEETINGS

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September 11-14, 2025	Uludağ Jinekolojik Endoskopi Kampı, Bursa, Türkiye
September 18-21, 2025	İç Anadolu Kadın Sağlığı Derneği Kongresi, Ankara, Türkiye
September 25-28, 2025	4. Tüp Bebek ve İnfertilite Derneği Kongresi, K.K.T.C.
October 01-05, 2025	7. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
October 29-November 02, 2025	12. Üreme Tıbbı ve Cerrahisi Derneği Kongresi, Antalya, Türkiye
November 06-09, 2025	Uluslararası Jinekoloji ve Obstetri Kongresi (UJOK), Antalya, Türkiye
November 20-23, 2025	13. Üreme Sağlığı ve İnfertilite Kongresi, Antalya, Türkiye
February 12-15, 2026	8. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, Ankara, Türkiye

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Answer form for the article titled “Transplacental cancer transmission: a comprehensive review focusing on mechanisms, challenges, and maternal-fetal outcomes” within the scope of CME/CPD

1. **Which maternal cancer is most frequently associated with confirmed transplacental transmission?**
   a. Leukemia
   b. Malignant melanoma
   c. Choriocarcinoma
   d. Cervical carcinoma

2. **In cases of cervical cancer with vertical transmission, what route of spread is often implicated?**
   a. Only hematogenous transplacental spread
   b. Aspiration of tumor-contaminated vaginal fluids during birth
   c. Transcutaneous exposure to maternal fluids
   d. Genetic inheritance of mutations

3. **Which of the following mechanisms facilitates maternal cancer cell survival in the fetus by reducing immune recognition?**
   a. Increased NK cell activity
   b. Overexpression of PD-L1 on tumour cells
   c. Enhanced fetal MHC-I expression
   d. Increased apoptosis in cancer cells

4. **Which of the following is NOT a diagnostic method used to confirm maternal origin of fetal tumours?**
   a. Fluorescent in situ hybridisation
   b. Karyotyping
   c. SNP array
   d. Amniotic fluid cytology

5. **What is the most common presenting site for infantile melanoma metastases transmitted transplacentally?**
   a. Lungs
   b. Brain
   c. Cutaneous sites
   d. Liver

6. **Which obstetric condition can cause placental microscopic trauma, predisposing to transplacental tumour spread?**
   a. Preeclampsia
   b. Polyhydramnios
   c. Twin gestation
   d. Hyperemesis gravidarum

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1st Question			
A	B	C	D

2nd Question			
A	B	C	D

3rd Question			
A	B	C	D

4th Question			
A	B	C	D

5th Question			
A	B	C	D

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