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Original Article

Asymptomatic short cervix and threatened preterm labor: A comparative study on perinatal outcomes

Clémentine Amalric [a], Yoann Athiel [a], Jacques Lepercq [a], Aude Girault [a,b,*]

[a] Cochin Hospital Port Royal, Port Royal Maternity, Department of Obstetrics, University of Paris, APHP, Paris, France
[b] Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Center for Research on Epidemiology and Statistics Sorbonne Paris Cité (CRESS), University of Paris, INSERM UMR 1153, Paris, France

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ABSTRACT

Objective: To determine the rate of delivery within 15 days of admission among patients with an asymptomatic short cervix (ASC) compared to those admitted for threatened preterm labor (TPL).
Material and methods: This retrospective study conducted in a tertiary maternity hospital, included patients with a singleton pregnancy admitted with a cervical length of less than 25 mm between 24 and 34 weeks. The population was divided into two groups, patients with ASC (i.e., with no contractions at admission) and patients with TPL. The primary outcome was the delivery rate within 15 days of admission. Secondary outcomes included gestational age at delivery, preterm delivery rate before $37^{\circ/7}$ weeks and before $34^{\circ/7}$ weeks, admission to delivery interval, 5 min Apgar score and transfer to neonatal intensive care unit rate. The characteristics of the two groups and the primary and secondary outcomes were compared between the two groups using univariate analysis. Two subgroup analysis were performed, one restricted to patients with a mildly modified CL ($15 \leq CL < 25$ mm), and one excluding patients at high risk of preterm birth.
Results: Among the 247 included patients, 136 (55.1 %) had TPL, and 111 (44.9 %) ASC. There were no significant differences in the rate of patient who delivered within 15 days of admission between the groups, 13.2 % in the TPL group vs 8.0 % in the ASC group ($p = 0.22$). Patients in the TPL group had a significantly higher frequency of delivery before 34 weeks compared to those in the ASC group (19.9 % versus 9.0 %, $p = 0.02$ This finding persisted in the subgroup analysis excluding patients at high risk of preterm birth (16.5 % in the TPL subgroup vs. 6.9 % in the ASC subgroup, $p = 0.04$). There were no significant differences in the rates of preterm delivery before 37 weeks, the admission-to-delivery interval, or neonatal outcomes between the two groups or within the subgroup analyses.
Conclusion: The frequency of delivery within 15 days of admission was not statistically different between patients with an asymptomatic short cervix and those with TPL. Nevertheless, these asymptomatic patients delivered significantly later and less frequently before 34 weeks, with only one in ten requiring corticosteroids.

Key message: This study demonstrates that asymptomatic short cervix patients deliver within 15 days as frequently as those with threatened preterm labor but have later gestations and fewer pre-34-week deliveries, challenging current management practices and highlighting the need for tailored interventions.

1. Introduction

Spontaneous preterm birth (PTB) responsible for 5 % to 18 % of all deliveries, remains the principal cause of perinatal morbidity and mortality worldwide [1–6]. Threatened preterm labor (TPL), characterized by regular uterine contractions and cervical changes before 37 weeks is the leading cause of antenatal hospitalization, accounting for 5 % to 25 % of all pregnancy-related hospital admissions [4,7–12]. International guidelines currently advocate for the hospitalization of patients with TPL to mitigate the risks of preterm birth and associated neonatal complications [8,13,14]. However, evidence suggests that fewer than 10

* Corresponding author at: 123 bvd Port Royal, 75014 Paris, France.
E-mail address: aude.girault@aphp.fr (A. Girault).

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% of these hospitalized patients deliver within 15 days of admission, while approximately 50 % experience preterm delivery [2,7,15,16].

Besides this well-defined population of patients with TPL, some patients have a short cervix but no uterine contractions or other symptoms. This entity of patients with an asymptomatic short cervix (ASC) and the consequences of such a diagnosis on the prognosis of pregnancy is poorly described in literature. Whether these patients should be hospitalized and treated as patients with TPL is not evaluated in a population of patients with a singleton pregnancy and no previous preterm birth. Preterm delivery rates for ASC vary greatly in literature (4.9 % to 42 %) [17–20], one explanation being that most of the available data is collected either in patients with a high risk of preterm birth (i.e. with a history of preterm birth), or with a short cervical length (CL) early in pregnancy (before 24 weeks).

Most international guidelines do not recommend using a universal CL screening program in patient without a prior preterm birth [13,20–24]. But the lack of guideline support for routine cervical assessments in asymptomatic individuals has not deterred clinical practice [25]. Many physicians continue to perform these evaluations, leading to ASC diagnoses and subsequent clinical decisions regarding hospitalization and antenatal corticosteroid administration, the benefits of which remain debatable due to their effectiveness window [26,27]. A more detailed understanding of the obstetric and neonatal outcomes in ASC patients is imperative to establish optimal management strategies and to appropriately counsel patients regarding their pregnancy prognosis.

Thus, the aim of this study was to determine the rate of delivery within 15 days of admission among patients with an asymptomatic short cervix (ASC) compared to those admitted for threatened preterm labor (TPL). The secondary objectives were to compare the obstetrical and neonatal outcomes of patients admitted with ASC to those of patients admitted with TPL.

2. Material and methods

This retrospective study included all patients with a singleton pregnancy, admitted with a CL $<$ 25 mm between $24^{\circ/7}$ weeks and $33^{6/7}$ weeks, from January 1, 2018, to December 31, 2019, at a tertiary maternity hospital in Paris (France). CL was assessed sonographically with a standardized protocol [28]. Patients presenting upon admission with vaginal bleeding, preterm premature rupture of membranes (PPROM), dilated cervix with protruding fetal membranes, immediate delivery post-admission, or absence of CL measurement at admission were excluded.

In the French healthcare system, patients receive monthly follow-ups from an obstetrician or midwife and undergo three recommended sonographic evaluations at 12, 22, and 32 weeks [25,29]. Routine cervical length screening is not recommended in the absence of symptoms of preterm labor, except for patients at high risk of preterm delivery, where cervical length monitoring is optional, and antenatal progesterone therapy is not systematically prescribed [29,30]. Nevertheless, routinely women at low obstetric risk are admitted in our maternity hospital for an ASC diagnosis following vaginal examination or sonographic cervical length assessment.

At the study center, ASC management aligns with TPL protocols, involving at least 48 h of hospitalization, administration of a tocolytic agent, and a single course of corticosteroids, followed by weekly outpatient monitoring if stable.

Patients who were admitted for TPL or ASC during our study period were identified through the electronical medical records searching for the words “short cervical length” and “threatened preterm labor”. Each patient’s paper medical file was analyzed to separate the population in two groups: the TPL group defined as patients presenting with clinical contractions at admission, and the ASC group defined as patients presenting with a short cervix without any clinical contraction. In the absence of written specification on whether the patient experienced contractions at admission or not, they were classified in the TPL group.

The primary outcome was the delivery rate within 15 days of admission. The secondary outcomes included gestational age at delivery, preterm delivery rate before 37 weeks, and before 34 weeks, admission to delivery interval, 5-minute Apgar score and transfer to neonatal intensive care unit (NICU).

Maternal characteristics such as age, Body Mass Index (BMI), geographical origin, working status during pregnancy and social deprivation (defined by the fact of not having a settled home and/or having financial difficulties and/or having a medico-psycho-social followed at the maternity hospital) were collected. In addition, a detailed past medical and obstetric history, including medical condition, gynecologic history, prior uterine surgery, parity, prior obstetric history (including late miscarriage (14–22 weeks), preterm birth (<37 weeks), TPL history) was collected. The hospital admission characteristics, gestational age, cervical length, detailed clinical vaginal exam, type of tocolysis, length of hospital stay, subsequent hospitalizations were also collected.

First, we described and compared the maternal characteristics and prior obstetrical history between the two groups. Then, we compared the primary and secondary outcomes between the two groups using univariate analysis.

Subgroup analyses were conducted for patients with mildly modified cervix (CL $\geq$ 15 mm at admission) and those not considered at high risk for preterm birth. High risk of preterm birth was defined as the presence of at least one previous preterm birth and/or a late miscarriage and/or a congenital uterine malformation (dysmorphic uterus, septate uterus, bicorporeal uterus, unilaterally formed uterus, aplastic/dysplastic uterus [31]) and/or conization history.

Data are presented as median and interquartile range (IQR) for quantitative variables and as n (%) for qualitative variables. The univariate analyses were performed using Chi 2 and Fisher Tests for qualitative data, and Wilcoxon test for quantitative data. Statistical significance was set at 5 %. All tests were performed with Stata 15.0 software.

This study was approved by the National Data Protection Authority (Commission Nationale de l’Informatique et des Libertés, CNIL n° 1755,849). Under French regulations, this study was exempt from IRB review because it was an observational study using anonymized data from medical records. Women were informed that their records could be used for the evaluation of medical practices and were allowed to opt out of these studies.

3. Results

Among the 412 patients admitted at the study center for a short cervix according to the electronical medical records during the study period, 247 met our inclusion criteria. Among these, 136 (55.1 %) had a TPL, and 111 (44.9 %) an ASC Diagnosis for the ASC group was primarily through clinical examination in 71 (64 %) cases, with the remaining 40 (36 %) identified via sonographic examination (Fig. 1).

The maternal and the past medical history characteristics of the patients were comparable between the two groups (Table 1 The prevalence of multiparity was comparable, with 42.7 % in the TPL group and 54.0 % in the ASC group (p = 0.16). The proportion of patients considered at high risk for preterm birth in the present study was similar across groups, with 27 (19.8 %) in the TPL group and 25 (22.5 %) in the ASC group. However, late miscarriage and/or preterm birth history were more frequent in the TPL group than in the ASC group (44.8% vs 25.0 %, p = 0.03).

Median gestational age (GA) at admission did not differ significantly between the groups, 29 weeks [IQR 25–32] for TPL and 30 weeks [IQR 26–32] for ASC (p = 0.50). Median cervical length at admission was also comparable: 18 mm [IQR 14–21] for TPL and 16 mm [IQR 12–20] for ASC (p = 0.57). Cervical consistency was notably softer in the ASC group (p = 0.05), but other clinical examination findings were consistent across both groups.

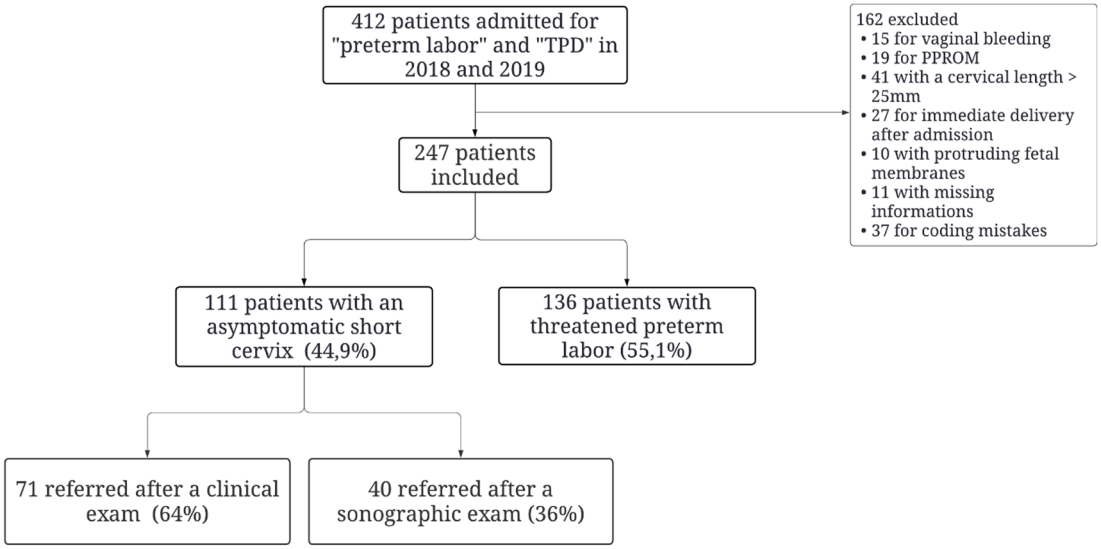

Fig. 1. Flow Chart. PPROM: Preterm premature rupture of membranes, TPD: Threatened preterm delivery.

Different agents were used for tocolysis, atosiban which is generally used as a second line tocolytic agent, was administered to 16.9 % of patients of the TPL group versus 3.6 % of the ASC group ($p < 0.01$) (Table 2). There were no differences in the administration of antenatal corticosteroid between the two groups, 98.5 % of patients in the TPL group versus 95.5 % of patients in the ASC group ($p = 0.25$).

Our primary outcome, the delivery rate within 15 days of admission was comparable in the two groups, 13.2 % ($n = 18$) in the TPL group compared to 8.0 % ($n = 9$) in the ASC group ($p = 0.22$) (Table 3). A larger but not significant number of patients delivered before 37 weeks in the TPL group (31.6 %) compared to the ASC group (25.2 %), $p = 0.27$. TPL patients had a significantly higher frequency of delivery before 34 weeks (19.9% vs. 9.0 %, $p = 0.02$) and a lower median gestational age at delivery (38 weeks for TPL vs. 39 weeks for ASC, $p = 0.04$). There were no significant differences in the admission to delivery interval or neonatal outcomes between groups (Table 3).

The subgroup analysis restricted to patients with a mildly modified cervix ($\geq$ 15 mm) included 172 patients (69.6 % of the study population), comprising 101 (74.3 %) from the TPL group and 71 (64.0 %) from the ASC group. The delivery rate within 15 days of admission was 6.9 % for TPL versus 4.2 % for the ASC subgroup, with no significant difference ($p = 0.46$). Primary and secondary outcomes were not statistically different across these subgroups (Appendix A).

The subgroup analysis excluding patients at high risk of preterm birth included 196 patients (79.4 % of the study population), 109 patients (80.1 %) in the TPL group and 87 (78.3 %) in the ASC group (Appendix B). While the primary outcome did not differ significantly between the groups, gestational age at delivery was lower in the TPL group (38 weeks) compared to the ASC group (39 weeks, $p = 0.03$). The rate of preterm birth before 34 weeks was significantly higher in the TPL group (16.5 %) versus the ASC group (6.9 %, $p = 0.04$) (Appendix B).

4. Discussion

Our study reveals that 1 in 12 patients with an asymptomatic short cervix (ASC) delivered within 15 days of admission, a rate comparable to those hospitalized for threatened preterm labor (TPL). Notably, TPL patients were more likely to deliver before 34 weeks compared to patients with ASC, especially after excluding those at high risk for preterm birth.

A recent retrospective study conducted by Gulersen et al. evaluated the risk of spontaneous preterm birth in patients with a singleton pregnancy and an ASC (CL <25 mm) at $23 - 27^{6/7}$ weeks, and reported a rate of preterm birth before 37 weeks of 23 % ($n = 29/126$) similar to ours (25.2 %) [16]. The median interval from diagnosis of a short CL to delivery (the primary outcome) was directly correlated with the CL, with significantly shorter diagnosis to delivery intervals in shorter-CL groups (10 weeks for CL <10 mm, 13.2 weeks for CL 21–25 mm). The admission to delivery interval in our study was shorter (7.8 weeks) but patients were diagnosed at later gestational age in our study (median 25 weeks in Gulerlsen et al.'s study vs 30 weeks in our study). Our preterm delivery rate is also consistent with a Japanese study [17] which included patients with an ASC diagnosed between 22 weeks to $33^{6/7}$ weeks and reported a preterm delivery rate (<37 weeks) of 27.6 % ($n = 37/134$).

In our study, 8.0 % of patients in the ASC group delivered within 15 days of admission, which is higher than the 0.8 % rate in Gulersen's study. Even though Gulersen included the same proportion of patients with a CL > 15 mm (64 %), he studied the diagnosis to delivery interval, and we can hypothesize that a large proportion of the ASC patients of our study would have had a short cervix between 23 and 27 weeks.

The 31.6 % preterm birth rate before 37 weeks in patients with TPL in our study is similar to previous studies [2,8,32]. The EVAPRIMA study evaluated different French national practices for the management of TPL in 2005 [33]. This large French cohort of TPL reported a higher preterm birth rate (41.5 %, $n = 305/734$) in a population with 80 % of patients with a CL > 15 mm (vs 74.6 % in our TPL group) but including twin pregnancies and patients with PPROM. In a meta-analysis, Berghella et al. [2] studied the benefits of having the knowledge of the ultrasound CL in patients presenting with uterine contractions from 24 weeks to $35^{6/7}$ weeks. The preterm birth rate before 37 weeks (28.2 %, $n = 81/287$) was equivalent to the rate reported in our study and the delivery rate within 14 days was 10.1 % ($n = 29/287$), slightly lower than in this study (13.2 %). This could be explained by a study population with a later median gestational age at diagnosis (31.7 SA $\pm$ 6.4) and less severe patients since the inclusion criteria did not take into account cervical measurement.

Our findings align with existing literature on the significance of a 15 mm cervical length (CL) threshold, which is considered clinically concerning and indicative of the need for active management [15,16,34,35]. Indeed, for patients with a cervical length > 15 mm, the delivery rate within 15 days of was only of 4 %.

Many studies have demonstrated an inverse relationship between CL and the probability of preterm birth i.e. the shorter the cervical length is, the greater the probability of TPL is [36]. The introduction of a second trimester universal transvaginal ultrasound ($18^{\circ/7}$ weeks to $23^{6/7}$ weeks) cervical length screening program for patients without a history

Table 1
Comparison of patient's characteristics between patients admitted for threatened preterm labor (TPL) and patients admitted for asymptomatic short cervix (ASC).

	TPL group $N = 136$ N (%)		ASC group $N = 111$ N (%)		p
Maternal characteristics					
Maternal age (year), median [IQR]	32.7 46	[30.3 ; 35.5]	33.1 39	[29.4 ; 36.1]	0.44 0.87
> 35 years		(36.0)		(35.4)	
BMI (kg/m^2), median [IQR]	21	[19 ; 24]	21	[20 ; 24]	0.21
Geographic origin					0.55
African	46	(33.8)	33	(29.7)	
Asian	8	(5.9)	9	(8.1)	
American	1	(0.7)	2	(1.8)	
European	79	(58.2)	66	(59.4)	
Working during pregnancy	115	(84.6)	93	(83.8)	0.63
Social deprivation[1]	12	(8.8)	10	(9.0)	0.96
Past medical and obstetric history					
Medical condition, including	10 4	(7.4) (2.9)	6 1	(5.4) (0.9)	0.61 0.38
Hypertension	4	(2.9)	1	(0.9)	0.38
Diabetes	2	(1.4)	4	(3.6)	0.80
Immunological					
Gynecologic condition[2] **including**	22 5	(15.1) (3.7)	24 7	(21.6) (6.3)	0.81 0.38
Congenital uterine malformation					
Prior uterine surgery [3]	11	(7.5)	12	(10.8)	0.64
Multiparous	58	(42.7)	60	(54.0)	0.16
Prior obstetric history					
Late miscarriage*	9	(15.5)	2	(3.3)	0.03
Preterm birth (PB)**	19	(32.8)	15	(25.0)	0.42
Late miscarriage and/or PB*	26 13	(44.8) (22.8)	15 15	(25.0) (25.0)	0.03 0.83
TPL[4]	23	(16.9)	17	(15.3)	0.86
Infertility	10	(17.2)	8	(13.3)	0.61
Cesarean delivery**					
High risk of preterm delivery[4]	27	(19.8)	24	(21.6)	0.73

[5]Threatened preterm labor.
[1] Defined by the fact of not having a settled home and/or having financial difficulties and/or having a medico-psycho-social followed at the maternity hospital.
[2] Polycystic ovary syndrome, Endometriosis, myoma, adnexal surgery, cervical lesions, uterine polyp.
[3] Myomectomy, endometriosis resection, conization, trachelectomy, congenital uterine malformations surgery, polypectomy.
[4] High risk of preterm birth was defined as the presence of at least one previous preterm birth and/or a late miscarriage and/or a congenital uterine malformation (dysmorphic uterus, septate uterus, bicorporeal uterus, unilaterally formed uterus, aplastic/dysplastic uterus) and/or conization history.
* in multigravida ($n = 166$).
** in multiparous ($n = 118$).

Table 2
Comparison of admission characteristics between patients admitted for threatened preterm labor (TPL) and patients admitted for asymptomatic short cervix (ASC).

	TPL group $N = 136$ N (%)		ASC group $N = 111$ N (%)		p
Gestational Age at admission (weeks, median [IQR])	29	[25 ; 32]	30	[26 ; 32]	0.50
Transvaginal CL at admission (mm, median [IQR])	18	[14 ; 21]	16.5	[12 ; 20]	0.57
≥ 15mm	102	(74.3)	71	(64.0)	0.08
< 15mm	35	(25.7)	40	(36.0)	
Effacement					0.21
0–30	10	(7.6)	9	(8.1)	
40–50	66	(50.0)	54	(48.6)	
>50	54	[41])	46	(41.4	
Position of cervix					
Posterior	94	(74.6)	34	(74.6)	0.79
Mid position	19	(15.1)	4	(11.8)	
Anterior	2	(1.6)	2	(1.8)	
Dilatation					0.31
Closed	61	(45.2)	37	(33.3)	
1–2 cm	66	(48.9)	63	(56.8)	
3–4 cm	7	(5.2)	8	(7.2)	
Cervical consistency					0.05
Firm	42	(30.8)	25	(22.5)	
Medium or Soft	60	(44.1)	66	(59.5)	
Station					0.26
−3	46	(34.1)	38	(34.2)	
−2	26	(19.3)	19	(17.1)	
−1	19	(14.1)	8	(7.2)	
Tocolysis					< 0.01
Nifedipine	111	(81.6)	94	(84.7)	
Atosiban	23	(16.9)	4	(3.6)	
None	1	(0.7)	13	(11.7)	
Antenatal corticosteroids	134	(98.5)	106	(95.5)	0.25
Length of hospital stay (days, median [IQR])	3	[3; 3]	3	[3 ; 4]	0.01
Subsequent hospitalization	48	(35.3)	30	(27.0)	0.22
Hospitalization indication	37	(27.2)	18	(16.2)	
TPL	1	(0.01)	4	(0.04)	
PPROM[1]	10	(7.4)	9	(8.1)	
Other[2]					

[1] PPROM: preterm premature rupture of membranes.
[2] Preeclampsia, gestational diabetes, fetal growth restriction, vaginal bleeding, fibroid necrobiosis.

Table 3
Comparison of primary and secondary outcomes between patients admitted for threatened preterm labor (TPL) and patients admitted for asymptomatic short cervix (ASC).

	TPL group $N = 136$ N (%)		ASC group $N = 111$ N (%)		p
Delivery within 15 days of admission	18	(13.2)	9	(8.0)	0.22
Gestational age at delivery (weeks, median [IQR])	38	[35 ; 39]	39	[37 ; 40]	0.04
Delivery before 37 weeks	43	(31.6)	28	(25.2)	0.27
Delivery before 34 weeks	27	(19.9)	10	(9.0)	0.02
Admission to delivery interval (days, median [IQR])	50	[34 ;70]	55	[45 ; 77]	0.35
Neonatal status					
Apgar < 7 at 5 min	14	(10.4)	4	(4.5)	0.10
Transfer to neonatal intensive care unit	38	(27.9)	23	(20.7)	0.19

of spontaneous preterm birth seems to be associated with a reduction in the incidence of TPL [37], but not of spontaneous preterm birth which remains the main burden [38,39]. This could be explained by inappropriate management of patients who were screened with a short CL.

Based on our results, despite a low, but not negligible, delivery rate within 15 days, it could be argued that in asymptomatic patients with a short CL there may be justification for routine hospitalization to allow antenatal corticosteroid administration. On the other hand, we found that a large majority of patients with a short CL received antenatal corticosteroids, while only 9 % of their infants benefited from them. Some studies attempt to determine the optimal CL threshold to limit the unnecessary administration of corticosteroid and suggest an action threshold of 15 mm [16,40]. Similarly, Alfirevic et al. concluded that no patient with a CL > 15 mm should receive tocolysis [41]. Therefore, to limit iatrogenicity, it appears necessary, to evaluate a lower action threshold of cervical length in a prospective study.

Other biological (hyperleukocytosis) or ultrasound markers (elastometry) are being studied, to better discern patients at risk of preterm birth. Some biomarkers will be evaluated in a French national study (PrediMAP NCT05586334) to predict preterm delivery in order to avoid

unnecessary prenatal hospitalizations for TPL and, or on the contrary, to hospitalize pregnant patients who are at high risk of preterm delivery.

This original study assessed not only the gestational age at delivery between patients with threatened preterm labor (TPL) and those with an asymptomatic short cervix (ASC) but also examined their obstetric and neonatal outcomes. Despite the limited sample size and a consequent lack of statistical power to detect differences in the 15-day delivery rate, the robustness of our data is assured by meticulous collection from medical files by obstetricians and gynecologists, resulting in minimal missing information.

The inherent challenge in studying ASC patients—given their lack of symptoms and consequently, irregular examinations—potentially overestimates the observed delivery rate within 15 days of admission. It's plausible that patients undergoing examination did so for specific reasons, potentially skewing the representation of ASC prevalence. Nonetheless, our selection criteria reflect actual clinical practices, focusing on hospitalization decisions based on diagnosed ASC cases.

The retrospective design of our study introduces uncertainties regarding the motivations for vaginal examinations leading to ASC diagnoses. Such examinations might have been prompted by patients' complaints or perceived risks of preterm birth, possibly inflating the observed preterm delivery rates within the ASC cohort. To mitigate this, we categorized indeterminate cases as TPL and refined our analysis through subgroup evaluations, specifically excluding patients identified as high-risk for preterm delivery.

5. Conclusion

This study reveals no significant differences in the rate of deliveries within 15 days of admission in patients with an asymptomatic short cervix (CL < 25 mm) and those presenting with threatened preterm labor (TPL). However, these patients typically deliver at a later gestational age and less often before 34 weeks, necessitating corticosteroid treatment in only a small fraction (1 in 10) of cases. The management of ASC poses a significant clinical dilemma due to the low but significant risk of early delivery, coupled with the current trend of potentially overtreating these patients. There is a pressing need for future prospective research aimed at accurately distinguishing patients at genuine risk of preterm birth. Such studies will be crucial in developing tailored management strategies, minimizing unnecessary interventions while ensuring optimal outcomes for both mothers and infants.

Conflict of interest

the authors have no conflict of interest to declare.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Comparison of obstetrical and neonatal outcomes of women admitted with a cervical length ≥ 15 mm between patients admitted for threatened preterm labor (TPL) and patients admitted for asymptomatic short cervix (ASC)

	TPL ***N* = 101** **N (%)**		**ASC** ***N* = 71** **N (%)**		p
Delivery within 15 days of admission	7	(6.9)	3	(4.2)	0.46
Gestational age at delivery (weeks, median [IQR])	38	[37 ; 40]	39	[37 ; 40]	0.51
Delivery before $37^{\circ}0^{/7}$ weeks	24	(23.8)	14	(19.7)	0.52
Delivery before $34^{\circ/7}$ weeks	13	(12.9)	4	(5.6)	0.12
Admission to delivery interval (days, median [IQR])	54	[39 ; 71]	57	[47 ; 77]	0.90
Neonatal status					
Apgar < 7 at 5 min	9	(9.0)	2	(2.8)	0.13
Transfer to neonatal intensive care unit	22	(21.8)	11	(15.5)	0.18

Appendix B. Comparison of obstetrical and neonatal outcomes between patients admitted for threatened preterm labor (TPL) and patients admitted for asymptomatic short cervix (ASC) after excluding women at high risk of preterm birth

	TPL ***N* = 109** **N (%)**		**ASC** ***N* = 87** **N (%)**		p
Delivery within 15 days of admission	14	(12.8)	7	(8.0)	0.30
Gestational age at delivery (weeks, median [IQR])	38	[36 ; 39]	39	[37 ; 40]	0.03
Delivery before $37^{\circ/7}$ weeks	30	(27.5)	18	(20.7)	0.27
Delivery before $34^{\circ/7}$ weeks	18	(16.5)	6	(6.9)	0.04
Admission to delivery interval (days, median [IQR])	52	[38 ; 71]	54	[46 ; 72]	0.89
Neonatal status					
Apgar < 7 at 5 min	11	(10.1)	2	(3.5)	0.09
Transfer to neonatal intensive care unit	23	(21.1)	15	(17.2)	0.59

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Original Article

Laparoscopic nerve lysis for deep endometriosis improves quality of life and chronic pain levels: A pilot study

Shlomo B Cohen [a,1], Yohann Dabi [b,*,1], Yechiel Burke [a], Nicole Mamadov [a], Nir Manoim [a], Roy Mashiach [a], Elad Berkowitz [a], Jerome Bouaziz [c], Alba Nicolas-Boluda [c], Maria Grazia Porpora [d], Tomer Ziv-Baran [e]

[a] Endometriosis and Chronic Pelvic Pain Unit, Department of obstetrics and gynecology, Sheba Medical Center, Ramat Gan, Israel and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[b] Sorbonne University,Department of obstetrics and gynecology Tenon Hospital (AP-HP), Paris, France
[c] Department of Research, One Clinic, 25 Boulevard Pasteur, 75015 Paris, France
[d] Department of maternal and child health, Sapienza University, Rome, Italy
[e] Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Objectives: To assess the benefit of surgical management of patients with endometriosis infiltrating pelvic nerves in terms of pain, analgesic consumption, and quality of life (QOL).
Methods: We conducted a retrospective cohort study In an Endometriosis referral center at a tertiary care university affiliated medical center. Patients diagnosed with endometriosis that underwent laparoscopic neurolysis for chronic pain were included. Patients rated their pain before and after surgery and differentiated between chronic pain and acute crises. Patients were requested to maintain a record of analgesic consumption and to evaluate their quality-of-life (QOL).
Results: Of the 21 patients in our study 15 (71.5 %) had obturator nerve involvement, 2 (9.5 %) had pudendal nerve involvement and 4 (19 %) had other pelvic nerve involvement. Median postoperative follow – up was of 8 months. All but 2 patients (9.6 %) had significant chronic pain improvement with a mean decrease of VAS of 3.05 (±2.5). Analgesic habits changed postoperatively with a significant decrease of 66 % of patients' daily consumption of any analgesics. Surgery improved QOL in 12 cases (57.1 %) and two patients (9.6 %) completely recovered with a high QOL.
Conclusion: Neurolysis and excision of endometriosis of pelvic nerves could results in significant improvement of quality of life.

Introduction

Endometriosis is a benign condition that may affect up to 10 % of women of reproductive age [1,2]. Exact prevalence is hard to determine since many patients are asymptomatic, including even cases with severe disease [3].It has been demonstrated that endometriosis might have a huge impact on the lives of affected women, their partners and their families [4]. In a previous retrospective study, 50 % of women with surgically confirmed endometriosis reported a significant effect on education, work ability, relationship and social life [5].

Extrapelvic localization is reported to represent 5% of lesions in patients with endometriosis, this rate is probably underestimated [6]. Several authors focused on clinical and pathological evidence on the involvement of pelvic nerves in women with endometriosis in recent years [7–11]. De Sousa et al. in their recent literature review reported 365 cases of patients with endometriosis and nerve infiltration, including involvement of the lumbosacral trunk in 57 % and of the sciatic nerve [12] in 39 % of cases. Further spread of the endometriotic lesions into the spinal nerves and even the dura of the spinal cord has been proposed to be a possible etiology of DIE [12,13].

The management of excessive endometriosis – related pain remains a medical challenge [14,15]. The benefit of surgery in endometriosis

* Corresponding auhor at: Tenon Hospital, AP-HP, 4 rue de la Chine, 75020, Paris, France.
E-mail address: yohann.dabi@gmail.com (Y. Dabi).
[1] These authors contributed equally to this work and should be considered as joint first authors.

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patients with pain and / or infertility has been extensively reported [16, 17]. Currently, various surgical procedures may be required from uterosacral ligament resection to complex excision of nodules from bowel, urinary tract, nerves or blood vessels. These procedures carry a relative increased risk of complications, which correlate to the extent of the lesions and their tissue penetrance [18].

Little data exist on endometriosis patients with pelvic nerve infiltration. The ESHRE guidelines recently underlined that evidence to predict endometriosis based on clinical symptoms alone is weak and incomplete and women may present to their practitioners with a variety of non-specific symptoms [15]. This statement seems particularly relevant in patients who have nervous lesions and are often under diagnosed, despite having more frequently specific neurologic complains. Possover et al. reported several cases as well as cohorts of patients that underwent laparoscopic neurolysis for severe endometriosis, and demonstrated feasibility of improvement in terms of pain scale intensity [10,19]. However, such procedures are considered to be highly advanced laparoscopic procedures and carry significant surgical risks, even in the hands of experienced surgeons[18].So far, the most appropriate treatment for patients with proven pelvic nerve infiltration is unclear, with only few authors focusing on this unique site.

The aim of our study was to assess the benefit of surgical management of patients with endometriosis infiltrating pelvic nerves in terms of pain, analgesic consumption and quality of life. (QOL)

Methods

Study design

A single center retrospective study that was performed in the Endometriosis and Chronic pelvic pain clinic of the Sheba Medical Center, Tel Hashomer (Israel). All patients surgically treated for deep infiltration endometriosis with nerves infiltration between 1/2020 and 1/2022 were included. The study was approved by the ethic committee of the hospital (number SMC – 8107 – 21) and all patients gave their consent for their data to be included.

Indications for surgery were based on the European Society of Human Reproduction and Embryology (ESHRE) guidelines and included medical treatment failure or intolerance in symptomatic patients [15]. All decisions for surgery were systematically validated by a multidisciplinary committee and cautiously discussed with the patients, especially balancing the risk and potential benefits of the procedure.

Confirmation of endometriosis diagnosis was histological if patients had lesion excision during the surgical procedure and visual if they underwent only nerve lysis.

Preoperative workup included physical examination, transvaginal ultrasonography, and pelvic neurographic MRI. The MRI protocol included 3D T2, 3D T1 sequences with and without fat saturation and gadolinium injection [20].

Selection criteria included patients who presented to our service with chronic pelvic pain of at least 6 months and signs and symptoms attributed to the affected nerve, for example in case of obturator nerve involvement, limping, and aggravation of pain in abduction of the knee insinuating involvement of the nerve. In some cases, we had an MRI scan that reveled fibrosis or endometriosis nodules at the nerve level.

Outcomes evaluation

Patients were followed for a minimum 8 months postoperatively. A Visual Analog Scale (VAS) of 0—no pain to 10—worst pain imaginable was used for standard quantification of the pain level. Patients rated their pain before and after surgery and differentiated between chronic pain and acute episodes. Patients were requested to maintain a record of analgesic consumption before and following surgery.

The main socio-demographic characteristics of the patients were collected. Two questionnaires were handed out to patients before and after surgery: (a) a general one to assess pain localization and type of painful symptoms associated with endometriosis and (b) a specific questionnaire to assess neurological symptoms. All symptoms investigated in patients are detailed in the corresponding tables of the results.

Surgical procedure

All operations were performed by a senior surgeon experienced with endometriosis (S.C). The surgical method has been previously described by Possover et al. [21]. Briefly, the lumbosacral space was developed to permit exposure of the sacral plexus ventral to the level of the cardinal ligament, (also known as the Mackenrodt ligament) - a paired, dense band of connective tissue that supports the uterus and upper vagina.. This space was opened laterally to the external iliac vessels and the exposure of the obturator nerve as well as the lumbosacral trunk is systematically performed in the depth of this space. By following the lumbosacral trunk distally, the superior gluteal nerve could be exposed in the supra-piriform part of the sciatic foramen as well as the upper border of the sciatic nerve itself. Suprapiriformis is located above the piriformis muscle, a flat, pear-shaped muscle deep in the buttock Elective dissection of the different branches of the internal iliac vessels and proximal transection of the obturator vessels permits good exposure of the distal part of the sacral plexus, the sciatic nerve and its endopelvic distal branches, making the further dissection of the endometriosis safe [21]. The involved nerves, obturator and pudendal (S2–3), are somatic in origin and function. Patients most frequently reported pain and limited motor function in these nerves. Consequently, laparoscopic dissection and release of endometriosis or fibrosis were performed after all other treatment modalities failed.

Surgical technique for the Sacral Nerve roots and fo the Pudendal nerve:

Sacral Nerve Root Dissection: Dissection to expose the sacral nerve roots (S1-S4) begins with a pararectal peritoneal incision medial to the ureter. The anatomic pararectal space is bluntly dissected downwards to the coccyx. This dissection is then carefully extended laterally, reaching the hypogastric fascia, which is then transected to expose the space beyond.

Pudendal Nerve Decompression: Laparoscopic decompression of the right pudendal nerve involves dissecting the ischiorectal fossa along the right internal obturator muscle. After visualizing the obturator vessels and identifying the pudendal nerve, the right sacrospinous ligament is sectioned and removed entirely. The nerve is then repositioned in its natural course and followed until it freely passes through Alcock's canal.

A standard follow-up visit was made between 4 and 6 weeks postoperatively. Following this visit, additional evaluations were determined based on symptoms reported by the patients.

Statistical analysis

Categorical variables were described as frequency and percentage and continuous variables as median and interquartile range (IQR). Wilcoxon signed-rank test and McNemar's test were used to compare pre- and post-surgical parameters. Since the sample size was limited, we also calculated the standardized difference and employed 0.2, 0.5 and 0.8 as cutoff values for small, medium, and large effect, respectively. All statistical tests were two-sided and $p < 0.05$ was considered as statistically significant, although calculated in a restrained number of cases due to the size of our cohort. Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics for Windows, version 27, IBM Corp., Armonk, NY, USA, 2020).

Results

Study population

Over the last 2 years, 21 patients underwent neurolysis for deep

infiltrating endometriosis in Sheba medical center. The main characteristics of the patients are displayed in table 1. Median age was 36 (IQR 27–41) and 81.0 % ($n = 17$) of patients had undergone previous surgery for endometriosis. The non-specific symptoms of endometriosis expressed by patients who underwent surgery are detailed in supplementary Table 1. The 3 most often reported symptoms were pelvic pain ($n = 14$, 55.7 %), dyspareunia ($n = 10$, 47.6 %), dysuria ($n = 9$, 42.9 %).

Neurological symptoms reported by patients are detailed in Table 2. Pain radiating to lower back ($n = 10$, 47.6 %), urinary frequency ($n = 10$, 47.6 %) and pain radiating to left lower limb ($n = 9$, 42.9 %) were frequently reported by patients with neural involvement of their endometriosis.

The nerve specific symptoms were as follows:

For obturator nerve involvement, Pain radiating to one leg, leg dragging, limping and difficulty in locomotion.

For pudendal nerve, the specific symptoms were vaginal and urinary bladder pain, tenesmus and burning sensation on the outer aspect of the groin and inner thigh, and dyspareunia.

Management prior to surgery

All but 2 patients used alternative treatments including arvigo therapy ($n = 1$), cupping ($n = 2$), occupational therapy ($n = 1$), dietary changes ($n = 2$), pilates ($n = 1$), physical activity ($n = 1$), shiatsu ($n = 2$), osteotherapy ($n = 2$), reflexology ($n = 3$), medical massage ($n = 4$), acupuncture ($n = 11$), hydrotherapy ($n = 6$), physiotherapy ($n = 12$).

Medical treatment including oral contraceptives improved symptoms in 28.6 % ($n = 6$), 47.6 % ($n = 10$) used them before and after surgery and 14.3 % ($n = 3$) did not neither before nor after.

Among the 21 patients included, 17 had undergone surgery for endometriosis before the current procedure (81.0 %). Among those, 6 (28.6 %) had hysterectomy, 1 (4.8 %) had a resection of rectovaginal endometriosis nodule, 2 (9.6 %) had a lysis of rectosigmoid adhesions, 1 (4.8 %) had ovarian cyst surgery and 1 (4.8 %) had ureteroscopy and ureteral catheterization.

Surgical management

Fifteen patients (71.4 %) underwent neurolysis of the obturator nerves, 2 (9.6 %) lysis of proximal part of the pudendal nerves, 8 patients (38.1 %) lysis of other pelvic nerves, one (4.8 %) laparoscopic excision of pelvic nerves endometriotic nodule.

Median operation time was 2.15 h. Median length of hospitalization was 3 days (IQR 3–5).The median duration of recovery was of 3 weeks (IQR 2–8). One patient experienced a postoperative complication of reduced locomotor motion due to possible nerve praxis which spontaneously waxed and waned till full recovery.

One case the patient had indwelling catheter infection and in one case we were required to instruct the patient regarding self-catheterization for three weeks post op.

Impact of surgery on pain intensity

Median follow up was8 months (IQR 6–11).Acute and chronic pain intensity in the 21 patients included before and after surgery is displayed in Figs. 1 and 2.

Among all patients operated, only one (4.8 %) experienced no change in chronic or acute pain scale. All except2 patients (9.6 %) had significant improvement in chronic pain with a median decrease of VAS of 3 (IQR 2–4). Two patients (9.6 %) had no residual chronic pain following surgery.

Five patients (23.8 %) had acute pain worsening following surgery, five patients (23.8 %) had no difference in acute pain intensity before and after surgery and 11 patients (52.4 %) had pain decrease after surgery. Acute pain following surgery decrease by a median of 1 (IQR 0–2).

Analgesic intake before and after surgery is displayed in table 3. Analgesics habits changed postoperatively with significant decrease of 66 % of patients consuming such medications daily($n = 9$ before versus $n = 3$ after, $p = 0.031$) with a tendency for more patients using them only during pain episodes ($n = 2$ beforehand versus $n = 8$ afterwards). Following surgery there was a decrease in consumption of strong opioids by 25 % ($n = 4$ before versus $n = 3$ after), weak opioids by 22 % ($n = 9$ before versus $n = 7$ after) and NSAIDS by 19 % ($n = 16$ before and $n = 13$ after). Furthermore, intake of Gabapentin or Amitriptyline decreased by 37.5 % ($n = 8$ before and $n = 5$ after). Medical cannabis consumption increased by 11 % after surgery ($n = 10$ versus 9 before).Two patients (9.6 %) had no improvement with analgesics (refractory pain) after surgery.

Impact of surgery on quality of life

QOL details following surgery are displayed in Supplementary Table 2. Surgery improved quality of life in 12 cases (57.1 %) and two patients

Table 1
Characteristics of the patients included.

Patients ID	Age (years)	Number of years of symptoms evolution	Number of Pregnancies	Vaginal delivery	Cesarean Section	Previous surgery for endometriosis	Any history of other surgery	Chronic morbidities	Follow up (in month)
1	34	7	1	1	0	1	0	1	11
2	36	23	4	4	0	1	1	1	11
3	44	6	5	4	0	1	0	0	11
4	40	27	4	0	3	1	0	1	10
5	46	1	4	0	4	1	0	0	10
6	29	16	0	0	0	0	1	1	10
7	36	23	2	1	1	0	1	0	8
8	22	5	0	0	0	1	0	0	8
9	38	9	4	0	4	0	1	1	8
10	40	7	3	3	0	1	1	1	8
11	29	7	0	0	0	1	1	1	8
12	37	26	0	0	0	1	1	0	7
13	21	10	0	0	0	1	1	1	6
14	35	3	0	0	0	0	1	0	6
15	24	4	0	0	0	1	1	1	5
16	41	15	2	1	1	1	1	1	3
17	42	31	1	0	0	1	1	1	3
18	25	14	0	0	0	1	0	1	7
19	46	10	2	0	0	1	1	1	2,5
20	22	6	0	0	0	1	1	1	15
21	33	22	2	1	1	1	0	1	13

Table 2
Neurological symptoms before and after surgery in the patients included.

Symptoms	Before surgery N = 21 (%)	After surgery N = 21 (%)	Number of patients with symptom "de novo" N = 21 (%)
Pain radiating to groin	8 (38.1)	4 (19.0)	0
Pain radiating to the vagina	4 (19.0)	2 (9.5)	1 (4.8)
Pain radiating to left lower limb	9 (42.9)	5 (23.8)	0
Pain radiating to the right lower limb	5 (23.8)	5 (23.8)	1 (4.8)
Pain radiating to lower digits	0	1 (4.8)	2 (9.5)
Pain radiating to lower back	10 (47.6)	7 (33.3)	1 (4.8)
Pain radiating to anus	6 (28.6)	2 (9.5)	0
Numbness in the right leg	4 (19.0)	1 (4.8)	0
Numbness in the left leg	6 (28.6)	4 (19.0)	0
Numbness in lower digits	1 (4.8)	1 (4.8)	0
Stabbing or burning sensation right leg	4 (19.0)	2 (9.5)	0
Stabbing or burning sensation left leg	3 (14.3)	3 (14.3)	1 (4.8)
Parashetsias in lower limbs	6 (28.6)	5 (23.8)	2 (9.5)
Anal and/or vaginal cramps	0	1 (4.8)	1 (4.8)
Dysesthesias in right leg	2 (9.5)	1 (4.8)	1 (4.8)
Dysesthesias in left leg	5 (23.8)	4 (19.0)	1 (4.8)
Dysesthesias in groin	0	0	0
Dragging left foot	5 (23.8)	2 (9.5)	0
Dragging right foot	2 (9.5)	0	0
Left leg tics	0	1 (4.8)	1 (4.8)
Right leg tics	0	0	0
Limping	2 (9.5)	1 (4.8)	0
Difficulty walking	8 (38.1)	4 (19.0)	0
Dorsiplantarflexion weakness	0	0	0
Weakness right leg	1 (4.8)	1 (4.8)	0
Weakness left leg	2 (9.5)	2 (9.5)	0
Urinary frequency	10 (47.6)	5 (23.8)	0
Urinary urgency	8 (38.1)	2 (9.5)	0
Urinary hesitancy	4 (19.0)	1 (4.8)	0
Urinary Incontinence	1 (4.8)	2 (9.5)	2 (9.5)
Stress Urinary Incontinence	0	0	0
Dyschezia	2 (9.5)	0	0
Fecal Incontinence	1 (4.8)	0	0
Sciatica	1 (4.8)	1 (4.8)	0
Loss of balance	0	1 (4.8)	1 (4.8)

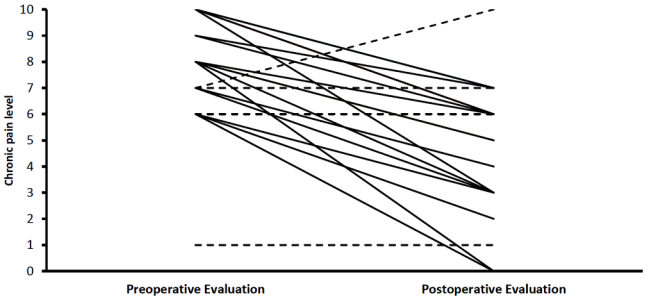

Fig. 1. Chronic pain level before and after surgery in the cohort.

(9.6 %) completely recovered with high QOL. Five patients (23.8 %) considered the surgery had no impact on their QOL. After surgery, seven patients (33.3 %) still reported having a low QOL.

During the follow up period, three patients (14.3 %) were free of residual symptoms, nine (42.9 %) experienced symptoms that were less severe, three (14.3 %) perceived more severe symptoms, three (14.3 %) had no improvement of their symptoms following surgery and three (14.3 %) were indeterminate. Three patients indicated that their symptoms relapsed after a period of improvement, one that only some symptoms returned after a period of improvement and five patients stated that episodes were less frequent and /or of shorter duration after surgery.

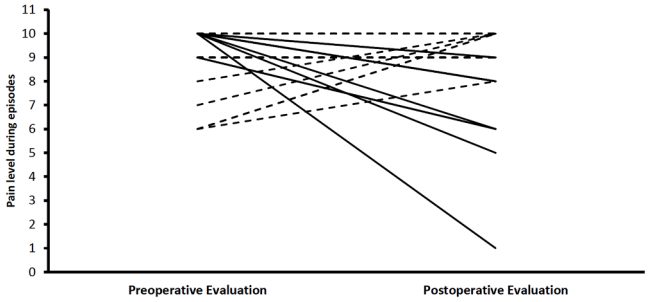

Fig. 2. Acute pain level before and after surgery in the cohort.

Table 3
Analgesics consumption and habits before and after surgery in the patients included.

Analgesics	Before surgery	After surgery	Standardized difference
Opiates	4 (19.0)	3 (14.3)	−25 %
Semi opiates	9 (42.9)	7 (33.3)	−22 %
NSAIDS	16 (76.2)	13 (61.9)	−18.7 %
Lyrica (gabapentin)	7 (33.3)	5 (23.8)	−28.6 %
Elatrol,Elatrolet (Amitrityline)	1 (4.8)	0	−100 %
Medical cannabis	9 (42.9)	10 (47.6)	+11 %
Takes them only during pain edisodes	2 (9.6)	8 (38.1)	+300 %
Takes them daily	9 (42.9)	3 (14.3)	−66 %
None	2 (9.6)	2 (9.6)	0
No improvement (Refractory) with analgesics	2 (9.6)	2 (9.6)	0

Discussion

We report here a cohort of 21 patients deep nerve infiltrating endometriosis who underwent laparoscopic management with neurolysis, mostly of the obturator nerves (15 patients, 71.4 %). In these subjects, medical treatment by oral contraceptives had improved symptoms in only 28.6 % cases. All except 2 patients (9.6 %) had significant chronic pain improvement with a mean decrease of VAS of 3.05 (±2.5). Analgesics habits changed postoperatively with a significant decrease of 66 % of patients consuming them daily. Surgery improved QOL in 12 cases (57.1 %) and two patients (9.6 %) completely recovered.

The mechanism of neuropathic pain in patients with endometriosis is complex. Proposed hypotheses [22,23] include: (a) real damage to a nerve trunk or to peripheral nerves leading to pain in certain dermatomes, muscle weakness and sensitivity disorders; (b) nerve irritation due to inflammation causing pain projection; this pain is frequently less well characterized at the dermatome level. A potential source of neuropathic symptoms is the infiltration of the parametrium by nodules compressing or involving nerves of large diameter, inducing somatic and vegetative symptoms [7]. In our cohort, sciatic pain radiating to the lower limb, urinary frequency and pain radiating to the lower back were frequently reported. In order to improve diagnostic strategy, clinicians should be aware of possible atypical presentation of nerve infiltration. In a prospective study, Possover et al. [9] published the findings of 213 laparoscopies performed for symptoms suggestive of sciatic or sacral plexus involvement with obscure etiology. In their cohort, 27 cases of isolated endometriosis of the sciatic nerve were found, principally in its

proximal suprapiriform part, and 148 cases of infiltration of the sacral plexus, especially at the level of the S1 and S2 roots. Of note, these patients had undergone an average off our "inconclusive" laparoscopies, highlighting the need for systematic opening of the retroperitoneal space together with progressive and meticulous exploration of these nerve trunks and nerves. Roman et al. published an educational video that could help endometriosis surgeons improve their skills [24].

There are no reports of a comparison of medical and surgical treatment in appropriate prospective randomized study to treat endometriosis patients with neural involvement. In our cohort, three out of four patients still complained of pain when using hormonal treatment alone. There have been similar reports for other deep infiltrating endometriosis locations such as urinary lesions [25]. In such patients, surgery is a "last chance" procedure to ease the pain and again attain a satisfying QOL, even though some patients will not experience significant enough improvement of their QOL. In a national Australian survey that included a total of 484 responses, Armour et al. reported that 76 % of the women with endometriosis used general self-management strategies within the last 6 months. Self-reported effectiveness in pain reduction was high (7.6 of 10), with 56 % also able to reduce pharmaceutical medications by at least half [26]. Among the 21 patients included in our cohort, medical cannabis consumption increased by 11 % after surgery ($n = 10$ versus 9 before): almost half patients were using cannabis following surgery. Several preclinical studies have shown the potential role of CBD to decrease the secretion of pro inflammatory cytokines such as IL-6 and TNF-α, and to increase the levels of anti–inflammatory cytokines IL-10 [27]. The other positive aspect of CBD to treat pain-related symptoms include its anxiolytic, antidepressant, sleep modulating effects etc. [28]

In patients with nerves infiltration of their endometriosis, the benefit of surgery to decrease post operative pain has been described in several reports [10,11,21,29]. Initial approaches focused on interrupting nerves transmission through neurotomy or neurectomy. Initial evidence of the safety and effectiveness of neurectomy of the superior hypogastric plexus was reported by Plancarte et al. [30] in patients with pelvic cancer pain. Subsequently the indications were expanded to include benign pathologies [31]. In a recent Cochrane review and meta-analysis by Proctor et al. [32], the effectiveness of surgical interruption of pelvic nerves for treating dysmenorrhea was analyzed. They summarized the findings of 7 controlled studies, including 3 RCT on treatment failure and complications, concluding that the procedure could benefit patients with midline pain. This raises the issue of the origin of neurogenic symptoms in these patients, and especially question the role of nerve infiltration in chronic pain. In our cohort, a large majority of patients had significant improvement of their chronic pain following surgery. As it has been correctly asserted by Soysal et al. [33], it is very difficult from the literature to ascertain the precise modality that accomplished relief of endometriosis symptomatology, since presacral neurectomy is often performed in conjunction with other procedures such as fulguration and excision of endometriotic foci [34]. According to our experience neurolysis and complete removal of endometriosis lesions should be the preferred approach whenever possible to improve symptoms and QOL. Improvement of QOL was observed in most patients following surgery in our cohort. These results are consistent with those of Roman et al. in their 52 patient cohort [11]. After a follow up of 5 years, M. Possover reported sciatic nerve function recovery, although normal gait function may take at least 3 years including intensive physiotherapy [10].

It is important to not the risk of such operations. Firstly, irreversible nerve damage, by erroneously cutting or heating the nerve. Another injury to the nerve might be praxis i.e. reversible injury to some sensory or temperature fibers. In our series we had no such complications.

Several limits of our work should be mentioned. First, despite the retrospective nature of our study, the extent of data collected, including analgesic consumption and precise symptoms description, is rare in the previous literature. While our cohort included solely 21 patients, very little data is currently available in the literature as these high-risk procedures require specific expertise introducing a center- bias reporting results. In addition, the questionnaires were given out at the end and not prior to the surgery. Second, the post operative follow up was limited to a few months in some patients which could have contributed to two forms of bias: 1. Underestimation of the benefit of the surgery on pain evolution. Indeed, persistence of immediate postoperative pain and analgesic consumption is difficult to interpret because the surgery itself could be responsible for transient pain increase. 2. Overestimation of the benefit of the surgery on disease management: one of the main issues in patients undergoing surgery for endometriosis – associated pain is the high – risk of recurrence almost reaching 25 % in deep endometriosis infiltrating patients [35]. Indeed, in our cohort, at the time of study, three patients reported that their symptoms returned after transient relief., and a further subject stated that only some symptoms recurred after a period of improvement. Similar results were reported by Roman et al. in their 52 patient's cohort [11]. Third, it is not precisely clear how patients were chosen for surgery. It is possible that the selection process for these complex procedures could lead to an overestimation of its benefit. However, the process of patients' selection is central in the role of expert center [18]. Eventually, around 25 % of patients had worsening of their pain following surgery without clear explanation and the use of standardized questionnaires such as EHP-30, SF-36 could have improved the reporting of these patients' outcomes.

Conclusion

In our cohort, neurolysis and excision of endometriotic pelvic nerves resulted in significant improvement of chronic pelvic pain VAS score analgesic agent consumption and improvement in neurological insult. These complex procedures require the expertise of senior surgeons specialized in endometriosis.

Declaration of competing interest

The authors have nothing to disclose.

Author contributions

Project administration, supervision, and resources: SBC, ANB, MGP, RM, YZB
Methodology: YD, EB, JB
Data acquisition: YB, NMam, NMan
Data analysis: SBC, YD, YZB
Writing original draft: YD, TM, JB, MGP
All authors reviewed the manuscript for critical intellectual content.

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Supplementary materials

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Original Article

Prognostic value of BRCA1 promoter methylation for patients with epithelial ovarian cancer

Henri Azaïs [a,b,c,*], Simon Garinet [b,c,d], Louise Benoit [a], Julie de Jesus [a], Mohamed Zizi [d], Samuel Landman [d], Anne-Sophie Bats [a,b,c], Valérie Taly [a,b,c,d], Pierre Laurent-Puig [b,c], Hélène Blons [b,c,d]

[a] AP-HP (Assistance Publique des Hôpitaux de Paris), Department of Gynaecological Oncological and Breast Surgery, Georges Pompidou European Hospital, Paris, France
[b] Paris CARPEM Cancer Institute, Université de Paris Cité, Paris, France
[c] INSERM UMR-S 1147, University of Paris Cité, Centre de Recherche des Cordeliers, Paris, France
[d] AP-HP (Assistance Publique des Hôpitaux de Paris), Department of Biochemistry, Unit of Pharmacogenetics and Molecular Oncology, Georges Pompidou European Hospital, Paris, France

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ABSTRACT

Objective: BRCA1 promoter methylation (BRCA1*pm*) is suspected to alter prognosis of patients with epithelial ovarian cancer (EOC). We aimed to evaluate the prognostic impact of this epigenetic modification.
Methods: We conducted a retrospective, monocentric study from 11/2006 to 08/2018. Patients with EOC and available status concerning somatic BRCA1/2 mutation and BRCA1*pm* were included. Three groups were defined: patients without BRCA1/2 mutation or BRCA1*pm*, patients with BRCA1/2 mutation and patients with BRCA1*pm*. BRCA1/2 mutations were analyzed in current care settings by next-generation sequencing (NGS). BRCA1*pm* analysis was assessed and quantified from bisulfite converted DNAs using fluorescent methylation specific polymerase chain reaction (PCR) and fragment analysis. All patients signed a consent form and the study was authorized by a Personal Protection Committee. Descriptive statistics were used to describe groups. Multivariate analysis was performed using the logistic regression model and including the variables that could be known at the time of diagnosis and that were significant at univariate analysis. Survival was compared between the groups. Kaplan-Mayer curves were used to express the differences in survival that were compared using log rank tests.
Results: 145 patients were included: 95 (65.5 %) patients without BRCA1/2 mutation or BRCA1*pm*, 32 (22.1 %) patients with BRCA1/2 mutation, 18 (12.4 %) patients with BRCA1*pm*. Median survival was decreased in patients with BRCA1*pm*. Comparison of survival revealed a significant difference in overall survival ($p = 0.0078$) with a worse prognosis for patients with a BRCA1*pm*.
Conclusion: BRCA1*pm* in patients with EOC is an independent factor associated with a decreased overall survival.
Synopsis: BRCA1 promotor methylation in patients with epithelial ovarian cancer is an independent factor associated with a decreased overall survival.

Introduction

With an incidence of approximately 65,000 cases per year, epithelial ovarian cancer (EOC) is the 7th most common cancer in women in Europe, and the 5th leading cause of cancer mortality [1]. All stages combined, EOC has a poor prognosis with a 5-year survival of 43 % [2] since it is often diagnosed at an advanced stage, defined by the presence of peritoneal carcinomatosis [3]. First-line treatment is based on a combination of platinum-based chemotherapy and cytoreductive surgery (CRS), followed by maintenance treatment with bevacizumab and/or Poly (ADP-ribose) polymerase inhibitors (PARPi). A major prognostic factor is the absence of macroscopic residual disease after CRS [4–8].

Early identification of a BRCA 1 or 2 mutation in EOC patients, as

* Corresponding author at: AP-HP (Assistance Publique des Hôpitaux de Paris), Department of Gynaecological Oncological and Breast Surgery, Georges Pompidou European Hospital, Paris, France.
E-mail address: henri.azais@aphp.fr (H. Azaïs).

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well as characterization of genomic instability status (GIS) in non-mutated patients, is a new determinant factor in defining patient prognosis, particularly as these factors are associated with PARPi effectiveness.

The Cancer Genome Atlas (TCGA) integrated genomic study of 489 high-grade serous ovarian carcinomas found approximately 61 mutations per exome. *TP53* mutations were the most frequently somatic event (96 %) and 17 % of patients had germline mutations in *BRCA1/2*. In sporadic forms, a BRCA loss profile is observed with inactivation of the *BRCA1/2* genes by genetic (somatic mutations in 6 % of cases) or epigenetic (methylation of the BRCA1 promoter in 11 % of cases) phenomena, resulting in chromosomal instability. In the TCGA study, recurrent genomic alterations outside of *TP53* and *BRCA* are rare, but an homologous recombination deficiency was found in approximately 50 % of cases [9].

Methylation of the *BRCA1* promoter is an epigenetic modification suspected to inactivate *BRCA1* gene and thus alter patient prognosis, but its clinical value remains uncertain. The objective of this study was to evaluate the prognostic impact of this *BRCA1* promotor methylation in a monocentric cohort of patients followed prospectively.

Material and method

Population

We conducted a retrospective, monocentric, study from 01/11/2006 to 31/08/2018 in the department of Gynecological Oncological and Breast Surgery in collaboration with the Unit of Pharmacogenetics and Molecular Oncology, at the Georges Pompidou European Hospital in Paris, France. Our department is certified for the surgical management of advanced EOC by the European Society of Gynecologic Oncology (ESGO) and the laboratory is certified by an independent organism for somatic oncogenetics (Cofrac 15,189).

Patients with histologically confirmed EOC and with information available concerning somatic *BRCA1/2* mutation and *BRCA1* promoter methylation status were included. Three groups of patients were defined in order to compare prognosis according to observed molecular profile at diagnosis:

- Patients without *BRCA1/2* mutation or *BRCA1* promoter methylation
- Patients with *BRCA1/2* mutation
- Patients with *BRCA1* promoter methylation

Data collected

The following data was collected, clinical characteristics (age, body mass index (BMI), American Society of anesthesia (ASA) score, notable medical and surgical history, pre-disposing genetic mutations, menopausal status), tumor characteristics (histological type, CA 125, International Federation of Gynecology and Obstetrics (FIGO) stage), oncological treatment (adjuvant chemotherapy, associated targeted therapies), surgical parameters (peritoneal carcinomatosis score (PCI), extent of surgery, possible tumor residue) and oncological outcomes (progression-free survival (PFS) and overall survival (OS)).

Objective

Our primary objective was to evaluate the prognostic impact of methylation of BRCA1 promoter in a monocentric cohort of patients followed prospectively.

Patient management

Therapeutic management was decided for each patient during multidisciplinary tumor boards that included surgeons, oncologists, radiologists, pathologists, and nuclear medicine physicians. All patients had an initial evaluation (computed tomography (CT) and laparoscopy) with histological confirmation of EOC. Surgery generally included a hysterectomy with bilateral adnexectomy, removal of all visible peritoneal lesions, omentectomy and lymphadenectomy if indicated according to the conclusion of the LION study [10] and the French guidelines [11].

After surgery, patients had platinum-based adjuvant chemotherapy and targeted therapies (bevacizumab, PARP inhibitors) if indicated by the tumor board.

Molecular biology protocol

Tumor samples were stored at the Biological Resources center and Tumor Bank Platform (PRB-HEGP BB-0033–00,063) before nucleic acids extraction.

Nucleic acid extraction/quantification from tumor

DNAs were extracted on a Maxwell® RSC Instrument (Promega, France) using Maxwell® RSC DNA FFPE Kit (Promega, France) for FFPE samples, quantified by Qubit Fluorometric Quantitation using the Qubit dsDNA BR Assay Kit (Life Technologies–Thermo Fisher Scientific, Saint Aubin, France) and stored at −20 °C before testing.

Next-generation DNA sequencing (NGS)

BRCA mutations were analyzed in current care settings by NGS using the Oncomine™ BRCA Research Assay, Chef Ready procedure (Thermo Fisher Scientific). Sequences were run on Ion PI Chips Kit v3 on the Ion Proton System. FASTQ were first processed and aligned to the human genome (hg19) using the Ion-Torrent Suite v5.0.4; variant call files were loaded on a galaxy platform and annotated using the Safir2report tool (https://github.com/OvoiDs/IonTorrentReport). Coverage depth data were used to detect gene deletion.

BRCA1 methylation analysis was assessed and quantified from bisulfite converted DNAs using fluorescent methylation specific PCR and fragment analysis. For a specific CpG site, 2 couples were designed with a reverse primer localized on CpG site and a forward outside of any CpG site. R primers were HEX tagged for methylated fragments and FAM tagged for non-methylated fragments. Migration was performed on ABI3730xl sequencer data were analyzed with Genemapper software (Thermofisher diagnostics).

For BRCA1, CpG regions described to be implicated in transcriptional regulation were selected on promoter (Table 1). Sensibility and specificity were assessed by serial dilutions of methylated DNA using commercially available 100 % and 0 % methylated DNA (Fig. 1). BRCA1 promoter methylation was defined by at least one positive region.

Ethics

All patients included in the study signed a consent form to collect data used in routine care for the research. The use of this consent form was authorized by a Personal Protection Committee (“OncoHEGP” CPP :2012–08–09 MS4). Anonymized data were collected on a secure server and the database was declared to the competent French authorities (ChirGyn_BaseOvaire_HEGP, CNIL id :1,922,081).

Statistical analysis

Basic descriptive statistics were used to describe groups. Categorical variables were reported as frequencies and percentages. Continuous variables were reported as mean and standard deviation (SD) or median and range. A Student-t-test and chi2 test were used to compare the continuous and categorical values, respectively. To compare the variables across groups, the Student’s *t*-test and ANOVA were used for normally distributed data, the Mann–Whitney U test for non-parametric data, and the Chi-Square test for categorical data. Statistical significance

Table 1
Primers used for BRCA1 promoter methylation detection.

Gene	Mix Primer	Orientation	Specificity	Oligonucleotides	CpG in amplicon	Amplicon size (base pairs)
BRCA1	1	Forward	Methylated	**CGATTGCGCGGCGTGAGTTCG**	8	152
		Forward	Unmethylated	**TGATTGTGTGGTGTGAGTTTGT**		151
		Reverse	Universal	**CACTTAAACCCCCTATCCCT**		
	2	Forward	Methylated	**TTTTGGTTTTCGTGGTAAC**	8	120
		Forward	Unmethylated	**TTTTTTGGTTTTTGTGGTAAT**		122
		Reverse	Universal	**TATCTAAAAAACCCCACAACCTATC**		
	3	Forward	Methylated	**TTAATTTAGAGTTTCGAGAGAC**	3	93
		Forward	Unmethylated	**AATTTAGAGTTTTGAGAGAT**		91
		Reverse	Universal	**CTAAACAACAACCTCTCAAAATA**		

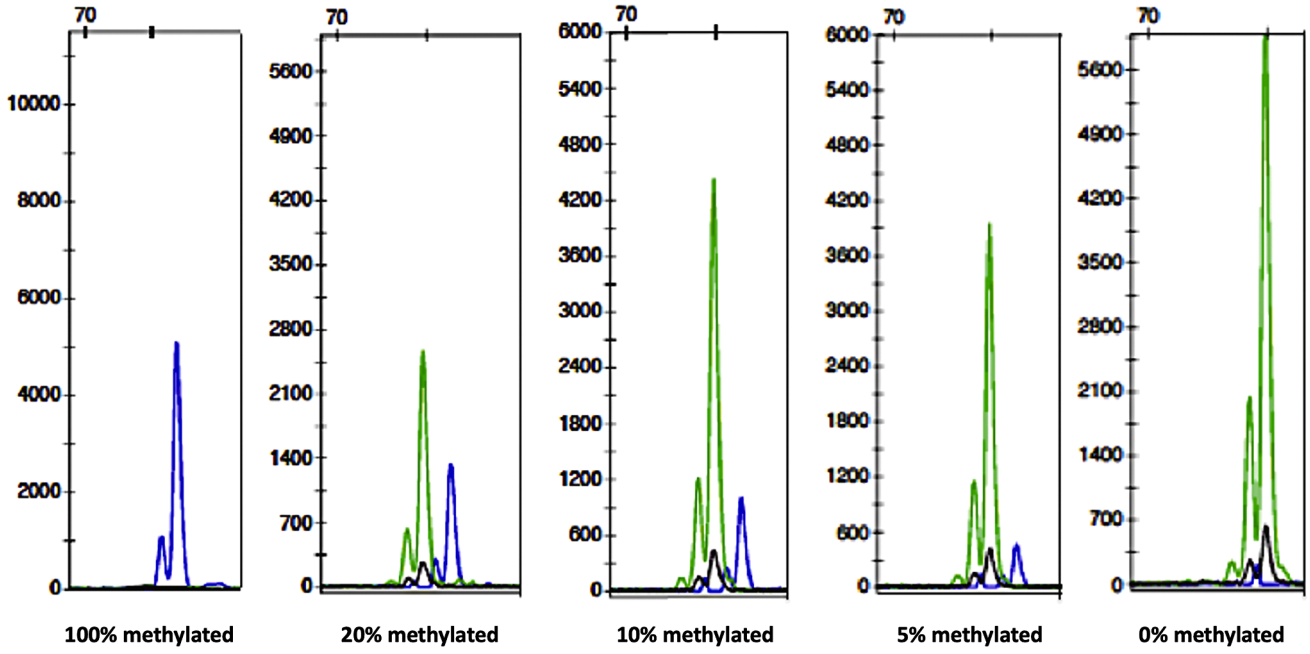

Fig. 1. Sensibility and specificity. Example of results showing serial dilution of 100 % methylated DNA in unmethylated DNA for BRCA1 mix « 3 » assessed by fragment analysis and migration in an ABI 3730xl genetic analyzer (Thermo Fisher Scientific). Methylated pic (blue), unmethylated (green).

was set at $p < 0.05$ for a bilateral test.

Multivariate analysis was performed using the logistic regression model and including the variables that could be known at the time of diagnosis and that were significant at univariate analysis. A P-value of 0.05 was considered significant.

The RFS and OS were compared between the groups of patients. RFS and OS were respectively defined as the time from the date of the initial diagnosis to tumor recurrence or death, of any cause. A cox survival model was used to search variables associated with RFS and OS. A Kaplan Mayer curve was used to graphically express the differences in RFS and OS. A log rank test compared the two curves.

Analysis was carried out using an Excel database and the R software (The CRAN Project, Version 3.0).

Results

Patient characteristics

One hundred and forty-five patients with EOC and for whom we had information regarding BRCA mutation status and BRCA1 promoter methylation status were included with the following repartition in the three groups:

- Patients without *BRCA 1/2* mutation or *BRCA1* promoter methylation ($n = 95$)
- Patients with *BRCA 1/2* mutation ($n = 32$)
- Patients with *BRCA 1* promoter methylation ($n = 18$)

Main characteristics of the population are detailed in Table 2. There was no difference between the three groups concerning patient characteristics. Briefly, mean age ranged from 60 to 64 years, depending on the group, and body mass index from 24 to 25.5. The most frequent histological type was high-grade serous carcinoma (87.5 % to 100 %). The disease was most often diagnosed at an advanced stage (stage 3–4 of the FIGO classification in 77.8 % to 93.8 %). The majority of patients underwent cytoreductive surgery with no macroscopic residual disease (72.6 % to 87.5 %). Almost all patients received chemotherapy (93.8 % to 100 %).

Survival in case of BRCA1 promoter methylation

Follow-up was similar in the three groups (median 44 +/- 30.6, 31.5 +/−28.1 and 41 +/- 26.7 months for BRCA mutation, BRCA methylation and no mutation respectively). During this follow-up period, the median times from diagnosis to recurrence were 26 (10–114), 16 (5–39), 21 (0–106) months for BRCA mutation, BRCA methylation and no mutation respectively with no significant difference between the groups (p

Table 2
Patient's characteristics.

	BRCA 1/2 mutation $n = 32$	BRCA1 promoter methylation $n = 18$	No mutation or methylation $n = 95$	P-value	P-value (ANOVA)
Age (years)				* 0.38	0.11
Mean ± SD	60.0 ± 10.8	62.2 ± 7.0	64.2 ± 13.0	$ 0.08	
Median (range)	61.0 (32.0 - 81.0)	62.0 (50.0 - 76.0)	67.0 (26.0 - 87.0)	# 0.34	
BMI (kg/m2)				* 0.43	0.21
Mean ± SD	25.5 ± 5.7	24.2 ± 5.3	24.0 ± 5.4	$0.23	
Median (range)	23.5 (16.3 - 39.4)	24.0 (18.4 - 39.0)	22.5 (15.6 - 41.1)	# 0.92	
Menopause				* 1	0.57
n (%)	26 (81.3)	16 (88.9)	70 (73.7)	$ 0.63	
				# 0.61	
ASA score					0.95
n (%)	3 (9.4)	1 (5.6)	7 (7.4)	* 0.76	
1	10 (31.3)	7 (38.9)	27 (28.4)	$ 0.86	
2	3 (9.4)	1 (5.6)	5 (5.3)	# 0.91	
3	1 (3.1)	0 (0)	1 (1.1)		
4	15 (46.9)	9 (50)	56 (58.9)		
NA					
Tumor histological type					
n (%)	28 (87.5)	18 (100.0)	83 (87.4)	* 1	0.51
High-grade Serous	1 (3.1)	0 (0)	8 (8.4)	$ 0.15	
Low-grade Serous	0 (0)	0 (0)	2 (2.1)	# 1	
Low-grade Endometrioid	1 (3.1)	0 (0)	0 (0)		
Undifferentiated	2 (6.2)	0 (0)	2 (2.1)		
NA					
CA125				* 0.33	0.92
Mean ± SD	1475.1 ± 2006.0	2195.8 ± 2623.5	1387.0 ± 2411.9	$ 0.84	
Median (range)	700.0 (6.0 - 8557.0)	847.0 (23.0 - 8609.0)	553.0 (8.0 - 16,230.0)	# 0.25	
Initial FIGO					0.09
n (%)	1 (3.1)	1 (5.6)	2 (2.1)	* 0.31	
1	0 (0)	2 (11.1)	4 (4.2)	$ 0.49	
2	19 (59.4)	10 (55.6)	69 (72.6)	# 0.06	
3	11 (34.4)	4 (22.2)	17 (17.9)		
4	1 (3.1)	1 (5.6)	3 (3.2)		
NA					
Initial PCI				* 0.83	0.23
Mean ± SD	13.2 ± 11.5	14.0 ± 9.8	16.3 ± 9.1	$ 0.23	
Median (range)	10.5 (0.0 - 34.0)	13.0 (0.0 - 30.0)	16.0 (0.0 - 34.0)	# 0.47	
CC score					0.34
n (%)	28 (87.5)	15 (83.3)	69 (72.6)	* 0.15	
CC0	2 (6.3)	0 (0)	8 (8.4)	$ 0.53	
CC1	1 (3.1)	3 (16.7)	7 (7.4)	# 0.25	
CC2	0 (0)	0 (0)	0 (0)		
CC3	1 (3.1)	0 (0)	11 (11.6)		
NA					
Chemotherapy				* 1	0.58
n (%)	30 (93.8)	18 (100)	92 (96.8)	$ 1	
				# 1	
Peroperative complication				* 0.11	0.39
	4 (12.5)	3 (16.7)	6 (6.3)	$ 0.52	
				# 0.44	

*: p-value for comparison « BRCA1/2 mutation » versus « BRCA1 promoter methylation ».
$: p-value for comparison « BRCA1/2 mutation » versus « No mutation or methylation ».
#: p-value for comparison « BRCA1 promoter methylation" versus *« No mutation or methylation ».*
BMI: Body Mass Index. ASA: American Society of Anesthesiologists.
PCI: Peritoneal Carcinomatosis Index. CC score: Completeness of Cytoreduction score.

= 0.66). The median times from diagnosis to death was higher in the mutation group in comparison with the methylation group, with 44 (1–114) months versus 31.5 (5–134) months respectively ($p = 0.04$), and it was also higher in the group without mutation or methylation in comparison with the methylation group, with 41 (0–149) months versus 31.5 (5–134) months respectively ($p = 0.04$).

The comparison of survival between the "BRCA1 promoter methylation" group, the "BRCA 1/2 mutation" group and the "No mutation or methylation" group by the Log rank test revealed a significant difference in OS with a worse prognosis for patients with a BRCA1 promoter methylation ($p = 0.0078$). The comparison is in favor of a worse PFS for this group with a p value at the limit of significance ($p = 0.05$) (Fig. 2).

To determine the prognostic value of BRCA1 promoter methylation, we compared it in a multivariate Cox model to other presumed prognostic factors ($p < 0.05$ in univariate analysis). Stage according to the FIGO classification and age were not associated with OS in univariate analysis. There was a prognostic impact of BRCA1 promoter methylation while this factor was found to be the only factor associated with a decrease in OS in multivariate analysis ($p = 0.02$) (Table 3).

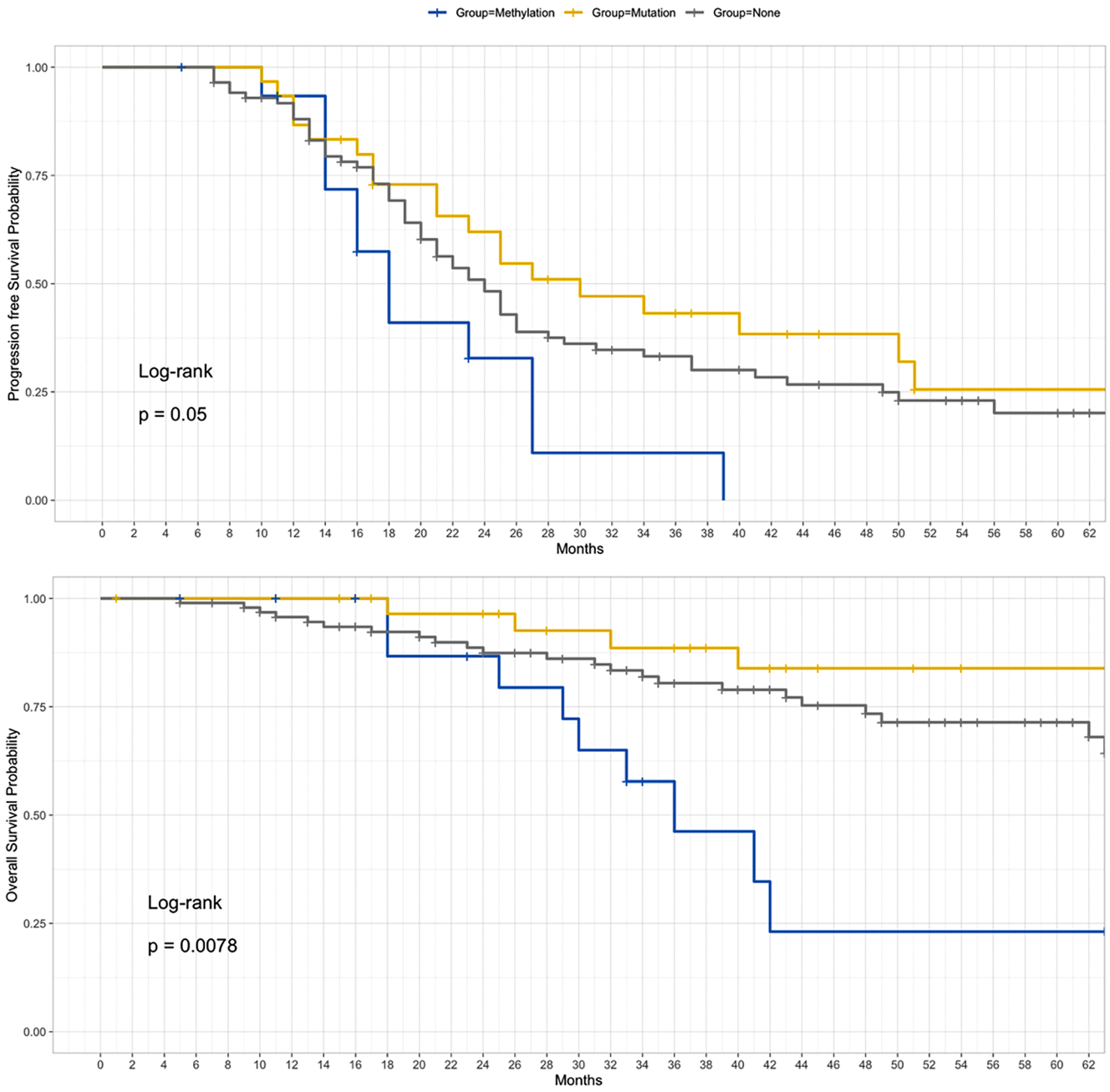

Fig. 2. Survival according to status regarding BRCA1/2 mutation and BRCA1 promoter methylation.

Discussion

In this study, we observed that BRCA1 promoter methylation in patients with EOC is an independent factor associated with a decreased overall survival.

In the TCGA study on 489 high-grade serous EOC, an inactivation of the BRCA1/2 genes by methylation of the BRCA1 promoter was found in 11 % of cases [9]. In another study on 332 patients with EOC conducted by Bernards et al., BRCA1 promoter methylation was detected in 22 carcinomas (6.6 %). The authors stated that patients with BRCA1 promoter methylated carcinomas shared clinical characteristics with patients with BRCA1-mutated carcinomas including younger age and predominantly high-grade serous histology. However, they observed that, unlike mutation, RAD51C and BRCA1 promoter methylation were not associated with improved survival or greater sensitivity to platinum chemotherapy [12]. This is consistent with our experience. On 145 patients studied in this study, BRCA1 promoter methylation was detected in 18 carcinomas (12.4 %) and the prognosis of this subgroup was poorer. The TCGA study also revealed EMSY amplification (8 % of cases), PTEN deletion (7 % of cases), RAD51C hypermethylation (3 % of cases), ATM/ATR mutation (2 %) or other mechanisms leading to a defect in homologous recombination [9]. We do not routinely look for these mutations in our center, as they are rare and the evidence for their theragnostic impact is currently limited.

Nevertheless, the data in the literature remain contradictory regarding the prognostic role of BRCA1 promoter methylation, probably because of heterogeneity regarding the impact of this epigenetic event, particularly on genomic instability. Thus, in the meta-analysis of Kalachand et al., among 2636 tumors, 430 (16.3 %) were BRCA1-methylated. BRCA1 methylation was associated with younger age and

Table 3
Multivariate analysis to determine prognostic value of BRCA1 promoter methylation concerning overall survival.

Overall survival		Univariate			Multivariate		
		Hazard ratio	95 % confidence interval	p-value	Hazard ratio	95 % confidence interval	p-value
Mutation or methylation status	-None	**Reference**			Ref		
	-Methylation	2.61	1.23–5.56	**0.01**	4.07	1.25–13.3	**0.02**
	-Mutation	0.66	0.28–1.54	0.3	0.91	0.26–3.18	0.9
CC score	-CCO	Ref			Ref		
	-CC1	2	0.68–5.85	0.2	1.66	0.18–15.3	0.6
	-CC2	4.06	1.50–11	**0.006**	1.06	0.21–5.42	0.9
Type of surgery	-Initial	**Reference**					
	-Interval	1.52	0.71–3.28	0.3	0.73	0.18–2.93	0.7
	-None	4.20	1.52–11.6	**0.006**	4.5	0.9–10	0.65
PCI		1.07	1.03–1.12	**0.002**	1.05	0.98–1.13	0.2
CA 125		1.01	1–1.02	**0.01**	1	1–1	0.4

PCI: Peritoneal Carcinomatosis Index. CC score: Completeness of Cytoreduction score.

advanced-stage, high-grade serous EOC, but there were no survival differences between BRCA1-methylated and non-BRCA1-methylated patients (median PFS = 20.0 vs 18.5 months, hazard ratio [HR] = 1.01, 95 % CI = 0.87 to 1.16; $P = 0.98$; median OS = 46.6 vs 48.0 months, HR = 1.02, 95 % CI = 0.87 to 1.18; $P = 0.96$). Authors stated that BRCA1 promoter methylation displayed no survival advantage over BRCA1/2 wild-type (BRCAwt) non-BRCA1-methylated EOC, and that method used to define BRCA1 promoter methylation may impact the observed prognosis, suggesting that refining these assays may allow better identification of cases with silenced BRCA1 function and improved patient outcomes [13]. We agree that the technique used to define BRCA1 promoter methylation should be discussed because it impacts the functional effect of the methylation, the allocation of patients to a given group and thus the prognostic analysis. In our series, we considered that BRCA1 promoter methylation was significant for a methylation ratio higher than 5 %, but this ratio was higher than 25 % in 75 % of patients. It is also important to specify the timing of the test in the therapeutic sequence as this may impact the result and its interpretation, depending on whether the BRCA1 promoter methylation test was performed at diagnosis, after neoadjuvant chemotherapy or after surgery, or their possible relapse.

Although the prognostic impact of BRCA1 promoter methylation is debated, this status is associated with greater genomic instability and homologous recombination deficiency making patients eligible for PARPi. In the study by Hodgson et al. about the long-term outcome of candidate biomarkers of sensitivity to olaparib in BRCAwt tumors, authors observed that a higher median Myriad MyChoice® HRD score was observed in BRCA mutated and BRCAwt tumors with BRCA1 methylation. They concluded that these patients may constitute molecularly identifiable and clinically relevant population who derive treatment benefit from olaparib similar to patients with BRCA mutation [14].

These results are consistent with those presented in the publication by Blanc-Durand et al. about 100 patients among which 11 % harbored a deleterious BRCA1/2 mutation, and 19 % of BRCA1/2 wild-type patients had BRCA1 promoter methylation. All of the methylated tumors were classified deficient for homologous recombination (HRD) with the genomic-instability score (GIS) by MyChoice CDx (Myriad Genetics). Mean GIS was 61.5 for BRCA mutated patients 66.4 for BRCA1 promotor high-methylated patients, 58.9 for BRCA1 promotor low-methylated patients and 33.3 for BRCA1/2 wild-type unmethylated patients. Low methylation levels detected in samples previously exposed to chemotherapy appeared to be associated with poor outcome. Authors concluded that patients with high levels of BRCA1 promotor methylation were very likely to have high GIS and therefore represent good candidates for PARPi treatment [15].

In the PAOLA-1/ENGOT-ov25 trial [16], promoter methylation was identified in 67 (12.9 %) samples for BRCA1 and 25 (4.8 %) for RAD51C (4 were methylated on both genes). Methylation and BRCA mutation were mutually exclusive except for 3 samples. Mean GIS scores were 62.5 [59.6–65.5]; 59.4 [57.2–61.5]; 54.2 [50.5–57.8]; 23.4 [21.6–25.2] for BRCA1 or RAD51C methylation group, BRCA mutation group, no-mutation/no-methylation HRD+ group, and HRP (proficient) tumors respectively. Among tumors with promotor methylation, 92 % (66/72) were GIS positive (>42). The mean GIS score of tumors with promotor methylation were significantly higher than that of no-mutation/no-methylation HRD+ samples ($p = 0.009$). Authors reported that methylated BRCA1/RAD51 tumors are HRD+ and provide to ovarian cancer patients a similar clinical benefit of olaparib/bevacizumab association as patients with HRD+ and no-mutation/no-methylation tumors. They concluded that methylation assessment may represent a rapid and cost-effective tool, which coupled with BRCA1–2 somatic testing allows the identification of the majority (81 %) of HRD+ patients.

It is possible that the poor prognosis observed in our study for the group of patients with BRCA1 promoter methylation is linked to the fact that this is a relatively old cohort and patients have not been routinely exposed to PARPi. Maintenance treatment with PARPi could improve the prognosis of this subgroup of patients. Thus, while the indications for PARPi are expanding, our results provide information on the prognosis in the absence of PARPi maintenance treatment of this patient population, which is often HRD+ but whose prognosis appears to be worse than that of other patients with homologous recombination deficiency.

Further research is needed to refine the criteria for defining BRCA1 promoter methylation in order to homogenize the definitions and functional interpretations of this observation according to the natural history of the disease.

Conclusion

In this study, we observed that BRCA1 promoter methylation is an epigenetic phenomenon of interest because it is associated with a worse prognosis but could be an indication for the prescription of targeted therapy, in particular PARP inhibitors, given its inactivating action on the BRCA1 gene. This epigenetic modification, not systematically sought in conventional panels, may result in higher genomic instability scores than in the population of non-mutated, non-methylated patients. This is an additional argument for systematically defining the genomic instability score for all patients managed for ovarian cancer, and thus guiding the prescription of maintenance treatments.

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None.

CRediT authorship contribution statement

Henri Azaïs: Conceptualization, Visualization, Methodology, Data curation, Formal analysis, Writing – review & editing. **Simon Garinet:** Formal analysis, Writing – review & editing. **Louise Benoit:** Formal analysis, Writing – review & editing. **Julie de Jesus:** Data curation. **Mohamed Zizi:** Data curation. **Samuel Landman:** Data curation. **Anne-Sophie Bats:** Formal analysis. **Valérie Taly:** . **Pierre Laurent-Puig:** Formal analysis. **Hélène Blons:** Conceptualization, Visualization, Methodology, Formal analysis, Writing – review & editing, Supervision.

Declaration of competing interest

No conflicts of interest were disclosed by the authors.

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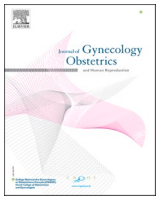

RETRACTED: Vaginal cleansing prior to caesarian section: to do or not to do?: A randomized trial

Nisreen Khaled Aref

Faculty of Medicine, Taif University, Saudi Arabia

This article has been retracted: please see Elsevier Policy on Article Withdrawal (https://www.elsevier.com/locate/withdrawalpolicy).

This article has been retracted at the request of the Editor-in-Chief and the journal's Ethics Committee.

After post-publication investigation, it was found that this paper and another published in *The Journal of Maternal-Fetal & Neonatal Medicine* (https://doi.org/10.1080/14767058.2016.1219996) contain mostly the same data in Tables 1 and 2. This constitutes duplication submission and duplicate publication. As such, this article represents a misuse of the scientific publishing system. The scientific community takes a very strong view on this matter and apologies to readers of the journal that this was not found during the submission process.

The author, Dr. Nisreen Khaled Aref, was contacted about this issue, but has not returned an answer.

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