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ORIGINAL RESEARCH

Vulvar and vaginal cancer during pregnancy: A pooled analysis of 15 cases from the International Network on Cancer, Infertility and Pregnancy and review of the literature

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Abstract

Introduction: Vulvovaginal cancer in pregnancy is rare. Limited data complicate decision-making and patient counseling. Our review, coupled with new case data, fills a current gap in the literature and provides practical insights.

Material and Methods: Oncological and obstetric data of these pregnancies were examined by a case collection from the International Network on Cancer, Infertility and Pregnancy (INCIP) registry (vulvar $n = 10$, vaginal $n = 5$) and a literature review (vulvar $n = 46$, vaginal $n = 37$).

Results: Although preoperative imaging of inguinofemoral lymph nodes is feasible, only 16.1% of vulvar cancer patients underwent ultrasound or MRI. Treatment was initiated during pregnancy for 69.1% of vulvar cancer and 28.4% of vaginal cancer patients. Surgical lymph node staging of vulvar cancer was postponed until after delivery in 10 cases, although uni- or bilateral lymphadenectomy during pregnancy was not associated with more complications. Delivery outcomes included a live birth rate of 96.4% for vulvar cancer and 50% for vaginal cancer due to the high rate of pregnancy terminations, with most births preterm. The overall 5-year survival rates for vulvar (81.3%) and vaginal (66.4%) cancer during pregnancy are comparable to nonpregnant populations, indicating that pregnancy does not adversely impact maternal prognosis.

Conclusions: This study underscores the feasibility of adapting standard oncological care for pregnant patients, emphasizing multidisciplinary teams to optimize maternal and fetal outcomes.

Abbreviations: CI, confidence interval; DES, diethylstilbestrol; FIGO, International Federation of Gynecology and Obstetrics; HPV, human papillomavirus; ICG, indocyanine green; INCIP, International Network on Cancer, Infertility and Pregnancy; IQR, interquartile range; MRI, magnetic resonance imaging; NIPS, non invasive prenatal screening; OS, overall survival; SLN, sentinel lymph node; Tc99m, Technetium-99 m; WHO, word health organization.

For affiliations refer to page 2197.

KEYWORDS
neoplasm staging, neoplastic, pregnancy complications, treatment outcome, vaginal neoplasms, vulvar neoplasms

1 | INTRODUCTION

An oncological diagnosis complicates 20–30 per 100000 pregnancies.[1] Over the last decades, the incidence of cancer during pregnancy has increased.[2–4] First, the trend to postpone childbirth to a later age results in increasing maternal age at pregnancy and a higher risk of cancer.[5] Second, more widespread implementation of noninvasive prenatal screening (NIPS) in routine obstetric care increases the number of incidental oncological diagnoses during pregnancy.[6] Melanoma, breast cancer, hematological cancers, thyroid cancer, and gynecological cancers are the most frequently diagnosed cancer types during pregnancy, mirroring the most frequent cancers found in nonpregnant women of reproductive age.[2,3,7] The most frequent gynecological malignancies found in pregnancy are cervical cancer and ovarian cancer.[8]

Vulvar and vaginal cancer are uncommon gynecological malignancies with an estimation of 47000 and 18800 new cases per year worldwide according to GLOBOCAN (Global cancer observatory, WHO) data.[9–11] Among women aged 15–49 years, approximately 7000 cases of vulvar cancer and 3300 cases of vaginal cancer are diagnosed yearly.[9–11] Vulvar cancer is a disease that mostly affects the elderly, with peak incidence in the 7th decade and 8th decade of life.[12] In recent years, there has been an increasing incidence of vulvar cancer in younger women,[13,14] likely due to changed sexual behavior and increased exposure to human papillomavirus (HPV).[12,15] Histologically, vulvar squamous cell carcinoma is the most frequent malignant vulvar tumor. Approximately, 30% of cases are associated with HPV.[12,16] Other risk factors are lichen sclerosus or planus.

Primary vaginal cancer accounts for less than 1% of all female genital tract malignancies, with significant regional variations.[10] Although postmenopausal women are more frequently diagnosed, an increase in incidence among younger women has been noted.[17,18] The most common subtype of primary vaginal cancer is squamous carcinoma, accounting for 80–90% of all cases, followed by adenocarcinoma.[12] Clear cell vaginal adenocarcinoma occurs in adolescent and young adult females who were exposed (between 1940 and 1970) to diethylstilbestrol (DES) in utero, with a 40-fold increased risk compared to unexposed young women.[19]

The estimated incidence of vulvar and vaginal cancer during pregnancy is 0.1–0.5 cases per 100000 pregnancies.[8] However, with the increasing incidence of vulvar or vaginal carcinoma in women of reproductive age, pregnancy-associated diagnoses are expected to rise. Given the scarcity of available information, the management of pregnant patients with vulvar or vaginal cancer during pregnancy is challenging for the gynecologists, oncologists, and obstetricians involved, balancing maternal benefits with fetal risks. Questions concerning the staging, treatment, and mode of delivery remain.

Key message

Vulvovaginal cancer in pregnancy is rare. This pooled analysis of 15 INCIP cases and 83 cases from the literature highlights the underuse of nodal imaging, the value of multidisciplinary care, and shows that standard oncologic treatment can be safely adapted without compromising maternal or fetal outcomes.

In 2005, an international registry for all cancers diagnosed in association with pregnancy was launched by the International Network on Cancer, Infertility and Pregnancy (INCIP) to fill the knowledge gaps. The database consists of oncological and obstetric data of women diagnosed with any pregnancy-associated malignancy, registered by participating centers. Currently, the registry contains 2949 women with a cancer diagnosis during pregnancy, registered by 64 European and non-European centers.

This study aims to synthesize the current knowledge of the tumor characteristics, management, and oncological and obstetrical outcomes of vulvar and vaginal cancer during pregnancy, based on clinical data of patients from the INCIP registry and a comprehensive literature review.

2 | MATERIAL AND METHODS

Data from women diagnosed with a primary or recurrent vulvar or vaginal cancer during pregnancy were retrieved from the INCIP registry in December 2024. Clinical data regarding disease characteristics, diagnosis, treatment, obstetric complications, neonatal outcome, and maternal outcome were collected. Based on registered tumor characteristics, all patients were staged according to the 2021 FIGO (International Federation of Gynecology and Obstetrics) staging system.

In addition, a comprehensive review was conducted, including case reports and case series of vulvar squamous cell carcinoma and vaginal squamous cell carcinoma and adenocarcinoma diagnosed during pregnancy. Articles were identified by a comprehensive search of the PubMed database, covering all records up to January 6, 2025, using the following MESH terms: pregnancy, vulvar neoplasms, vaginal neoplasms, and variations thereof. The full search strategy, including the exact search strings, is detailed in Appendix S1. We excluded articles with postpartum diagnoses, non-English/French/German languages, unavailable full texts, or missing individual patient data. Cross-references were checked for additional cases. The INCIP network cases included in this study have not been published

previously and do not overlap with cases described in the existing literature.

For analysis of obstetrical and oncological outcomes, data from the 15 INCIP cases were pooled with cases identified through literature review. Statistical analysis was conducted using R Software (version 4.3.3; R Core Team, 2024), within the RStudio integrated development environment (version 2024.09.0). Standardized descriptive analyses were conducted with medians, percentages, and interquartile ranges (IQR) reported to one decimal place, and ranges. No formal statistical comparison was performed because of the small number of patients. Trimesters of pregnancy were defined as first trimester (0–12 + 6 weeks), second trimester (13–27 + 6 weeks) and third trimester (28 weeks - delivery). Preterm delivery was defined as a delivery before 37 weeks of gestation.

3 | RESULTS

A total of 10 women with primary vulvar cancer and 5 women with primary vaginal cancer were identified from the INCIP registry, representing 0.34% and 0.17% of all registered INCIP cases (Table 1). There were no patients with a recurrence diagnosed during pregnancy. Patients were diagnosed between May 1999 and September 2021 in 9 academic centers in 7 countries (The Netherlands, $n = 6$; Czech Republic, $n = 4$; USA, $n = 1$; Italy, $n = 1$; Denmark, $n = 1$; Russia, $n = 1$ and Germany, $n = 1$). In addition, 46 cases of vulvar cancer and 37 cases of vaginal cancer during pregnancy were retrieved from the literature. The cases, published between 1931 and 2024, originated from 19 countries, with the United States accounting for 44 cases (53.0%; Table S1). Figure 1 presents the PRISMA flow chart with a summary of search results. References for all included articles are listed in Appendix S2.

3.1 | Vulvar cancer

Median maternal age at diagnosis was 30 years (range 17–43; interquartile range (IQR) 28–34). Median gestational age at diagnosis was 21 weeks (range 3.3–40; IQR 18–31). A complete overview of the characteristics of the INCIP study population, the literature review, and the total group ($n = 56$) can be found in Table 2. Thirty-five patients were diagnosed with early-stage disease (62.5%), five with locally advanced disease (8.9%), 13 with lymph node metastasis (23.2%) and three with distant metastatic disease (5.4%). Most patients presented with a vulvar mass ($n = 34$, 60.7%) or vulvar pruritus ($n = 8$, 14.3%). Five patients were asymptomatic, with a vulvar mass incidentally discovered during clinical examination or delivery.

Locoregional staging was performed during pregnancy in nine cases (16.1%): two patients underwent inguinal ultrasound at 6 and 34 weeks of gestation, six patients received a pelvic MRI between 3 and 26 weeks of gestation; in one patient, a positron emission tomography/computed tomography (PET/CT) was performed at 34 weeks of gestation. Median gestational age at diagnosis of patients who did not undergo imaging was 23 weeks (range 7–40; IQR 18–31); these case reports spanned from 1941 to 2024.

Eighteen patients (32.1%) did not receive treatment during pregnancy. In six patients (10.7%), vulvar cancer was discovered in the peripartum period. Additionally, six patients (10.7%), diagnosed between 30 and 36 weeks of gestation, opted for preterm delivery. Five patients (8.9%), diagnosed between 16 and 33 weeks of gestation, chose to delay treatment for 5–20 weeks until after delivery. Of the patients with only postpartum treatment, 16 received surgical treatment, one received radiotherapy, and one never received treatment.

In 38 patients (69.1%), treatment of vulvar cancer was initiated during pregnancy. Surgical treatment, consisting of local excision, partial or radical vulvectomy, was performed during pregnancy in 36 patients (64.3%). Of these, one had resection of a palpable inguinal lymph node, two (3.6%) underwent a unilateral inguinofemoral lymphadenectomy, and 10 (17.9%) a bilateral lymphadenectomy during pregnancy. Sentinel lymph node (SLN) mapping was performed during pregnancy in five patients (8.9%), using Technetium-99 m ($Tc\text{-}99^{m}$), in the second and third trimester. One patient, diagnosed with Stage IVB vulvar cancer, received carboplatin–vinorelbine chemotherapy between 18 and 28 weeks of gestation, [20] and one patient received radiotherapy during pregnancy without fetal demise. In 23 patients (41.1%), additional surgery consisting of re-excision and/or lymph node surgery was performed after delivery. In these patients who received surgery during pregnancy, chemotherapy and radiotherapy were administered after delivery in 1 (1.8%) and 9 cases (16.1%), respectively.

Delivery outcome included one stillbirth and 54 live births (missing $n = 1$; Table 2). Median gestational age at delivery was 38 weeks (range 29–42 weeks); 12 (22.2%) were born preterm. In 27 (48.2%) patients, an elective cesarean delivery was planned, while six (10.7%) patients underwent secondary cesarean delivery due to maternal diagnosis ($n = 2$), fetal distress ($n = 2$), antepartum bleeding ($n = 1$) and maternal sepsis ($n = 1$). Twenty patients (35.7%) had a vaginal delivery, of which two were assisted vaginal deliveries (missing $n = 3$).

Maternal follow-up after pregnancy-associated vulvar cancer was reported for 49 patients (87.5%). Two patients were alive and well at the moment of the case report's publication; however, follow-up periods were not available.[21] For the remaining patients ($n = 47$, 83.9%), the median maternal follow-up was 28 months (range 2–204 months). Recurrent disease was observed in 15 cases (31.9%). Recurrences included nine cases with local vulvar recurrence, four with inguinofemoral lymph node recurrence, and two with metastatic recurrence (lung and abdomen). One patient who never received treatment died due to rapid disease progression 2.5 month after diagnosis.[22] While the sample size is very small, the route of delivery did not seem to alter the risk of recurrence: 15% (3/20) after vaginal delivery and 30.3% (10/33) after cesarean section ($p = 0.209$). The 2-year and 5-year overall survival (OS) for vaginal squamous cell carcinoma during pregnancy was 86.0% (95% confidence interval [CI]: 76.2–97.1%) and 81.3% (95% CI: 68.9–95.8%; See Kaplan–Meier survival curve in Figure S1; INCIP case 10, where definitive pathology indicated an epithelioid sarcoma, was excluded

TABLE 1 Management and outcome of the 10 women with primary vulvar cancer and 5 women with primary vaginal cancer from the registry of the International Network on Cancer, Infertility and Pregnancy.

	Maternal age at diagnosis (years)	Gravidity - Parity	Symptoms	Tumor	FIGO stage	GA at diagnosis (weeks)	Treatment during pregnancy	Obstetrical outcome	Treatment postdelivery	Maternal outcome
Vulvar Cancer										
Case 1	40	G1P0	Vulvar mass	Squamous cell carcinoma	IB	17+4	V-shaped excision (20+1 weeks)	Live birth; Elective C-section (37+3 weeks)	NA	Local recurrence with re-excision (PFS: 6 months); CR (FU: 115 months)
Case 2	34	G2P1	Vaginal bleeding	Squamous cell carcinoma	IIIA	35+3	Radical vulvectomy (37+0 weeks)	Live birth; Elective C-section (38+6 weeks)	Re-excision with bilateral SLN procedure. Additional bilateral inguinofemoral lymphadenectomy	CR (FU: 63 months)
Case 3	32	G1P0	Vulvar mass	Squamous cell carcinoma	IA	18+6	Wide excision (25+3 weeks)	Live birth; Vaginal delivery (41+1 weeks)	NA	Lost for follow-up
Case 4	24	G2P1	Vulvar mass	Squamous cell carcinoma	Unknown	3+2	Wide excision (3+3 weeks), re-excision at 12+6 weeks)	Live birth; Vaginal delivery (40+0 weeks)	NA	CR (FU: 56 months)
Case 5	43	Unknown	Incidental finding at clinical examination	Squamous cell carcinoma	IA	14+6	Wide excision (15+0 weeks)	Live birth; Vaginal delivery (40+0 weeks)	NA	Lost for follow-up
Case 6	37	G2P1	Vulvar mass	Squamous cell carcinoma	IA	18+3	Wide excision (21+6 weeks)	Live birth; Vaginal delivery (38+0 weeks)	NA	CR (FU: 46 months)
Case 7	25	G2P1	Vulvar mass	Squamous cell carcinoma	II	6+0	Wide excision (31+2 weeks)	Live birth; Elective C-section (38+4 weeks)	NA	Lost for follow-up
Case 8	29	G3P2	NA	Squamous cell carcinoma	III	21+0	Wide excision (21+0 weeks), re-excision (22+2 weeks)	Live birth; Vaginal delivery (38+6 weeks)	NA	Lost for follow-up
Case 9	32	G1P0	Vulvar itching	Squamous cell carcinoma	II	12+4	Radical vulvectomy and inguinofemoral lymph node dissection (15+5 days)	Live birth; Elective C-section (38+6 weeks)	NA	CR (FU: 84 months)

TABLE 1 (Continued)

	Maternal age at diagnosis (years)	Gravidity - Parity	Symptoms	Tumor	FIGO stage	GA at diagnosis (weeks)	Treatment during pregnancy	Obstetrical outcome	Treatment postdelivery	Maternal outcome
Case 10	31	G2P1	Vulvar mass	Epitheloid sarcoma	IB	33+3	Local excision (30+1 weeks)	Live birth; Elective C-section (37+0 weeks)	Vulvectomy and bilateral SLN procedure.	Lung metastases (PFS: 1,5 months); DOD (OS: 8 months)
Vaginal cancer										
Case 11	31	G4P3	Abnormal discharge	Squamous cell carcinoma	IVA	28+5	No treatment	Live birth; Elective caesarean section (30+2 weeks)	CHT (cisplatin 6 cycles); RT (pelvis + brachytherapy)	CR (FU: 111 months)
Case 12	34	G2P1	Mass left vaginal wall	Mucinous adenocarcinoma	I	25+5	Local tumor excision (25+5 weeks)	Live birth; Elective caesarean section (32+4 weeks)	Pelvic LN dissection; brachytherapy	Locoregional recurrence (PFS 25 months); DOD (FU: 57 months)
Case 13	38	G6P5	NA	Squamous cell carcinoma	IA	20+0	No treatment	Live birth; Elective caesarean section (33+2 weeks)	Abdominal hysterectomy with partial vaginectomy + SLN, treatment delayed due to DVT of patient	CR (FU: 96.7 months)
Case 14	31	G1P0	Asymptomatic	Squamous cell carcinoma	III	39+4	No treatment	Live birth; Vaginal delivery (39+4 weeks)	Posterior pelvic exenteration, CHT (cDDP, 2 cycles); RT (pelvis + brachytherapy)	DOD (FU: 28.9 months)
Case 15	28	G1P0	Asymptomatic	Squamous cell carcinoma	I	25+3	CHT (initiation 26+5 weeks; cisplatin 75 mg/m^2, 3 cycles)	Live birth; Elective cesarean section (36+6 weeks)	Radical hysterectomy with vaginectomy and pelvic lymphadenectomy	CR (FU: 179.6 months)

Abbreviations: CHT, chemotherapy; CR, complete remission; DOD, death of disease; FU, follow-up; LN, lymph node; PFS, progression-free survival; RT, radiotherapy; SLN, sentinel lymph node.

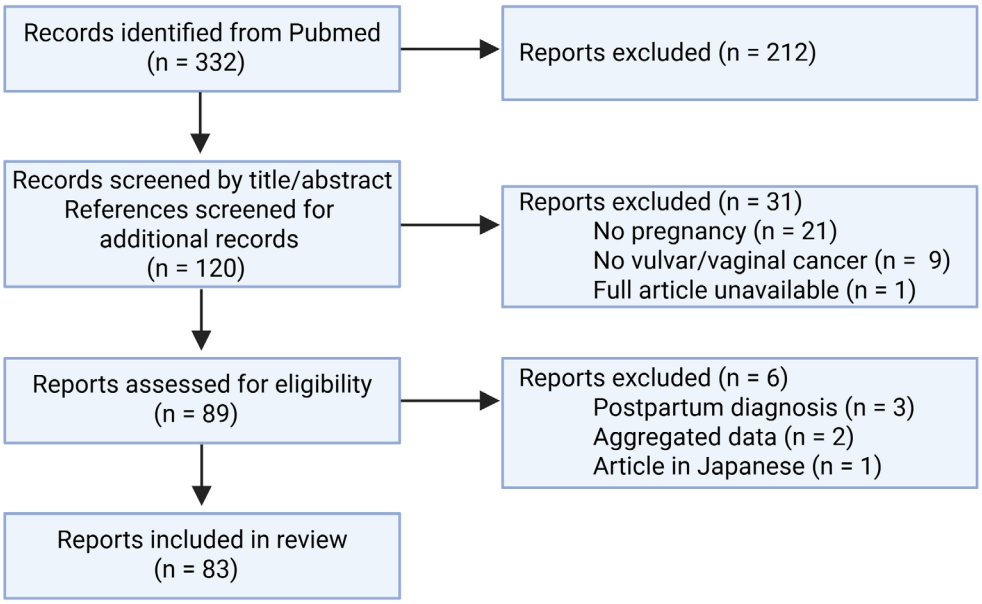

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flowchart for selected case reports. Search performed on January 6, 2025.

for survival analysis). Notably, except for one patient who experienced a lymph node recurrence at 36 months and passed away at 48 months,[23] all reported maternal deaths occurred within the first year after diagnosis.

3.2 | Vaginal cancer

Median maternal age at diagnosis was 22 years (range 14–38, IQR 21–28). Median gestational age at diagnosis was 20 weeks (range 4–41, IQR 12–26). Seventeen patients (40.5%) presented with bleeding or spotting, 16 (38.1%) with abnormal discharge, three (7.1%) with abdominal pain or dyspareunia, one (2.4%) with genital warts, and one (2.4%) with a palpable mass. Fifteen patients (35.7%) were asymptomatic at the time of diagnosis. Clear cell adenocarcinoma was the most frequently diagnosed subtype, with 23 cases (54.8%), while squamous cell carcinoma was diagnosed in 17 patients (40.5%). There was one (2.4%) patient with mucinous adenocarcinoma and one (2.4%) with adenocarcinoma of unspecified subtype. As seen in Table 3, 24 patients (57.1%) were diagnosed with early-stage disease (FIGO I) and 18 patients (42.8%) had locally advanced or metastatic disease (FIGO II-IVB).

Termination of pregnancy was reported in 17 of 42 cases (40.5%) in the first trimester ($n=12$, 28.6%) or second trimester ($n=5$, 11.9%). Of these, seven underwent termination to allow radiotherapy, five following fetal evacuation, and two with fetus in situ. In 10 patients, termination was followed by surgical intervention: eight patients underwent hysterectomy with partial or total vaginectomy, one underwent pelvic exenteration, and one underwent partial vaginectomy. Thirteen patients (31.0%) did not receive treatment during pregnancy. Two patients (4.8%) were diagnosed late in the third trimester and treated postpartum, and one (2.4%) was diagnosed at the time of delivery. In four patients (9.5%), preterm delivery between 27 and 34 weeks of gestation was planned to allow treatment in the postpartum period. In seven patients (16.7%), treatment was intentionally delayed following diagnosis between 16 and 30 weeks of gestation, resulting in a deferral of 6–21 weeks. In two additional cases (4.8%), treatment timing was not clearly documented, although both were diagnosed in the third trimester.

During pregnancy, seven patients (16.7%) underwent local tumor excision between 13 and 26 weeks of gestation. Of these, two patients, both diagnosed with adenocarcinoma, received additional brachytherapy without fetal demise at 20 weeks of gestation. An additional two patients (4.76%) received radiotherapy during pregnancy: one received radium seed implantation, and in one patient, the type of radiotherapy administered was not specified. Only one patient (INCIP case nr. 15) received chemotherapy during pregnancy, consisting of three cycles of three-weekly cisplatin (75 mg/m^2) starting at 26 weeks and 5 days of gestation for Stage I vaginal squamous cell carcinoma.

Radical hysterectomy with partial or total vaginectomy was performed in 12 patients (28.6%), either resulting in termination of pregnancy ($n=8$, 19.0%) or conducted at delivery or postpartum ($n=4$, 9.5%). After delivery, three patients (7.1%) had a local tumoral excision, one patient (2.4%) underwent a partial vaginectomy, and one patient (2.4%) underwent a posterior pelvic exenteration postpartum. Four patients (9.5%) received postnatal chemotherapy: two (4.8%) in the adjuvant setting following surgery and two (4.8%) for metastatic disease. Radiotherapy, including pelvic radiation or brachytherapy, was administered to 21 patients (50.0%). One patient (2.4%) remained untreated due to the failure to recognize vaginal cancer at the time of pregnancy.

TABLE 2 Characteristics of patients with primary vulvar cancer during pregnancy.

	INCIP study population ($n=10$)		Case reports ($n=46$)		All ($n=56$)	
	Number	%	Number	%	Number	%
Age at diagnosis (years)						
Median (range)	32 (24–43)		30 (17–42)		30 (17–43)	
Parity						
Nulliparous	3	30.0%	14	30.4%	17	30.4%
Multiparous	6	60.0%	30	65.2%	36	64.3%
Not reported	1	10.0%	1	2.2%	2	3.6%
Clinical presentation						
Vulvar mass	6	60.0%	28	60.9%	34	60.7%
Vulvar itching	1	10.0%	7	15.2%	8	14.3%
Vaginal bleeding	1	10.0%	0	0.0%	1	1.8%
Vulvar pain	0	0.0%	3	6.5%	3	5.4%
Asymptomatic	1	10.0%	4	8.7%	5	8.9%
Not reported	1	10.0%	4	8.7%	5	8.9%
Gestational age at diagnosis, weeks						
Median (range)	18 (3.3–35.4)		21 (7–40)		21 (3.3–40)	
Stage at diagnosis (FIGO 2021)						
Stage I	0	10.0%	2	4.3%	2	3.6%
Stage IA	3	30.0%	4	8.7%	7	12.5%
Stage IB	3	30.0%	23	50.0%	26	46.4%
Stage II	2	20.0%	3	6.5%	5	8.9%
Stage III	1	10.0%	2	4.3%	3	5.4%
Stage IIIA	1	10.0%	7	15.2%	8	14.3%
Stage IIIB	0	0.0%	1	2.2%	1	1.8%
Stage IVA	0	0.0%	1	2.2%	1	1.8%
Stage IVB	0	0.0%	3	6.5%	3	5.4%
Treatment						
Antenatal treatment						
Local wide excision	10	100.0%	26	56.5%	36	65.5%
Inguinofemoral surgery	1	10.0%	16	34.8%	17	30.9%
Pelvic radiotherapy	0	0.0%	1	2.2%	1	1.8%
Chemotherapy	0	0.0%	1	2.2%	1	1.8%
Postnatal treatment						
Local wide excision/ re-excision	2	0.0%	16	34.8%	18	32.1%
Inguinofemoral surgery	2	20.0%	21	45.7%	23	41.1%
Pelvic radiotherapy	0	0.0%	9	19.6%	9	16.1%
Chemotherapy	0	0.0%	1	2.2%	1	1.8%
No treatment	0	0.0%	1	2.2%	1	1.8%
Obstetric outcome						
Live birth	10	100.0%	44	95.7%	54	96.4%
Stil birth	0	0.0%	1	2.2%	1	1.8%
Not reported	0	0.0%	1	2.2%	1	1.8%
Gestational age at delivery, weeks						
Median (range)	38.8 (37–41.1)		38 (29–42)		38 (29–42)	

(Continues)

TABLE 2 (Continued)

	INCIP study population ($n=10$)		Case reports ($n=46$)		All ($n=56$)	
	Number	%	Number	%	Number	%
Mode of delivery						
Elective caesarean delivery	5	50.0%	23	50.0%	27	48.2%
Secondary caesarean delivery	0	0.0%	7	15.2%	6	10.7%
Spontaneous vaginal delivery	5	50.0%	13	28.3%	18	32.1%
Assisted vaginal delivery	0	0.0%	2	4.3%	2	3.6%
Not reported	0	0.0%	3	6.5%	3	5.4%
Oncological outcome						
Complete remission	5	50.0%	35	76.1%	40	71.4%
Recurrent disease	0	0.0%	2	4.3%	2	3.6%
Died due to disease	1	10.0%	6	13.0%	7	12.5%
Lost in follow-up	4	40.0%	3	6.5%	7	12.5%
Maternal follow-up, months						
Median (range)	59.5 (8–115)		22 (2–204)		28 (2–204)	

In 17 cases (40.5%), patients opted for termination of the pregnancy. Of the remaining patients, 20 patients (47.6%) underwent cesarean delivery (median GA = 33 weeks, range 26–40 weeks), while five patients (11.9%) had a vaginal delivery (median GA = 40 weeks, range 27–41 weeks), with tumor in situ, resulting in 21 live births (50.0%) and four neonatal deaths (9.5%): two (4.8%) due to prematurity and one (2.4%) due to an unsuccessful forceps delivery. In one (2.4%) case, the cause of neonatal death was not reported, but the patient did receive radiotherapy at 12 weeks of gestation. Of the 25 births, 14 (56.0%) were preterm.

Median time of maternal follow-up was 48 months (range 1–240 months); however, maternal follow-up was not reported in three cases (7.1%). Twenty-four patients (57.1%) achieved complete remission following treatment, with a median maternal follow-up of 84 months (range 12–240 months). Fifteen patients (35.7%) died due to their disease. The 2-year and 5-year OS for vaginal cancer during pregnancy was 78.8% (95% confidence interval [CI]: 66.8–93.0%) and 66.4% (95% CI: 52.3–84.2%; See Figure S1 for Kaplan–Meier survival curve).

4 | DISCUSSION

This study represents the largest collection of patients with vulvar and vaginal cancer during pregnancy, combining a previously unpublished collection of ten patients with vulvar cancer and five patients with vaginal cancer during pregnancy registered in the INCIP database and 83 cases identified in a comprehensive literature review; highlighting the rarity of this clinical entity.

Most reported cases of vaginal cancer during pregnancy in the literature were clear cell adenocarcinoma, while 80% in the INCIP cohort had HPV-related squamous cell carcinoma (Table 3). This difference likely reflects the time periods studied: the literature spans 1930–2020, while INCIP covers 2008–2015. As DES was banned in 1971, clear cell adenocarcinoma is expected to decline further.[17]

Due to the rarity of vulvar and vaginal cancer during pregnancy and the small number of case reports published, there are limited consensus-based guidelines available. Patients are managed on an individual basis, considering gestational age at diagnosis, disease stage, physician experience, and patient preference. In general, treatment during pregnancy should closely follow the guidelines established for nonpregnant patients to preserve maternal prognosis. Specialized multidisciplinary teams are essential and should consist of a gynecological oncologist, anesthesiologist, medical and radiation oncologist, histopathologist, neonatologist, psychologist, and an obstetrician, focusing on fetal health, obstetric monitoring, and planning and timing of the delivery.[24,25]

Vaginal and vulvar cancers are often overlooked in younger individuals, as they are traditionally regarded as diseases of the elderly. However, during pregnancy, symptoms, such as vulvar masses, vulvar pruritus, bleeding, or abnormal discharge should always prompt careful evaluation. While such changes are common in pregnancy, they may also signal malignancy and warrant attention. Among the analyzed cases of vaginal cancer, 40.5% of patients presented with bleeding or spotting as their primary symptom, while 35.7% were asymptomatic at the time of diagnosis. In the case of suspicion of vulvar or vaginal cancer during pregnancy, biopsy for histological diagnosis should always be performed.[26]

For vulvar cancer, metastatic involvement of the inguinofemoral lymph nodes is the most important prognostic factor and influences the surgical approach.[27–29] Accurate preoperative evaluation

TABLE 3 Characteristics of patients with primary vaginal carcinoma during pregnancy.

	INCIP study population ($n=5$)		Case reports ($n=37$)		All ($n=42$)	
	Number	%	Number	%	Number	%
Age at diagnosis (years)						
Median (range)	31 (28–38)		21 (14–38)		22 (14–38)	
Parity						
Nulliparous	2	40.0%	10	27.0%	12	28.6%
Multiparous	3	60.0%	7	18.9%	10	23.8%
Not reported	0	0.0%	22	59.5%	22	52.4%
Clinical presentation						
Vaginal discharge	1	20.0%	15	40.5%	16	38.1%
Vaginal mass	1	20.0%	0	0.0%	1	2.4%
Bleeding/spotting	0	0.0%	17	45.9%	17	40.5%
Vaginal warts	0	0.0%	1	2.7%	1	2.4%
Pain	0	0.0%	3	8.1%	3	7.1%
Asymptomatic	2	40.0%	13	35.1%	15	35.7%
Not reported	1	20.0%	2	5.4%	3	7.1%
Gestational age at diagnosis. weeks						
Median (range)	26 (20–40)		17.5 (4–41)		20 (4–41)	
Stage at diagnosis (FIGO 2021)						
Stage I	2	40.0%	21	56.8%	23	54.8%
Stage IA	1	20.0%	0	0.0%	1	2.4%
Stage II	0	0.0%	8	21.6%	8	19.0%
Stage III	1	20.0%	8	21.6%	9	21.4%
Stage IVA	1	20.0%	0	0.0%	1	2.4%
Pathology						
Squamous cell carcinoma	4	80.0%	13	35.1%	17	40.5%
Adenocarcinoma	1	20.0%	24	64.9%	25	59.5%
Treatment						
Antenatal treatment						
Local excision	1	20.0%	6	16.2%	7	16.7%
Chemotherapy	1	20.0%	0	0.0%	1	2.4%
Radiotherapy	0	0.0%	6[a]	16.2%	6	14.3%
Postnatal treatment						
Pelvic exenteration	1	20.00%	1	2.7%	2	4.8%
Radical hysterectomy and vaginectomy	2	40.0%	10	27.0%	12	28.6%
Local excision/re-excision	0	0.0%	3	8.1%	3	7.1%
Vaginectomy	0	0.0%	2	5.4%	2	4.8%
Pelvic lymphadenectomy	3	60.0%	16	43.2%	19	45.2%
Chemotherapy	2	40.0%	2	5.4%	4	9.5%
Pelvic radiotherapy	2	40.0%	9	24.3%	12	28.6%
Brachytherapy	3	60.0%	6	16.2%	9	21.4%
No treatment	0	0.0%	1	2.7%	1	2,4%
Obstetric outcome						
Live birth	5	100%	16	43.2%	21	50.0%
Neonatal death	0	0.0%	4	10.8%	4	9.5%
Termination of pregnancy	0	0,0%	17	45.9%	17	40.5%

(Continues)

TABLE 3 (Continued)

	INCIP study population ($n=5$)		Case reports ($n=37$)		All ($n=42$)	
	Number	%	Number	%	Number	%
Gestational age at delivery. weeks						
Median (range)	37 (34–40)		29 (4–41)		31.5 (4–41)	
Mode of delivery						
Caesarean delivery	4	80.0%	16	43.2%	20	47.6%
Spontaneous vaginal delivery	1	20.0%	4	10.8%	5	11.9%
Oncological outcome						
Complete remission	3	60.0%	21	56.8%	24	57.1%
Died due to disease	2	40.0%	13	35.1%	15	35.7%
Lost in follow-up	0	0.0%	3	8.11%	3	7.14%
Maternal follow-up. months						
Median (range)	96.7 (28.9–179.6)		42 (1–240)		48 (1–240)	

[a]Radiotherapy initiated in two patients during early pregnancy and at 23 weeks gestation with fetus in situ with the therapeutic objective of pregnancy termination.

of the regional lymph nodes with ultrasound should be performed in addition to the physical examination, except in T1a tumors.[26,30] For tumors with potential involvement of the urethra, vagina, or rectum or locally advanced tumors, the depth of infiltration into pelvic structures should be evaluated using ultrasound or pelvic MRI. Of the seven INCIP patients with disease stage larger than 2021 FIGO IA, four patients underwent pre-operative locoregional imaging, whereas literature only reports preoperative imaging during pregnancy in five out of 46 cases. It must be stressed that accurate staging should not be overlooked in pregnant patients, especially since it relies on nonionizing imaging modalities that can be safely used during pregnancy.

The primary local treatment of early-stage vulvar cancer consists of a radical local excision and can be carried out safely in all trimesters.[8,26,27] All INCIP cases and 26 cases from literature (56.6%) underwent local excision of the tumor during pregnancy. Increased gestational vulvar blood flow can lead to more perioperative blood loss; though no perioperative complications were reported.

Patients diagnosed with a 2021 FIGO Stage IA do not need inguinofemoral lymph node treatment. In all other patients with early-stage disease, unilateral (for lateralized tumors) or bilateral (for nonlateralized tumors <1 cm or <2 cm from the midline according ESGO and the National Comprehensive Cancer Network, respectively) surgical lymph node staging is advised.[26,27]

Surgical lymph node staging during pregnancy remains a topic of controversy. In nonpregnant patients with clinically negative lymph nodes, SLN mapping is a safe, accurate, and cost-effective approach, with comparable accuracy to total inguinal lymphadenectomy but significantly fewer complications.[31,32] The gold standard for SLN mapping is the radioactive tracer Tc-99^{m}, alone or in combination with blue dye.[26,33,34] During pregnancy, blue dye should be omitted due to the risk of anaphylaxis.[8] Indocyanine green (ICG) has proved to be a promising nonionizing alternative in gynecologic malignancies, but ICG-SLN mapping protocols in vulvar cancer are heterogeneous.[35,36] Five cases of SLN mapping using Tc-99^{m}during pregnancy (19–34 weeks of gestation) have been reported.[37–39] Inguinofemoral SLN mapping with the use of Tc-99^{m} seems feasible during pregnancy: fetal exposure to Tc-99^{m} is low, especially with a short treatment protocol where the procedure is performed 2 hours after injection.[8]

Due to uncertainty regarding the safety of lymph node staging during pregnancy, it was postponed until after delivery in 10 patients, despite radical local excision being performed during pregnancy. Concerns have been raised that inguinofemoral lymphadenectomy during pregnancy may increase the risk of leg lymphedema and inguinal seroma due to impaired venous return, leading to the recommendation that the procedure should be delayed until at least 6 weeks postpartum.[21] Review of the evidence contradicts this notion, as 13 patients underwent uni- or bilateral lymphadenectomy between 15 and 31 weeks of pregnancy, with mild vulvar edema occurring in only one case; whereas the others did not report any postoperative complications.[40] Performing lymph node surgery during pregnancy does not result in a higher occurrence of lymphedema. Moreover, delaying lymph node surgery until after delivery may lead to rapid progression of undiagnosed inguinal lymph node metastases and a delay in necessary adjuvant radiotherapy.[8,26] Lastly, dividing surgical treatment into two stages, with local excision performed prior to delivery and lymph node surgery after, could compromise the accuracy of SLN mapping. Consequently, many pregnant patients would require complete lymphadenectomy, in contrast to their nonpregnant counterparts.

The standard treatment for vaginal cancer in nonpregnant patients generally involves surgical excision, including vaginectomy, with hysterectomy recommended for tumors located in the upper vagina.[41] Although in the past, radical hysterectomy with partial or total vaginectomy was considered an effective therapeutic option for Stages I and II vaginal cancer.[42] For larger tumors (>2 cm), or tumors with deeper invasion, cases with lymph node involvement, or

situations where clear margins cannot be achieved, (chemo)radiation is recommended.[41] Pelvic irradiation should never be performed during pregnancy as the high fetal radiation exposure could result in severe or fatal consequences for the fetus, although live births after irradiation for vaginal cancer have been reported.[42–44] Some patients may opt to terminate the pregnancy following a vaginal cancer diagnosis, dependent on local regulations. In our study, 17 patients (40.5%) opted for termination of the pregnancy to receive radical surgery and/or radiotherapy. Due to the rarity of vaginal cancer, evidence concerning the use of neoadjuvant chemotherapy followed by radical surgery is scarce, mostly based on case reports or small case series, but has been demonstrated to be an effective treatment strategy in locally advanced cervical tumors.[41,45] Clinical response to neoadjuvant chemotherapy for vaginal cancer has been observed in 91–100% of patients, based on small sample sizes of 10 and three patients, respectively.[46,47] In the INCIP cohort, one patient with FIGO Stage I vaginal squamous cell carcinoma was treated with chemotherapy during pregnancy, before radical surgery postpartum, with a reassuring neonatal and oncological outcome. If patients wish for pregnancy-preservation after diagnosis of vaginal cancer before 24 weeks of gestation, antenatal chemotherapy could be considered as an experimental option in the second trimester, after extensive counseling.

Although the majority of patients had an elective cesarean section due to the maternal disease, vaginal delivery was reported in 37.7% of patients with vulvar cancer. In theory, tumor dissemination is possible by mechanical dilatation of the vulva during labor and delivery, but our study demonstrates that in selected cases, vaginal delivery does not seem to be associated with a higher risk of recurrence. Indications for an elective cesarean delivery are major vulvar or vaginal surgery with or without reconstruction during pregnancy or the presence of a tumor at the moment of delivery. In case of complete resection of a small vulvar tumor, vaginal delivery can be considered.[8] Among patients with vaginal cancer, only five (11.9%) patients underwent vaginal delivery. Concerns associated with vaginal delivery in the presence of a tumor include the risk of infection, hemorrhage, obstructed labor, and potential tumor cell dissemination. Additionally, the possibility of recurrence at the episiotomy site should be considered. Given these risks, cesarean delivery is recommended as the preferred mode of delivery for pregnant patients with vaginal cancer.

The overall 5-year survival rate for vulvar cancer during pregnancy in our study was 81.3%. In the nonpregnant population, reported 5-year OS ranges between 65% and 69.5%,[48–50] with significant variation based on FIGO stage: 86.3% for Stage IA and 18.3% for Stage IVB.[51] The prognosis for vaginal cancer is less favorable, with a 5-year OS rate of 69–85% for localized disease and 57–58% for regional disease. According to our study, in the pregnant population, survival rates are comparable, with a 5-year OS of 66.4%.[17,52] While our study is limited in sample size, it suggests that the survival of patients diagnosed with vulvar or vaginal cancer during pregnancy is comparable to nonpregnant patients and the pregnancy itself does not alter the maternal prognosis.

This review is the largest study concerning feto-maternal outcomes of pregnancy complicated by vulvar and vaginal cancer, combining all available evidence in literature with 15 previously unpublished cases. Nevertheless, this study has several limitations. Its retrospective design resulted in missing data, and despite the extended study period (1941–2024), the sample size remains limited. Additionally, a potential publication bias may exist, as cases of vulvar or vaginal cancer during pregnancy with uncomplicated courses and favorable outcomes may have been underreported. Finally, in most cases, follow-up data were available only for the first 2 years following diagnosis, with no information on long-term disease recurrence or OS. While the majority of vulvar cancer recurrences occur within the first 2 years after initial surgery, ~35% of patients experience relapse five or more years postdiagnosis.[53]

5 | CONCLUSION

In conclusion, while rare, vaginal and vulvar cancer can occur during pregnancy, as evidenced by this largest case collection to date. These cancers should be considered in the differential diagnosis when a pregnant patient presents with vulvar pruritus, vaginal bleeding, or abnormal discharge, and biopsies should not be omitted because of the pregnancy. Lymph node staging for vulvar cancer, including preoperative ultrasound and/or pelvic MRI and surgical staging, can be safely performed during pregnancy. In cases of vulvar or vaginal cancer diagnosed during pregnancy, surgery should not be electively delayed until the postpartum period when indicated. Timely surgical intervention, when feasible, can be safely performed during pregnancy. For unresectable or advanced vulvar tumors and vaginal cancer, maternal health should take priority, and pregnancy termination may be considered. Given the rarity of these cancers in pregnancy, each case should be managed by a multidisciplinary, specialized team to optimize maternal and neonatal outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization: FA, MH. Methodology: CLL. Investigation: CLL, GS. Writing – original draft: CLL, GS. Writing – review and editing: ASK, MAdB, CARL, NO, EC, RF, RGS, LS, KVC, MH, and FA.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The international 'Cancer in Pregnancy' study was approved by the Ethics committee of the University Hospitals Leuven (Ethics committee research KU/UZ Leuven, initial approval on 26 January 2004, protocol version 4.4 approved on 20 January 2022) and participating centers according to local policies (Clinicaltrials.gov, numberNTC00330447). Written informed consent was acquired from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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