ANTICANCER RESEARCH *45*: 843-853 (2025)
doi: 10.21873/anticanres.17473

Review

Diagnosis and Treatment of Gestational Non-Epithelial Ovarian Cancer: A Systematic Review

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Abstract

Background/Aim: Ovarian cancer is categorized into epithelial ovarian cancer and non-epithelial ovarian cancer (NEOC), with NEOC accounting for approximately 10% of cases, predominantly affecting young women and adolescents. The incidence of gestational ovarian cancer is expected to rise in developed nations due to delayed childbearing. NEOC in pregnancy presents various risks, including spontaneous abortion, ventriculomegaly, respiratory distress, and maternal-fetal mortality. This review aims to evaluate the diagnostic tools and management strategies for early NEOC detection during pregnancy to improve maternal and fetal outcomes.

Materials and Methods: A systematic literature search was conducted in PubMed and Embase, covering studies from January 2019 to January 2024. The search terms included "pregnan*" AND "non-epithelial ovarian cancer" AND "diagnos*" AND "manage*" to identify relevant studies. Only articles addressing the diagnosis and management of NEOC during pregnancy were included.

Results: Four relevant articles published between 2019 and 2021 were identified, reporting a total of 44 NEOC cases during pregnancy. In 34 of these cases, NEOC was diagnosed at International Federation of Gynecology and Obstetrics

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Received November 20, 2024 | Revised January 13, 2025 | Accepted February 4, 2025

(FIGO) stage I, primarily through routine ultrasonography. Fertility-sparing unilateral salpingo-oophorectomy (USO), often combined with adjuvant platinum-based chemotherapy, was the standard treatment for stage I cases.
Conclusion: Currently, no standardized management guidelines exist for NEOC during pregnancy, due to factors such as FIGO staging, gestational age, and maternal preferences. Routine ultrasonography is effective for the early identification of NEOC, particularly in asymptomatic patients. For pregnant women with stage I NEOC who wish to continue their pregnancy and preserve fertility, fertility-sparing surgery with chemotherapy represents a promising treatment approach.

Keywords: Non-epithelial ovarian cancer, pregnancy, gestational, ultrasonography, fertility-sparing treatment, review.

Introduction

Ovarian cancer is the most lethal gynecological cancer worldwide, and effective tools for general population screening are still lacking. Cost-effective strategies for early detection and prevention of ovarian cancer have been investigated over the last decade (1). Currently, CA125 and HE4 are the only approved biomarkers for use in epithelial ovarian cancer; however, they are insufficient for early detection. To address the limitations of single serum biomarkers, multivariate index (MVI) assays have been developed, particularly for pre-surgical evaluation of adnexal masses. The Risk of Malignancy Algorithm (ROMA) incorporates menopausal status along with CA125 and HE4 levels to aid in diagnosing women with a pelvic mass (2). Epithelial ovarian cancers are the most common pathological type, accounting for 90% of cases. Type I epithelial ovarian cancers are considered relatively indolent and genetically stable tumors, often arising from identifiable precursor lesions such as endometriosis or borderline tumors with low malignant potential. In contrast, type II epithelial ovarian cancers are believed to be biologically aggressive from the start, with a tendency to metastasize even from small primary lesions (3). High-grade serous carcinoma, the most common type of epithelial ovarian cancer, accounts for approximately 75% of cases and follows the type II pathway, frequently presenting with p53 and BRCA mutations (4). The remaining 10% consist of non-epithelial ovarian cancers (NEOC), which primarily include germ cell tumors (GCT), sex cord-stromal tumors, and rare types such as small-cell carcinomas (5-7). GCT differ from epithelial ovarian cancers in their earlier age of onset, faster growth rate, unilateral localization, and generally favorable prognosis (8). Currently, knowledge about ovarian GCT in postmenopausal patients is limited. However, although rare, ovarian GCT should be considered in postmenopausal women presenting with an ovarian mass and elevated serum alpha-fetoprotein (AFP) levels (9). Ovarian carcinosarcomas, also known as mixed malignant Müllerian tumors, are rare, biphasic neoplasms composed of both epithelial and sarcomatous components, accounting for only 1-4% of all ovarian cancers. The prognosis for these tumors is poor, with most patients experiencing relapse within one year of completing initial treatment (10, 11).

Gestational cancer remains rare, with a global occurrence rate between 0.05% and 1% (12). However, this incidence is expected to rise, as childbearing nowadays is often delayed to later reproductive ages (13). Early diagnosis of gestational cancer is challenging due to overlapping symptoms. Common symptoms such as fatigue, abdominal pain, and breast changes can be attributed to both pregnancy and cancer, making early-stage cancer diagnosis more difficult (14-16). The most common maternal malignancies include breast cancer, cervical cancer, lymphomas, and melanoma (17). Although liver cancer is relatively common in the general adult population, it appears to be extremely rare among pregnant women. A possible explanation for this rarity is the strong association between cirrhosis and infertility (18). Gestational urinary tract cancers are extremely rare, with renal cell carcinoma being the most commonly diagnosed gestational urological cancer (19, 20). Fetal metastases most commonly occur in patients with placental metastases from melanoma and lung cancer and

are associated with a poor prognosis (21). Ovarian tumors are estimated to complicate approximately 2.8-11 per 100,000 pregnancies (22), with about 5% of these tumors being malignant (23). A significant portion of gestational ovarian malignancies are Krukenberg tumors. In this context, any new ovarian growth should be actively managed in women with a history of gastrointestinal tract cancers (24). The prevalence of gestational NEOC has gradually increased in recent years, partly due to advancements in prenatal imaging technologies, particularly ultrasonography. NEOC presents a unique challenge, as treatment strategies must consider gestational age, tumor staging, and maternal decisions regarding pregnancy continuation. Surgery, particularly unilateral salpingo-oophorectomy (USO), has been recognized as a fertility-sparing option for early-stage NEOC and is typically performed in the second trimester to minimize pregnancy risks (12). This approach allows for tumor removal while preserving ovarian function and potential future fertility. For advanced cases, chemotherapy – particularly platinum-based regimens – may be used alongside surgery, though careful consideration of the potential fetal impact is essential (25). Current guidelines lack evidence-based support, and certain aspects of management remain without consensus. This systematic review aims to provide insights that could enhance clinical decision-making, improve maternal-fetal outcomes, and guide future research toward developing evidence-based guidelines for managing NEOC during pregnancy.

Materials and Methods

Literature search strategy. Two primary medical databases, PubMed and Embase (Ovid), were searched for biomedical literature on NEOC diagnosed during pregnancy. Additionally, grey literature was reviewed, and reference lists of relevant studies were hand-searched to ensure comprehensive coverage. Articles were limited to those published in English between January 2019 and January 2024 to maintain methodological relevance and account for language limitations.

Table I. *Search terms using Boolean Operators and number of hits for each search.*

Database	Search term	Number of hits
PubMed	#1 pregnan*	1,160,141
	#2 non-epithelial ovarian cancer	186
	#3 diagnos*	6,270,953
	#4 manage*	2,231,841
	#5 #1 AND #2 AND #3 AND #4	2
Embase (Ovid)	#1 pregnan*	747,045
	#2 non-epithelial ovarian cancer	64
	#3 diagnos*	3,795,781
	#4 manage*	2,796,510
	#5 #1 AND #2 AND #3 AND #4	9

The search terms used in PubMed and Embase were designed to capture various aspects of the research question, utilizing Boolean operators to combine terms. Terms such as 'pregnan*', 'non-epithelial ovarian cancer', 'diagnos*', and 'manage*' were used, with truncation symbols to retrieve variations like 'pregnant', 'diagnostic', and 'management'. These terms were derived from relevant prior work, particularly the systematic review by Boussios *et al.* on ovarian cancers in pregnancy, published in 2018 (26). However, this systematic review focused specifically on NEOC and used a more restricted set of terms to maintain a targeted scope, excluding broader terms that might generate an unmanageable number of irrelevant hits. The breakdown of search terms and their respective hits is shown in Table I.

Inclusion and exclusion criteria. To refine the search results and ensure reliability, included studies had to focus on NEOC diagnosed during pregnancy, be published within the last five years, and provide detailed case descriptions covering tumor, maternal, and fetal characteristics. Exclusion criteria included articles on NEOC diagnosed outside of pregnancy, studies published more than five years ago, and non-English publications. Peer-reviewed articles considering all lifestyle factors and ethnicities were included to ensure a diverse dataset.

Study design. Given the rare nature of gestational NEOC, this project adopted a non-experimental approach, as

experimental designs would be neither practical nor ethical. The study focused on naturally occurring cases to examine management strategies relevant to maternal and fetal health. A qualitative descriptive analysis was employed to capture diverse management practices, recognizing that a meta-analysis was unsuitable due to heterogeneous methodologies and the qualitative nature of the data. This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (27). The PRISMA guidelines ensured a structured and transparent approach to data collection and reporting.

Screening and selection process. The initial search was conducted on November 20, 2023, with an update on January 22, 2024, to include the most recent literature. All search results were imported into Mendeley reference management software, where duplicates were removed. Titles and abstracts were screened by one reviewer, followed by a full-text evaluation based on the inclusion and exclusion criteria. Eligible articles were further assessed through hand-searching reference lists using the snowballing method to identify additional relevant studies.

Results

Literature search, study design, and description of included studies. A comprehensive search across PubMed and Embase databases identified 11 records (2 from PubMed and 9 from Embase). After applying a 5-year publication limit, seven records remained for screening. Title and abstract screening led to the exclusion of three articles due to irrelevance. Four articles were then assessed for eligibility, with three excluded for not aligning with the study's focus on gestational NEOC or for including outdated data. Additional snowballing techniques identified four more studies, one of which was excluded due to a benign tumor. Ultimately, four studies met the inclusion criteria and passed the Critical Appraisal Skills Programme (CASP) quality assessment (28). The selected studies, published between 2019 and 2021, originated from China, Indonesia, Poland, and Taiwan. They provided diverse perspectives on diagnostic and management approaches for gestational NEOC, offering insights from different geographical and healthcare contexts. A PRISMA flow diagram summarizing the screening process is shown in Figure 1.

Histological subtypes and case distribution and symptoms and diagnostic tools. Among the 44 reported cases of NEOC, the majority were GCT, including subtypes such as immature teratoma (14 cases), yolk sac tumor (12 cases), and dysgerminoma (11 cases). Additionally, there were a few rare cases, including Sertoli-Leydig cell tumors, granulosa cell tumors, and small-cell carcinoma (hypercalcemic type). Symptoms observed in gestational NEOC cases were generally nonspecific, often presenting as abdominal pain, dyspnea, and stress-related psychological symptoms. Notably, a significant number of patients were asymptomatic, with NEOC frequently detected incidentally during routine ultrasonography. Three of the studies used ultrasonography as a diagnostic tool, while magnetic resonance imaging (MRI) and tumor markers such as CA-125 and AFP were also utilized as supportive diagnostic methods, especially when ultrasonography results were inconclusive.

Management of gestational NEOC, mode of delivery, and maternal/fetal outcomes. Management strategies for gestational NEOC included both conservative and fertility-sparing surgical options, depending on the cancer stage and histological subtype. Common conservative approaches included hysterectomy and USO, while more aggressive procedures, such as cytoreductive surgery with hysterectomy, were performed when necessary. For advanced-stage cases, platinum-based chemotherapy, often combined with biological agents, was primarily administered not earlier than the second trimester to minimize fetal risk.

Among the 24 cases with reported delivery outcomes, 20% involved vaginal deliveries, while approximately 34% underwent cesarean sections. The details regarding whether these were planned or emergency procedures

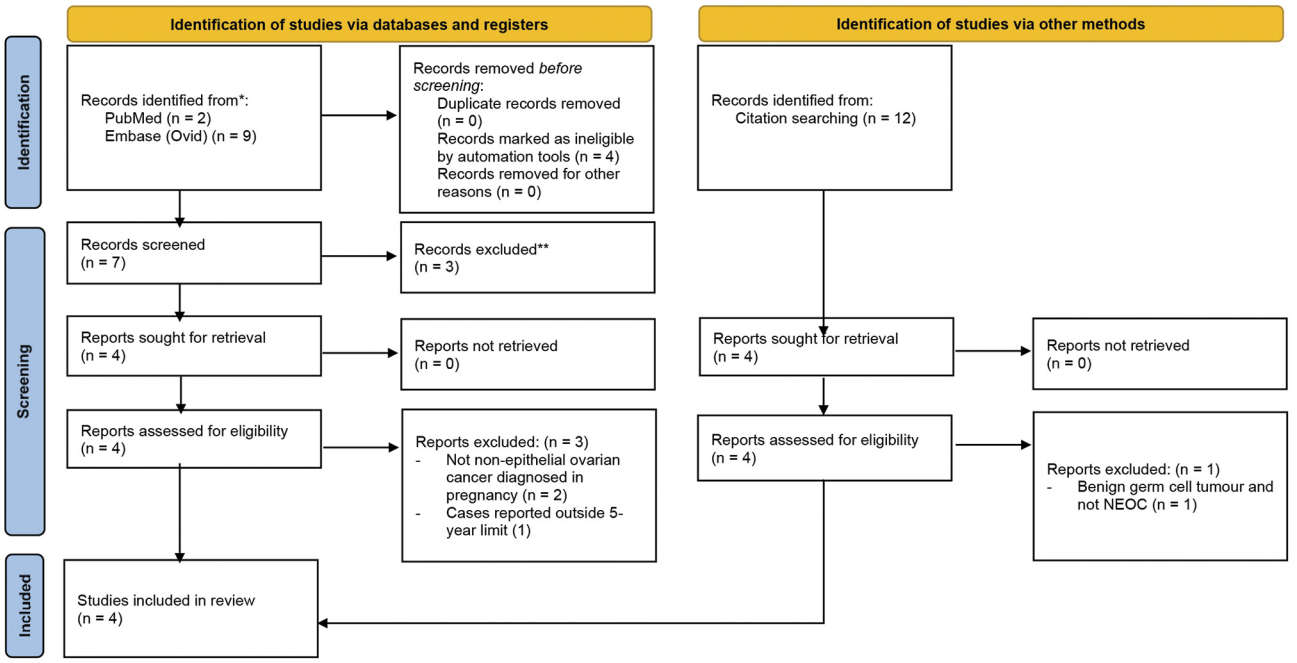

Figure 1. *PRISMA 2020 flow diagram for the identification of articles included in the systematic review.*

were not specified, highlighting a need for further documentation in clinical case reports. Postpartum treatment for NEOC was recorded in 27 cases, with various surgeries performed, including total hysterectomy, bilateral salpingo-oophorectomy (BSO), and lymphadenectomy. Fetal outcomes were generally positive, with 57% resulting in live births. One case involved abortion in a patient with stage IV small-cell ovarian cancer, while another case of stage IC dysgerminoma reported normal child development two years post-treatment.

Identified themes and summary of diagnosis and management from included articles. The analysis revealed three key themes: (a) NEOC were frequently identified through routine ultrasound rather than presenting with symptoms, (b) fertility-sparing surgery was the preferred treatment for stage IA NEOC, and (c) platinum-based chemotherapy was commonly administered for advanced stages, typically during the second trimester to minimize fetal risks. Table II offers a detailed summary of the diagnostic methods, findings, and management strategies for each of the 44 NEOC cases included in the studies. It includes information such as maternal age, gestational age at diagnosis, FIGO stage, type of surgical procedure performed during pregnancy, and the chemotherapy regimen used, specifying the number of cycles and timing relative to gestational age. The table also outlines the mode of delivery and highlights any relevant maternal/fetal outcomes or complications. Among the cases, 35 were diagnosed at FIGO stage I, with sub-classifications of stage IA (3 cases), IC (15 cases), and IC1 (1 case). One case was identified at stage IIC, four at stage IIIC, and two at stage IV (including one case in stage IVB). FIGO stages were not reported for two of the cases.

Discussion

Ultrasonography for diagnosis of gestational NEOC. A key theme emerging from the analyzed studies is the crucial role of routine ultrasonography in the initial detection of

Table II. *Summary of the demographics, diagnostic methods, findings, and management strategies for each of the 44 NEOC cases reviewed in the study.*

#	Author (Ref)/ Year of publication	Maternal age at diagnosis (years)	Gestational age at diagnosis (weeks)	Description of ultrasound findings	Histological subtype	FIGO Stage	Surgical management	Chemotherapy type and timing	Maternal/ Fetal outcome
1	Luh LCPN, *et al.* (29)/ 2019	31	19+5	Hypo-hyperechoic mass, circumscribed, rough surface, papillary, with septa	IT grade II	IC1	Left oophorectomy, OME	4 cycles of BEP at 27+2 weeks GA	VD No congenital abnormalities Secondary surgery (re-laparotomy complete surgical staging) including TAH 58 days postpartum
2		24	30	Hypo-hyperechoic papillary mass	DYS	IC	Left salpingo-oophorectomy	4 cycles of BEP at 33 weeks GA	VD No congenital abnormalities TAH post delivery
3		27	21	Hypo-hyperechoic mass, with septa	YST	IC	Right salpingo-oophorectomy, OME, AE	6 cycles of TC at 21+3 weeks GA	CS at 38 weeks gestation No congenital abnormalities
4	Wang L, *et al.* (32)/ 2020	NA	NA	NA	IT	I	Conservative surgery	NA	NA
5		NA	NA	NA	IT	I	Conservative surgery	NA	NA
6		NA	NA	NA	IT	I	Conservative surgery	NA	NA
7		NA	NA	NA	IT	I	FSS	NA	NA
8		NA	NA	NA	IT	I	FSS	NA	NA
9		NA	NA	NA	IT	I	Radical surgery	NA	NA
10		NA	NA	NA	IT	I	FSS	NA	NA
11		NA	NA	NA	DYS	I	FSS	NA	NA
12		NA	NA	NA	DYS	I	FSS	NA	NA
13		NA	NA	NA	DYS	I	FSS	NA	NA
14		NA	NA	NA	DYS	I	FSS	NA	NA
15		NA	NA	NA	DYS	I	FSS	NA	NA
16		NA	NA	NA	DYS	I	FSS	NA	NA
17		NA	NA	NA	Stromal carcinoid	I	Radical surgery	NA	NA
18		NA	NA	NA	SLCT	I	Conservative surgery	NA	NA
19		NA	NA	NA	GCT	I	FSS	NA	NA
20		NA	NA	NA	SCC	IV	Radical surgery	NA	Abortion
21	Pei Y, *et al.* (33)/ 2021	25	25	NA	YST	IC	USO	2 cycles of PVB at 27 weeks GA	CS
22		29	15	NA	IT	IC	USO	1 cycle of PVB at 19 weeks GA	VD
23		21	26	NA	DYS	IVB	USO, OME	4 cycles of EP at 27 weeks GA	VD
24		18	20	NA	IT and YST	IA	USO	3 cycles of BEP at 21 weeks GA	VD
25		26	23	NA	YST	IIC	USO	1 cycle of BEP at 25 weeks GA	CS
26		19	15	NA	YST	IIIC	None	2 cycles of BEP at 18 weeks GA	CS
27		25	20	NA	YST	IC	USO, OME	5 cycles of BEP at 22 weeks GA	VD

Table II. *Continued*

Table II. *Continued*

#	Author (Ref)/ Year of publication	Maternal age at diagnosis (years)	Gestational age at diagnosis (weeks)	Description of ultrasound findings	Histological subtype	FIGO Stage	Surgical management	Chemotherapy type and timing	Maternal/ Fetal outcome
28		27	26	NA	IT	IA	USO	2 cycles of BEP at 20 weeks GA	VD
29		22	9	NA	DYS and EST	IA	USO	NA	NA
30		33	25	NA	DYS	IC	None	3 cycles of PC at 25 weeks GA	CS
31		22	13	NA	DYS	IC	USO	5 cycles of EP	NA
32		35	18	NA	YST	IC	BSO	5 cycles of EP	NA
33		33	18	NA	YST	IC	USO, OME	3 cycles of PVB at 19 weeks GA	CS
34		34	21	NA	YST	IC	USO, OME	4 cycles of cisplatin at 22 weeks GA	CS
35		26	28	NA	IT	IIIC	USO, OME	2 cycles of BEP at 29 weeks GA	CS
36		36	22	NA	IT	NA	USO	3 cycles of EP at 23 weeks GA	CS
37		25	21	NA	IT	NA	USO	3 cycles of BEP at 21 weeks GA	CS
38		23	13	NA	YST	IC	USO, OME	4 cycles of BEP at 15 weeks GA	CS
39		20	14	NA	YST	IIIC	USO	6 cycles of EP at 15 weeks GA	CS
40		33	17	NA	YST	IC	USO, OME	4 cycles of PVB	CS
41		37	18	NA	SCC	IIIC	BSO, OME, AE	6 cycles of CC at 19 weeks GA	CS
42		31	19	NA	IT	IC	USO, OME	4 cycles of BEP at 28 weeks GA	VD
43		24	29	NA	DYS	IC	USO, OME	4 cycles of BEP at 34 weeks GA	VD
44		27	19	NA	YST	IC	USO, OME	6 cycles of TC at 22 weeks GA	CS

NEOC: Non-epithelial ovarian cancer; Ref: reference; FIGO: International Federation of Gynecology and Obstetrics; IT: immature teratoma; OME: omentectomy; BEP: bleomycin/etoposide/cisplatin; GA: gestational age; VD: vaginal delivery; TAH: total abdominal hysterectomy; DYS: dysgerminoma; YST: yolk sac tumor; OME: omentectomy; AE: appendicectomy; TC: docetaxel/carboplatin; USO: unilateral salpingo-oophorectomy; PVB: cisplatin/vinblastine/bleomycin; CS: caesarean section; EP: etoposide/cisplatin; EST: endodermal sinus tumor; PC: paclitaxel/carboplatin; BSO: bilateral salpingo-oophorectomy; SCC: small-cell carcinoma; CC: cyclophosamide/carboplatin; NA: not available; FSS: fertility-sparing surgery; SLCT: Sertoli-Leydig cell tumor; GCT: granulosa cell tumor.

gestational NEOC. Luh LCPN *et al.* highlighted ultrasonography findings in three cases of GCT diagnosed during pregnancy, each showing a hypo-hyperechoic mass with solid and cystic features characteristic of NEOC (29). These cases, which included an immature teratoma, dysgerminoma, and yolk sac tumor, underscore the value of ultrasonography as a key tool for preliminary identification, aiding clinicians in recognizing abnormal ovarian masses during routine scans. Importantly, most NEOC cases were detected at FIGO stage I, emphasizing ultrasonography's effectiveness in early-stage identification. Early detection is essential for timely intervention, potentially preventing disease progression that could complicate pregnancy and management. In England, standard prenatal care includes at least two ultrasound scans, with the first performed between 11-14 weeks of gestation (30). This routine scan not only evaluates the fetus and placenta but also allows for the observation of maternal ovaries, facilitating the

incidental detection of ovarian abnormalities in asymptomatic patients. Thus, ultrasonography proves to be an essential tool for routine pregnancy assessments and for the early detection of NEOC.

Tumor markers and MRI. Tumor markers, including CA-125, were not primarily used for diagnosing gestational NEOC but were more effective as indicators for monitoring treatment response, particularly following chemotherapy. This is likely because certain tumor markers can naturally increase during pregnancy, leading to potentially misleading results if relied upon solely for diagnosis. MRI, meanwhile, was not a primary diagnostic tool but played an essential role in staging NEOC. Staging through MRI aids in evaluating the extent of tumor growth, helping clinicians make informed treatment decisions. Therefore, while ultrasonography remains the first-line tool for early detection, MRI provides valuable detailed assessment when abnormalities are detected.

Fertility-sparing surgical management. The management of NEOC during pregnancy varied across cases, underscoring the need for an individualized approach that considers factors such as gestational age, FIGO stage, and patient preferences. Despite these variations, a common practice was the use of fertility-sparing surgery for early-stage NEOC, particularly in FIGO stage I cases. This typically involves USO with subsequent staging when only one ovary is affected, allowing the preservation of fertility for future pregnancies. This method aligns with patients' wishes to maintain fertility while effectively managing the cancer during pregnancy. However, for gestational NEOC at stage IC or higher, fertility-sparing surgery is generally not the recommended first-line option due to the increased risk of recurrence beyond the ovary. Studies indicate that delaying future pregnancies for at least two years post-treatment is advisable, as the risk of recurrence is higher during this period (31). The optimal timing for surgery during pregnancy remains debated, though adjuvant chemotherapy is usually initiated in the second trimester to avoid disruption of fetal organogenesis. This strategy seeks to balance effective cancer treatment with minimizing risks to fetal development.

Platinum-based chemotherapy. Platinum-based chemotherapy, particularly the BEP regimen (bleomycin, etoposide, and cisplatin), emerged as an essential adjunctive therapy for managing advanced NEOC during pregnancy. While BEP therapy has demonstrated therapeutic efficacy in treating NEOC, cisplatin, a core component, is associated with systemic side effects, including nephrotoxicity and myelosuppression. Luh LCPN *et al.* reported using a docetaxel-carboplatin regimen as an alternative, which resulted in no complications for either the mother or fetus (29). Carboplatin is considered safer than cisplatin, with a reduced profile of toxic effects on both the mother and fetus, making it a viable option when cisplatin's side effects present significant concerns. Chemotherapy administration during pregnancy is generally limited to the second trimester and beyond, as fetal risks – such as congenital malformations, preterm labor, and the need for neonatal intensive care – are significantly higher if given during the first trimester. This timing ensures safer fetal development while facilitating necessary maternal cancer treatment.

Maternal/fetal outcomes. The impact of NEOC on pregnancy outcomes is multifactorial, influenced by factors such as tumor stage, histological subtype, and gestational age at diagnosis. Wang L, *et al.* reported six cases where pregnancy was terminated, including five involving GCT and one case of small-cell ovarian cancer (32). Although the specific GCT subtypes were not detailed, these cases illustrate the complex decision-making required when balancing cancer treatment with pregnancy continuation. In contrast, successful treatment in most FIGO stage I GCT cases allowed pregnancies to proceed without significant risk, highlighting the critical role of early detection in safeguarding maternal and fetal health. Some studies lacked detailed reporting on maternal and fetal outcomes, limiting comprehensive understanding of the long-term effects of NEOC

management during pregnancy. Nonetheless, the existing data underscore the importance of early staging and diagnosis, as early-stage NEOC often correlates with better pregnancy outcomes. Additionally, discontinuing chemotherapy three weeks before delivery, as noted by Luh LCPN *et al.*, facilitated bone marrow recovery for both the mother and fetus, reducing hematologic risks and underscoring the importance of precise treatment timing (29).

Study limitations. This systematic review encountered several limitations that impacted the generalizability and comprehensiveness of its findings. Firstly, the rarity of the gestational NEOC led to a limited pool of eligible studies, complicating the ability to draw robust conclusions across all NEOC subtypes. The small sample size and geographical diversity of the included studies introduced heterogeneity, as variations in healthcare settings, diagnostic protocols, and treatment standards could influence the applicability of the findings across different regions and patient populations. Additionally, most studies were retrospective case reports or case series, limiting the capacity to assess causative relationships and definitively evaluate treatment effectiveness. The absence of randomized controlled trials or prospective cohort studies hindered the ability to make strong recommendations for optimal diagnostic and management approaches for NEOC during pregnancy. Moreover, inconsistencies in standardized outcome measures across studies made direct comparisons of maternal/fetal outcomes challenging.

A notable limitation was the incomplete data reporting in the included studies. Some articles lacked detailed information on tumor markers, specific gestational ages at treatment, and long-term maternal and fetal outcomes. These gaps hinder a comprehensive understanding of the full impact of NEOC management, particularly regarding post-treatment recovery and the risk of recurrence. Additionally, this systematic review only included articles published in English and limited to the past five years to maintain methodological relevance. This language restriction may have excluded valuable studies published in other languages, potentially limiting the diversity of the evidence base. Furthermore, while the five-year publication window ensured contemporary relevance, it may have omitted studies with long-term outcome data, which are essential for understanding the extended impact of fertility-sparing treatments and chemotherapy on maternal and fetal health. Future reviews should aim to include a broader timeframe and consider studies in multiple languages to mitigate these limitations.

Conclusion

The diagnosis of gestational NEOC is exceptionally rare compared to other types of cancer in pregnancy. Routine first-trimester ultrasound scans have proven valuable for early detection and diagnosis of NEOC, particularly through the identification of hypo-hyperechoic masses, which are indicative of potential malignancy. Most cases included in this review were diagnosed at FIGO stage I, facilitating the use of fertility-sparing surgical treatments without the immediate need for adjuvant chemotherapy. Early detection often enabled crucial decisions prioritizing cancer treatment, including instances where pregnancy continuation was reassessed.

Platinum-based chemotherapy, effective for treating GCT, has been utilized as adjuvant therapy following surgery for advanced NEOC. While these agents are highly sensitive to cancer cells, their side-effects are comparable in both pregnant and non-pregnant patients. The absence of standardized treatment guidelines for NEOC during pregnancy highlights a significant gap in knowledge regarding optimal management strategies to enhance maternal and fetal outcomes. It is essential for clinicians to document and publish cases of NEOC diagnosed during pregnancy, as these contributions are vital for expanding the limited knowledge base in this field. Due to the rarity of gestational NEOC, existing literature lacks a large enough sample size to determine the most effective diagnostic tools, the ideal timing for diagnosis, and the best management practices. This limitation raises questions about the feasibility of establishing standardized treatment

protocols, as individualized care is often necessary to account for factors such as gestational age, tumor subtype, cancer stage, and maternal preferences.

Future research should aim to develop treatment protocols tailored to specific NEOC histological subtypes, cancer stages, and gestational ages. Investigating the long-term effects of platinum-based chemotherapy on both mothers and their children post-delivery would yield vital information on the safety and effectiveness of current treatment practices. Additionally, studies focusing on long-term maternal and child health follow-up could uncover potential impacts on future conception and pregnancies. Ultimately, a deeper understanding of these outcomes could help shape future guidelines, equipping clinicians with better-informed strategies for managing NEOC during pregnancy and minimizing risks for both mother and child.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: T.A., S.S., and S.B.; Data curation: D.B.O., J.T., and M.E.B.; Formal analysis: R.R., S.A., and S.V.O.; Funding acquisition: E.S.; Investigation: D.B.O, J.T., and M.E.B.; Methodology: V.P., S.V.O., and S.B.; Project administration: J.T.; Resources: S.A., and E.S.; Software: T.A.; Supervision: S.V.O., and S.B.; Validation: D.B.O.; Visualization: R.R., S.A., and E.S.; original draft: T.A., D.B.O., and S.B.; Writing – review & editing: T.A., D.B.O., J.T., M.E.B., R.R., S.A., E.S., V.P., S.V.O., and S.B.

Acknowledgements

The work was supported by the Kent Medway Medical School, University of Kent, Canterbury, Kent, UK and by the Department of Research and Innovation, Medway NHS Foundation Trust, Gillingham, Kent, UK.

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