ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 06 | June - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A CASE OF OVARIAN CLEAR CELL CARCINOMA IN PREGNANT WOMAN: CLINICAL PRESENTATION AND MANAGEMENT

Obstetrics & Gynaecology

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ABSTRACT

The adnexal masses are uncommon during pregnancy. They are usually picked up incidentally during antenatal scans. Most of the adnexal masses are benign and resolve spontaneously. The incidence of ovarian clear cell carcinoma (OCCC) is rare during pregnancy. OCCC is strongly linked with the history of endometriosis. Here is such an example of OCCC in women with a history of endometriosis. Here we present a 42-year-old primiparous woman who had incidental finding of complex ovarian cyst on her dating scan. Her CA-125 was 58 units. The MRI scan at 18 weeks of gestation showed 9.9*9.9*9.7cms complex cyst with endometrioma features. The patient underwent left salpingo-oophorectomy with peritoneal biopsy and washings at 20 weeks of gestation. There was no evidence of metastatic disease intra-op. The histology confirmed grade 3 OCCC. Following multi-disciplinary team (MDT) discussion, [patient was offered three different options of management involving the combination of chemotherapy, caesarean section and completion surgery. According to the patient's wishes, an elective caesarean section was performed at 35 weeks of gestation. The mother and baby were healthy in the immediate post-op period. She was later booked for 3-6 cycles of combination chemotherapy followed by completion surgery in the post-partum period. The patient will be under constant follow up till 5 years after completion surgery. This case report shows the importance of constant supervision of adnexal masses during pregnancy which leads to early intervention in the disease process. In management of these types of rare cases, it is necessary to formulate a new set of guidelines.

KEYWORDS

BACKGROUND

Ovarian cancers are the second most common gynaecological cancers. Ovarian cancer is further divided into different types depending on the origin of the cancerous cell. Epithelial ovarian cancer (EOC) is most common type of ovarian cancer (90%).[1] EOC are further divided into various subtypes like serous, mucinous, clear cell, endometroid and others.[2] The incidence of OCCC is 5-10 % of all EOC. OCCC is common in pre-menopausal women with mean age group of 50-55 years.[2] OCCC is strongly linked with history of endometriosis. OCCC is also associated with genetic changes in ARID1A (AT- rich interaction domain 1A) and PIK3CA (phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha) mutations and MET (mesenchymal-epithelial transition) amplification.[3]

The incidence of ovarian cancer during pregnancy is 2.4-5.7%.[4,5] The early stages of ovarian cancer show few or no symptoms. The advanced stage of ovarian cancer can present as dull abdominal pain, bloating sensation, weight loss and fatigue. The symptoms are not usually picked up in pregnancy because of the physiological changes of pregnancy itself. Most of the cases detected in pregnancy are incidental. Here is such a case with incidental detection of OCCC during routine antenatal dating scan.

CASE PRESENTATION

A 42-year-old primiparous woman of Polish background was referred to our gynaecology outpatient clinic at approximately 7 weeks of pregnancy due to incidental finding of complex ovarian cyst on ultrasound examination. She gave a history of spontaneous conception. She complained of occasional pain in the periumbilical region, dull aching, moderate grade in severity and no aggravating or relieving factors. There was no history of bloating, loss of appetite or change in bowel habits. She has had a previous normal delivery of a son aged eight years. She gave a history of endometriosis which was managed medically. There was no history of ovarian cyst or fertility treatment. She gave no history of gynaecological cancers or breast cancer in her family. She was a non-smoker, non-alcoholic and had no allergies. On initial presentation, her general condition was fair. Her observations were stable. Cardiovascular and respiratory examination was normal. On a per-abdominal examination, the abdomen was soft, non-tender and no palpable masses were felt. On an internal examination, the uterus was the size of 7 to 8 weeks. The adnexal mass of size approximately 5*4 cm was felt, non-tender and easily mobile. The margins were not well defined because of the gravid uterus.

Investigations

The diagnostic work up was done as per ESMO clinical practice guidelines.[6] The basic blood investigations were done at the general practitioner clinic. They showed haemoglobin of 11.2gm%, total leucocyte count was 12,000, platelet count of 4.5 lakhs, CRP was 5.5mg/L, TSH was 16.8pmol/L, liver and kidney functions tests were normal. The transvaginal scan (TVS) sent with her referral showed a complex ovarian cyst of 66*64mm with echogenic content and vegetation with positive doppler changes. The TVS was repeated at our hospital. The TVS done at our hospital showed intrauterine pregnancy of 7 weeks with a cyst of 65*53mm in pouch of Doughlas (POD). There was a projection measuring 14*21mm on the distal edge of the cyst. These findings were reported as possible decidualized endometrioma. The CA125 levels was 58 units, Alpha fetoprotein (AFP) was 3 and lactate dehydrogenase (LDH) was 271 units/L. Due to diagnostic difficulty with ultrasound, patient was booked for MRI according to the current Royal College of Obstetricians & Gynaecology guidelines for ovarian masses in pregnancy.[7] MRI showed a cyst in POD measuring 9.9*9.9*9.7cms. MRI also showed some peripheral projections that measured 2.8cms with marked diffusion restriction. There was no evidence of extra ovarian disease.

Differential Diagnosis

There was no history suggesting the diagnosis of ovarian cyst. Internal examination was also not helpful because of the presence of a gravid uterus. The various differential diagnosis for adnexal mass is ovarian mass, tubal mass or pedunculated fibroid were considered. The ultrasound helped to arrive at the final diagnosis of complex ovarian cyst. The diagnosis of endometrioma was also considered since the patient had a history of endometriosis. This was also supported by normal levels of tumour markers like AFP, LDH except for borderline raised CA 125. The finalization of the diagnosis was difficult as the patient was pregnant. The tumour markers are also not reliable since they will be produced by placenta. The size of cyst with features of solid components made us consider chances of malignant ovarian tumours. Thus, the decision of MRI which showed features of a borderline or a malignant lesion. Finally, histopathology confirmed the presence of grade 3 clear cell carcinoma.

Treatment

After the reporting of a borderline or a malignant lesion on MRI, the patient was discussed at the gynae-oncology multi-disciplinary team (MDT). The patient was around 17-18 weeks of pregnancy with good performance status. The MDT decided to offer the patient laparotomy, unilateral oophorectomy, peritoneal biopsy and washings. After consenting with the patient, laparotomy with left salpingo-oophorectomty was done during 20th week of gestation. Intra operative findings included 12 cm cyst arising from the left ovary with normal tubes, right ovary and peritoneal surfaces. Omentum appeared grossly normal. The liver and rest of the abdominal organs were normal with

no palpable retro-peritoneal nodes. The cyst had ruptured during manipulation leaking serous yellow fluid. Good peritoneal wash was given. The histology confirmed grade 3 OCCC with no evidence of metastatic disease. Staging of the tumour was TNM stage T1c and Stage 1c as per FIGO. Immunohistochemistry showed positive CK7 and patchy staining for CD 10. The patient was again discussed at the MDT. At the MDT, three options were discussed, including an early delivery and completion surgery and adjuvant chemotherapy as option one. Option two was continuation of pregnancy with chemotherapy during pregnancy and a planned delivery at 38 weeks followed by completion surgery and option three was a planned delivery after antenatal steroids for fetal maturity followed by completion surgery and chemotherapy. After discussing pros and cons of all the three options, the patient decided to have elective caesarean section at 35 weeks with the cover of antenatal steroids followed by adjuvant chemotherapy of 3-6 cycles and completion surgery that is hysterectomy with bilateral pelvic lymphadenectomy.

Outcome And Follow-up

The patient delivered a healthy baby weighing 3kg by elective caesarean section. The mother and baby were doing well in the postoperative period. Since there was no evidence of metastasis on histopathology report, she was planned for 3-6 cycles of chemotherapy with carboplatin and paclitaxel. After completion of chemotherapy, she will have a completion surgery. She will be under constant follow up till the completion of treatment with us and the oncology team. The patient and her family were offered constant support by the MDT team.

DISCUSSION

In recent years, the diagnosis of adnexal masses during early weeks of pregnancy has increased due to regular use of ultrasound in the first trimester for dating, viability and determining nuchal fold thickness. The incidence of adnexal masses in pregnancy is up to 4% of all pregnant women.[8] The gynaecological causes for adnexal masses are benign or malignant ovarian cysts, tubal cysts and pedunculated fibroids. The non-gynaecological causes for the adnexal masses are mesenteric cyst, appendix mass, pelvic kidney and others.

Most of the ovarian masses found during pregnancy are benign in nature. The rate of malignant ovarian tumours in pregnancy varies from 3 to 5%.[9] Most causes of ovarian cancer are epithelial origin approximately 90%. One can see all types of Epithelial Ovarian Cancers (EOC) in the pregnancy.[10] EOCs are further divided into various types based on histological features such as serous, endometroid, clear cell, mucinous, Brenner, mixed epithelial and undifferentiated types. Each of these subtypes is further divided into different grades (1-3) based on architectural features, mitotic count and nuclear atypia. Clear cell carcinoma (CCC) is the second most common type after serous carcinoma. These are commonly seen in the Japanese population. There is strong association between clear cell carcinoma and history of endometriosis and most of the population carry ARIDIA mutations. [11.] Endometriosis is a condition characterised by the presence of ectopic endometrium outside the uterine cavity. Endometriosis is associated with dysmenorrhoea, dyspareunia, and infertility problems. Several studies have shown association between risk of ovarian cancer and IVF treatments.[12,13] The risk specifically increases with the number of IVF cycles.

The diagnosis of ovarian tumours is incidental in most of all the cases. Initial work up included full blood count, tumour markers, liver and renal function tests, pelvic ultrasound, and chest X ray. Tumour markers include CA-125, AFP, Beta HCG and LDH. The level of these tumour markers is routinely not used in the diagnosis of CCC in pregnancy. The pelvic ultrasound will be a helpful initial tool for diagnosis in case of non-pregnant women. In case of pregnant women diagnosis will be difficult due to the presence of a gravid uterus. In such cases, MRI can be safely used in pregnancy. MRI provides superior resolution as per compared to CT scan. MRI also helps to clearly define characters of cyst like vegetations, solid areas, dermoid and endometroid features.[14]

The benign ovarian masses less than 5 cm are managed conservatively. Most of the benign cysts with size less than 5 cm undergo spontaneous resolution during pregnancy. The complex cysts should be followed up with serial ultrasound to look for increase in size of cyst. The benign cysts such as dermoid can complicate the pregnancy by undergoing torsion.

Surgery is indicated if there are any suspicion of borderline lesions or malignancy. Surgery is done in second trimester of pregnancy to reduce chances of miscarriage. Laparotomy is considered the best approach in the pregnancy when compared to laparoscopy because laparoscopy is skill dependent and takes longer operating hours.[15] The routine use of tocolytic drugs after the surgery is not indicated. The foetal monitoring should be done before and after the surgery.

The aim of the primary surgery for early ovarian cancers is to remove the entire tumour mass and do adequate staging. Staging is very necessary to plan post op chemotherapy. The usual approach in early CCC is initial debulking surgery followed by chemotherapy and completion surgery at last that is total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. The initial debulking surgery varies with each individual and intra-operative finding. However, there are no specific guidelines for the management of ovarian cancer in pregnancy.

Chemotherapy is not started in the first trimester because of effects of teratogenicity.[16] They are not perfectly safe in other trimesters as these agents can still affect the haematopoietic system and central nervous system. Hence it is necessary to keep such children under long term surveillance. Breastfeeding is contra-indicated when a patient is on chemotherapy. The usual chemotherapeutic agents used for the CCC are paclitaxel and carboplatin.[17] These agents are given intravenously every three weeks for 6 cycles. The chemotherapy will be followed by completion surgery.

The management also depends on the stage of disease at the time of diagnosis. If the disease is diagnosed in early stages, continuation of pregnancy with adjuvant chemotherapy can be done. If the disease has already reached an advanced stage, termination of pregnancy should be suggested after MDT meeting.[18] If the patient wishes to continue her pregnancy, it should be respected and given all supportive care.

The follow up after the completion surgery is usually done at every 3 months interval in the first two years followed by every 6 months in the next 3-5 years. At each follow up clinical examination, Ca-125 levels and CT scan or PET scan in case of suspicion of any residual disease or recurrence. GCIG criteria states that if the levels of CA-125 are progressively rising during follow up, it suggests recurrent disease.[19] But the Ca 125 levels are not reliable during pregnancy due to physiological rise during pregnancy. In terms of prognosis, CCC in their stage 1&2 respond well to platinum-based chemotherapy. However, in their later stages, they become chemo resistant due to the presence of ARID1A and MET genes. In our case, initial debulking surgery was done at 20 weeks due to suspicious findings on MRI followed by elective caesarean section at 34 weeks with good fetal outcome. The patient was then referred to another hospital for adjuvant chemotherapy followed by completion surgery. The patient will be seen regularly by the gynae-oncology team till 5 years.

Learning Points

1. The incidence of ovarian clear cell cancer in pregnancy is rare.
2. There are no specific guidelines for the management of ovarian cancer in pregnancy.
3. The management should be decided on an individual basis considering stage of ovarian cancer, presence of metastasis, period of gestation, choice of the patient to continue pregnancy and foetal outcomes. It is necessary to involve a multidisciplinary team to finalise on the decisions.
4. It is crucial to give the patient and her family proper support throughout the process.

Conflict Of Interest: None declared.
Funding: No external or internal funding was involved.
Ethical Committee: Not involved as details of patient are kept anonymous.

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