Review,

Ovarian Pregnancy: A Systematic Review and 2 Case Reports

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Abstract: Objective Ovarian pregnancy is a rare but well-known pathology. However, pathophysiology, diagnosis and treatment are not clearly established. **Data sources.** All case reports published in Pubmed from Nov 2011 till Nov 2022. **Study eligibility criteria**. A systematic review and 2 case reports of ovarian pregnancy **Study appraisal and synthesis methods.** Not applicable. **Results:** Ovarian pregnancies occur in 8% of women without or blocked oviducts and in 23% on the other side than the corpus luteum and the symptoms of ovarian pregnancies are not specific. Therefore ovarian pregnancy has to be suspected in all women with abdominal bleeding. As for extrauterine pregnancies, the presence of an intrauterine pregnancy does not rule out an ovarian pregnancy. Surgical excision is the preferred treatment. Important is that in women with both an intra-uterine and an ovarian pregnancy, care should be taken not to damage the corpus luteum. **Conclusions:** Ovarian pregnancies can occur in women with blocked tubes, on the other side of the corpus luteum, in the presence of an intrauterine pregnancy, and even when pregnancy tests or tranvaginal ultrasonography are negative. The diagnosis being difficult to exclude, a laparoscopy is indicated in all women with intra-abdominal bleeding, keeping in mind that an intra-uterine pregnancy cannot be exluded and that a corpus luteum need to be respected.

Keywords: ectopic pregnancy; heterotopic pregnancy; laparoscopy; methotrexate; corpus luteum

Introduction

Ovarian pregnancy could be considered a rare but well-known pathology considering the 667 articles found in PUBMED. Since 1945 the yearly number of articles has been constant at around 10 with over the last 10 years 111 articles including 12 small series with some narrative reviews (1-6).

Ovarian pregnancies are a rare form of ectopic pregnancy, occurring in 0.5% to 1% of ectopic gestations, or 1 in 7000 to 40,000 live births (1, 7). Although a potentially life-threatening event, the pathophysiology is not understood and the diagnosis remains challenging (8). The accuracy of the diagnosis with clinical exam, HCG concentrations and ultrasound or MRI imaging (9) is limited with the risk of missing the diagnosis and of overdiagnosing because of cognitive bias(10). Even the laparoscopic diagnosis can be difficult and many ectopic pregnancies are only diagnosed by pathology after surgery. Therapy is variable and ovarian-sparing surgery is poorly discussed. Also, the follow-up after treatment is not clear.

Therefore, we decided to perform a systematic review of ovarian pregnancies, triggered by 2 recent cases of ovarian pregnancy.

Objectives

The aim of the review was to understand better pathophysiology and to improve diagnosis and therapy.

 doi:10.20944/preprints202212.0520.v1

Materials and Methods

Case reports

Written informed consent for publication was obtained from both patients. Local institutional review board (IRB) was not required for anonymous case reports

Systematic review

Study selection

Pubmed was searched for ("ovarian pregnancy") OR ("ovarian ectopic pregnancy") on 5/11/2022. The 111 articles retrieved were screened, 99 were reviewed and 82 case reports were retained. We did not include 5 reviews of imaging, or pathology, and 12 reports in which the information of individual cases could not be retrieved (5 discussed ectopic pregnancies, one did not contain data and 3 were reviews of small series, not permitting extraction of details) (Fig 1).

Data extraction

These case reports were searched for age and antecedents of the woman such as gravity, parity, abortions, ectopic pregnancies, in-vitro fertilisation (IVF), intrauterine insemination (IUI), tubal or endometriosis or pelvic surgery, pelvic inflammatory disease (PID) and the use of an intrauterine device (IUD). For the ovarian pregnancies, we retrieved the duration of the pregnancy, presenting symptoms (pain, vaginal bleeding, shock), HCG concentration, ultrasound and MRI exams, treatment and outcome.

Assessment of risk of bias

Since only case reports were reviewed, PROSPERO was not done and the risk of bias was not assessed.

Statistics

Data were analyzed with SAS (11) using Spearman correlations, chi-square and logistic regression. Unless indicated otherwise medians (10th - 90th percentiles), or mean $\pm$ standard deviations are indicated. Results are given as exact P-values as suggested by the American statistical association (12).

Results

Case reports

Case 1. A 36-year-old woman was referred because of a suspicion of a ruptured ectopic pregnancy at 5 weeks of amenorrhea because of increasingly severe acute lower abdominal pain (7/10) for 24 hours although without vaginal bleeding. Besides 2 uneventful pregnancies, her gynaecological, medical or surgical history was uneventful. The clinical exam was suggestive of abdominal bleeding since abdominal tenderness and guarding, in a pale woman with tachycardia (109/min) although vitally stable (BP 101/63 mm Hg). A transvaginal scan confirmed an abdomen full of fluid suspected of being clots up to Morison`s pouch. Haemoglobin was 8.3 g/dl and the urine pregnancy test was positive but the uterus was empty. Adnexae were not visualized. The coagulation profile was normal. Suspecting a ruptured ectopic pregnancy an emergency laparoscopy was performed, confirming a 2 litres hemoperitoneum but bilaterally normal oviducts and a right ovary bleeding from a small 1*1 cm lesion with an everted edge (Fig. 2). The lesion was excised and 2 units of packed red blood cells and 2 units of fresh frozen plasma were given. The postoperative period was uneventful and the day after surgery the B-HCG had dropped from 2923 international units (IU) to 1018 IU, becoming negative by day 12. The histopathological examination of the excised lesion found to our surprise trophoblastic cells confirming an ovarian ectopic pregnancy (Fig. 2).

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Case2. A 33-year-old woman was referred because suspected of a ruptured ectopic pregnancy. She had acute abdominal pain, giddiness and shoulder tip pain for 8 hours and 32 days of amenorrhea, but no vaginal bleeding. Besides 2 vaginal deliveries, her antecedents were negative. She was pale, with severe pain (5/10) but stable with a pulse at 83/min and BP of 111/65 mmHg. The abdomen was distended with tenderness and guarding. The bedside transvaginal scan did not find an intrauterine gestational sac, but a left adnexal mass of 3x3.5 cm and moderate fluid in the pelvis. Considering an HCG of 9693 mIU/mL, Hb 8.7, PLT 257 and normal coagulation an emergency laparoscopy was performed. Besides a 1000 ml hemoperitoneum, the fallopian tubes were normal but the left ovary was suspected of a ruptured ovarian pregnancy (fig 2). The lesion was resected, hemostasis was performed and 2 units of blood transfusion were given. The postoperative recovery was uneventful and after 2 days HCG had dropped to 4200 mIU/mL The pathology report confirmed the ovarian pregnancy.

Review

Study selection, study characteristics and risk of bias.

All publication on ovarian pregnancy from which data of the individual women could be retrieved were case reports, and thus without a risk of bias.

Synthesis of results

The age of the women ranged from 16 to 45 years (30, 23 -38), gravity from 1 to 9 (2.6,1-5), parity from 0 to 7 (1,0-3) (suppl fig1) and abortions from 0 to 4 (0.4,0-1). The frequency of previous ectopic pregnancies, IVF, IUI, tubal surgery, endometriosis, pelvic surgery, PID or IUD is shown in Fig 3. Surprisingly, 6 women had blocked or no fallopian tubes (13-18). Also, the incidences of IVF, IUD and PID seem rather high. A history of endometriosis was associated (Spearman) with a history of PID (P=0.0078) or IUD (P=0.0074) but not with ovarian pregnancies.

Most ectopic pregnancies were diagnosed within 8 weeks of amenorrhoea, but 15% of pregnancies had a duration of up to 44 weeks (Fig 4). Surprisingly, in 10 cases symptoms started before the end of a menstrual cycle (before 28 days of amenorrhoea). HCG concentrations were mentioned in only 60 cases and not surprisingly a later diagnosis was associated with slightly higher concentrations of HCG (P<0.0001). Symptoms were not specific with pelvic pain, vaginal bleeding and hypovolemic shock occurring in 77.4%,45.2% and 11.5 % respectively (Fig 5). The diagnosis was made by ultrasound in only 21%, and by MRI in 25%. Pregnancy was confirmed by HCG concentrations in 50%, unknown in 43%, but negative in 2 cases (2%).(19, 20)

Rare cases were one woman with a bilateral ovarian pregnancy (21), another with a left ovarian pregnancy diagnosed 3 weeks after left salpingectomy for tubal pregnancy after ovulation induction (22), 2 women with a tubal pregnancy and an ovarian pregnancy on the other side (23, 24) and 6 ovarian pregnancies associated with an intrauterine pregnancy (heterotopic pregnancy), 2 of them spontaneously (25, 26), 1 after ovulation induction (27), 1 after IUI (28) and 2 with IVF(14, 29). In 5 of them, the intrauterine pregnancies continued uneventfully after the excision of the ovarian pregnancy. One woman had an intrauterine pregnancy and bilateral corpus luteum. After a miscarriage at 7 weeks, a laparoscopy for persisting lower abdominal pain revealed a ruptured ovarian pregnancy (25).

The site of the corpus luteum was mentioned in 22 reports only. However, 5 (22%) ovarian pregnancies occurred in the controlateral ovary (25, 27, 29-31), 3 of them being heterotopic.(25, 27, 29)

Medical treatment was given to 8 women (7.2%) without specific criteria of HCG concentrations, pelvic masses or fetal cardiac activity, using hyperosmolar glucose or methotrexate. Methotrexate was successful in 5 cases (22, 27, 32-34) but otherwise failed and surgical treatment was needed in 2 cases. In the first case (35), HCG was 3495 with

 doi:10.20944/preprints202212.0520.v1

a gestational sac of 7x6x7 mm and 3 days after a single dose of methotrexate, fetal heart activity was detected and HCG had increased to 5148. In the second case (36), the ectopic pregnancy mass size was 9x11 mm, the HCG concentration remained unchanged notwithstanding multiple doses of methotrexate, and the patient became unstable with severe abdominal pain.

The majority of women (95%) underwent surgery (Fig 6). Not surprisingly more advanced pregnancies were treated more frequently with a laparotomy (Spearman P=0.0130.) and surgery was less conservative with more adnexectomies (Spearman P=0.0001). Laparoscopic surgery was more frequent in women with a history of endometriosis (P=0.0089) or IVF (P=0.0005). Laparoscopies were performed in 43%, 50%, 47% and 10% for durations of amenorrhea of <6 (n=47), 7-8 (n=32), 9-10 (n=17), and more than 10 (n=10) weeks of gestation respectively. Adnexectomies instead of conservative surgery were performed in 30%, 6%, 41% and 78% respectively. Not surprisingly women in shock had more adnexectomies (P<0.0001) In 2 women a hysterectomy was performed (1.8%), one with a gestation of 44 weeks with the placenta involving the uterus (37), and one in a 45 years old lady (38). Follow-up after surgery was uneventful in all except in 1 woman in whom medical treatment was given because an HCG of 2134 IU/ml suggested residual trophoblastic tissue (39).

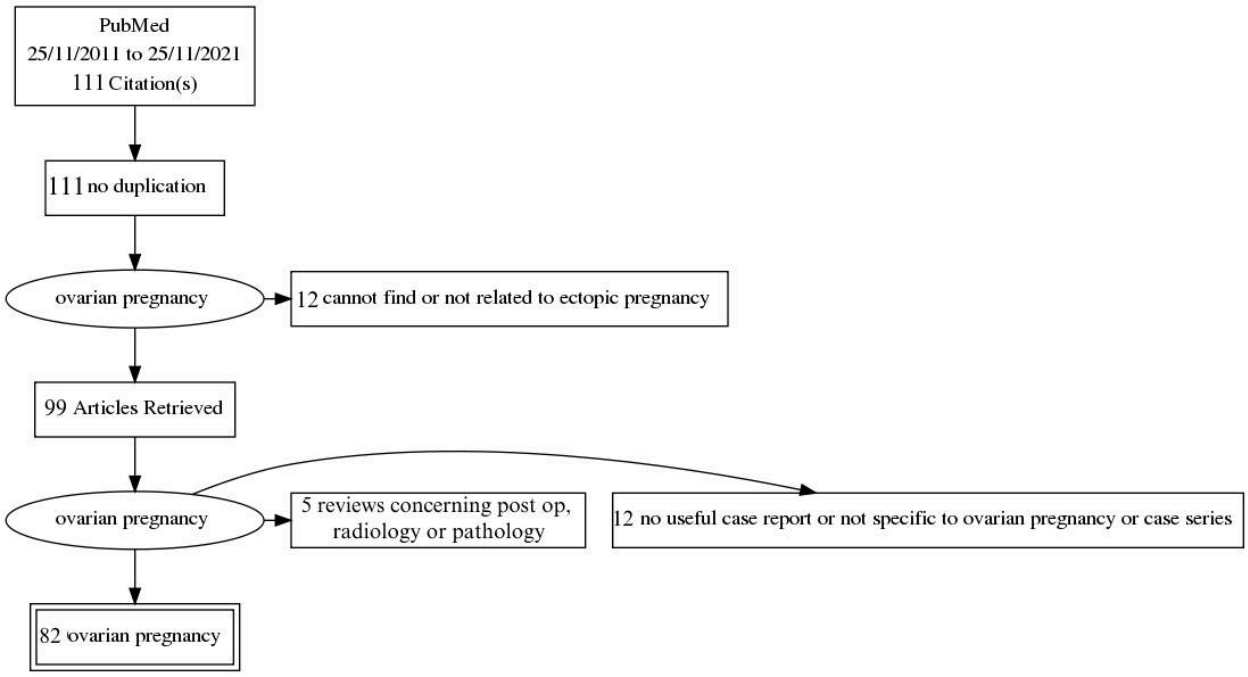

Fig 1:Prisma flow diagram for ovarian pregnancy search in PubMed from 2011 to 2021

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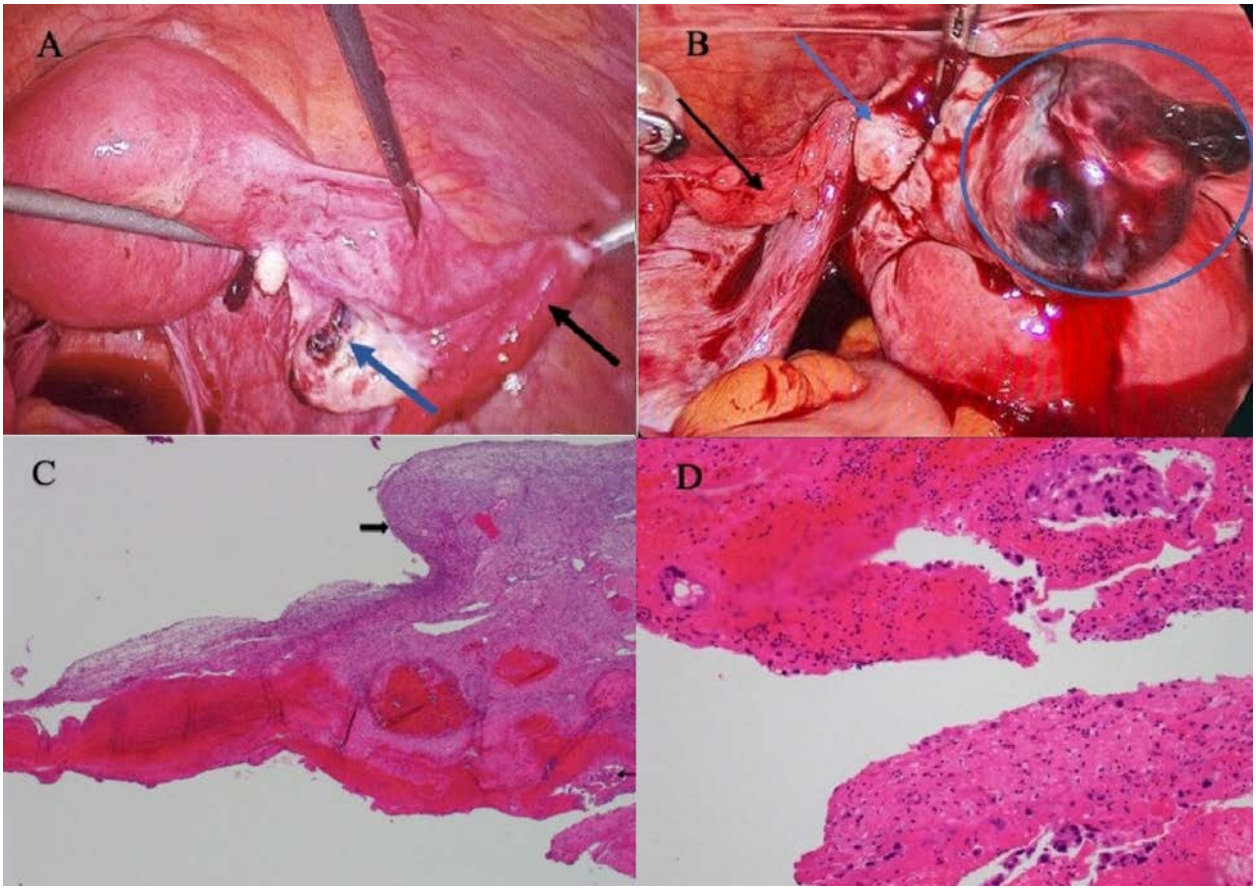

Fig 2 The laparoscopic diagnosis of ovarian pregnancy is not obvious. A: Normal right Fallopian tube (black arrow) and right ovary with a lesion suspicious of right ovarian ectopic pregnancy (blue arrow) B: Normal right tube (black arrow), right ovary (blue arrow) with ruptured ovarian pregnancy (blue circle) C: A piece of a cyst-like wall lined by fibrinous hemorrhagic material with scattered trophoblastic nests (thin arrow) on top of the ovarian edematous stroma with a primordial follicle (thick arrow) and covered by a mesothelial lining (Hematoxylin and eosin (H&E) stain, original magnification x40). D: Foci of trophoblastic elements are embedded within a fibrinous inflamed decidualized tissue (H&E, ×200)Fig 2A: Normal right Fallopian tube (black arrow) and right ovary with a lesion suspicious of right ovarian ectopic pregnancy (blue arrow)

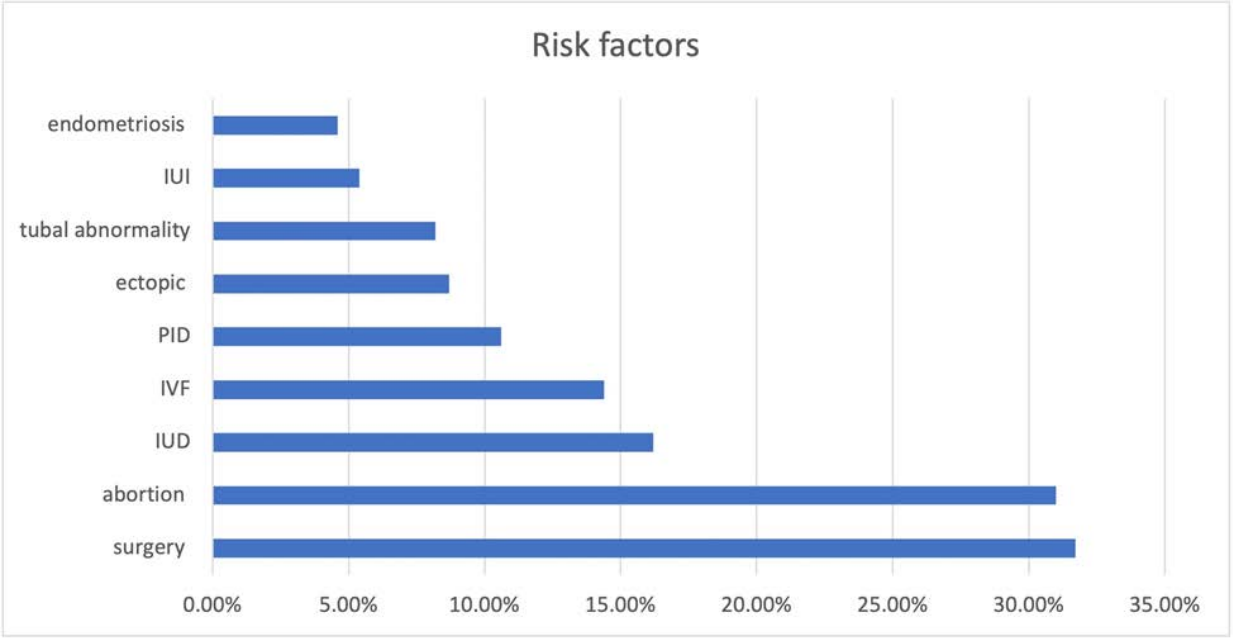

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Fig 3 Incidences of previous ectopic pregnancies, IVF, IUI, tubal surgery, endometriosis, pelvic surgery, PID or IUD in women with ovarian pregnancies

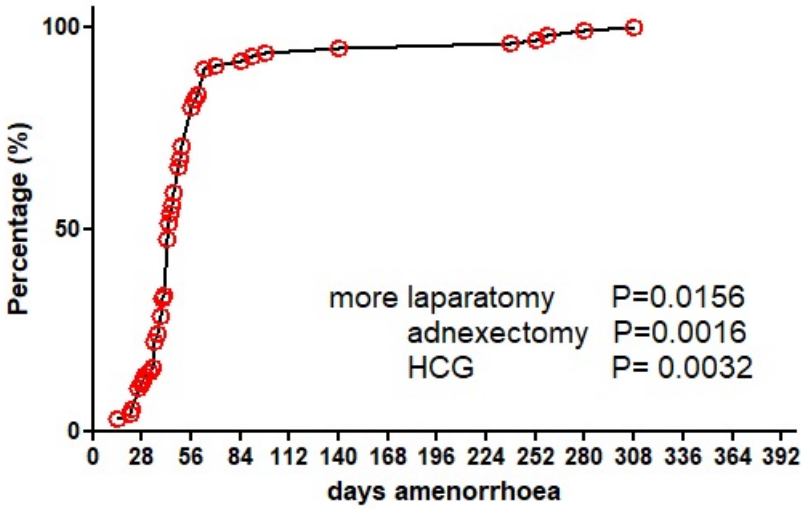

Fig 4 Duration of amenorrhoea in ovarian pregnancies.

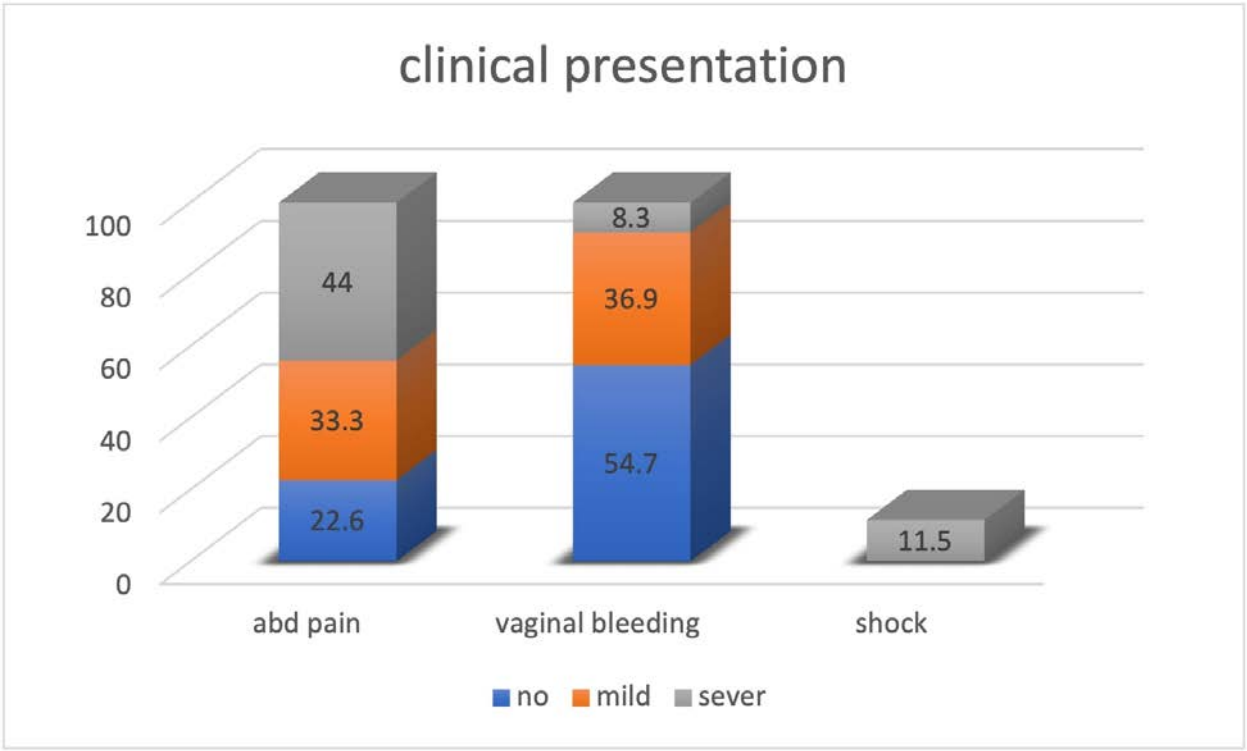

Fig 5 Presenting symptoms of ovarian pregnancies

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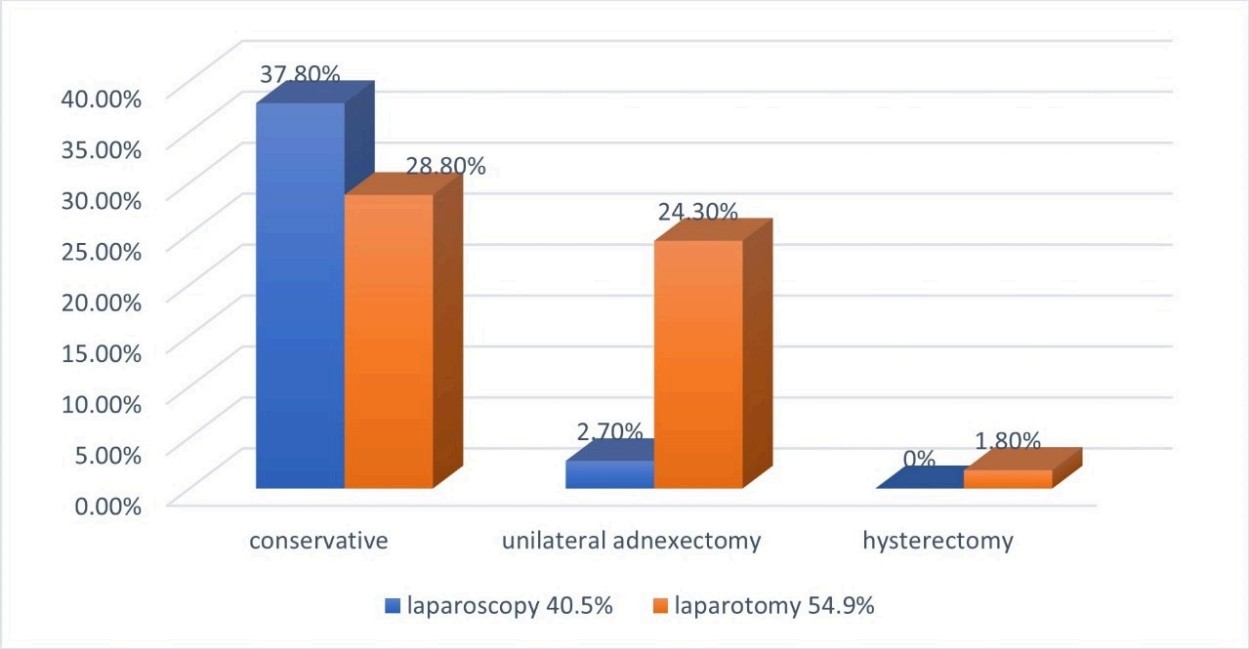

Fig 6 Treatment of ovarian pregnancies

Discussion

Main findings

Ovarian pregnancies seem to be associated with similar causal factors as extrauterine pregnancies, such as a history of PID or tubal surgery (1, 40). However, some aspects are unexpected, such as ovarian pregnancies in the contralateral ovary as the corpus luteum, similar to the observations of contralateral tubal pregnancies (41, 42). Also, ovarian pregnancies in women without or with blocked oviducts are surprising, and micro fistula between the fallopian stump and peritoneal cavity to permit sperm transport seems rather speculative (15-17).

The diagnosis of ovarian pregnancy is not aspecific, and ovarian pregnancy should therefore be considered in all women suspected of extrauterine pregnancy with or without vaginal bleeding. The diagnostic accuracy of imaging such as ultrasound or MRI is insufficient to exclude an ovarian pregnancy and most are unexpected findings during surgery. Most ovarian pregnancies are diagnosed in the first 8 weeks of pregnancy but surprisingly some occur before a missed period and some are diagnosed as late as after 44 weeks of gestation. The suggestion that ovarian pregnancies are associated with more blood loss than tubal pregnancies could not be confirmed (2, 3, 13, 18). Occasionally an ovarian pregnancy can result in a choriocarcinoma(43).

The laparoscopic diagnosis of a bleeding ovarian lesion as an ovarian pregnancy and the differentiation from a bleeding corpus luteum(1) can be difficult as illustrated in Fig 2. The insertion of a uterine manipulator is not obvious considering that a beginning intrauterine pregnancy is difficult to exclude.

The preferred treatment is surgical excision since the diagnosis is generally made during surgery. The results of medical treatment are variable. Care should be taken not to damage the corpus luteum during surgery since a co-existing intra-uterine pregnancy was reported to continue uneventfully

Comparison with existing literature

These data confirm and extend the literature which is limited to case reports and small series. The diagnosis is difficult and most ovarian pregnancies are unexpected findings during surgery(1).

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Unexpected are the relatively frequent occurrences of ovarian pregnancies before a delay in menstruation, in women with blocked tubes and the association with intra-uterine pregnancies.

Strengths and limitations

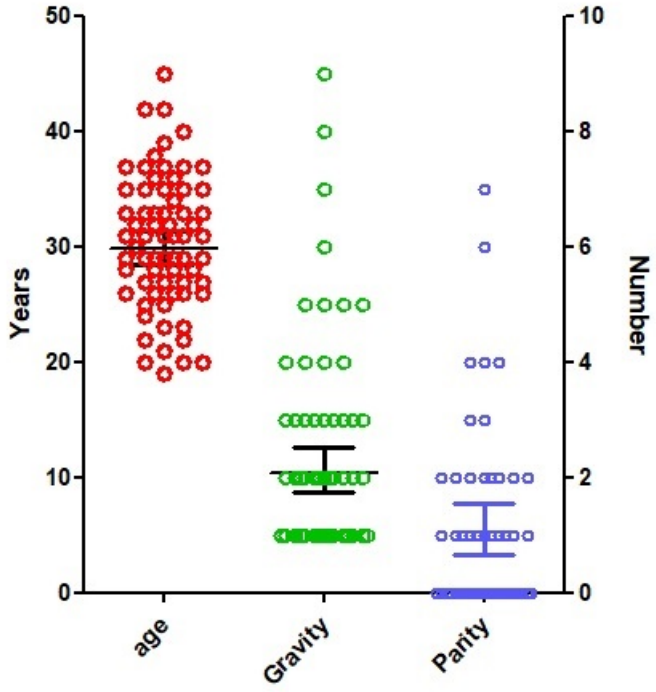
This is the largest series of ovarian pregnancies, permitting us to judge better incidences and associations. Unfortunately, these data do not improve diagnosis or judge ovarian sparing surgery.

Conclusions and Implications

Conclusions

In conclusion, the diagnosis of ovarian pregnancy remains aspecific and surgery is the treatment of choice. However, clinicians should be aware that ovarian pregnancies can occur before a delay in menstruation, in women with blocked tubes and the association with an intra-uterine pregnancy.

Supplementary Materials:



Supplementary Fig Age, parity and gravity of women with an ovarian pregnancy. Geometric means and confidence limits are indicated.

Author Contributions: ZK, PK and MA conceived the manuscript. ZA, BA,ZK, IA and ZA searched the literature. Aqll authors discussed and approved the manuscript

Funding: Please add: "This research received no external funding"

Institutional Review Board Statement: Local institutional review board (IRB) was not required for anonymous case reports

Informed Consent Statement: Written informed consent for publication was obtained from all patients.

Data Availability Statement: original data are available upon simlple request to the corresponding author

Conflicts of Interest: The authors declare no conflict of interest.

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