

Primary Ovarian Pregnancy: 43 Years Experience in a Single Institute and still a Medical Challenge

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ABSTRACT: **Background:** Despite awareness regarding tubal pregnancy, ovarian pregnancy still remains a diagnostic challenge. The correct diagnosis is most frequently made intraoperatively and requires histopathologic confirmation. Therefore, additional diagnostic measurements are needed for earlier and more accurate detection of ovarian pregnancies which will allow more rapid and efficient treatment.

Objectives: To assess the time trends, clinical manifestations, surgical management and post-procedure outcome of 46 primary ovarian pregnancies in a single institution during three time periods.

Methods: In this retrospective study we compared 20 patients with primary ovarian pregnancy during the years 1971–1989 (first period), 19 patients in 1990–2001 (second period) and 7 patients in 2002–2013 (third period). In all cases the pathology examination confirmed primary ovarian pregnancy.

Results: The number of tubal ectopic pregnancies almost doubled, from 637 in the first period to 1279 in the third period ($P < 0.001$). However, there was a significant fall in the number of ovarian ectopic pregnancies, from 20 cases in the first period to 7 cases in the third ($P = 0.009$). A significant difference was noted when we compared the postoperative hospitalization time (4.06 ± 1.4 vs. 2.0 ± 0.6 days respectively, $P = 0.001$) in the second versus the third time period.

Conclusions: Ovarian pregnancy continues to be a diagnostic challenge, associated with a high rate of circulatory collapse, hemoperitoneum and requirements for blood transfusions, all leading to longer hospitalization.

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In recent decades, the diagnosis and treatment of tubal pregnancies (the most common site for ectopic pregnancies) [1] has undergone a tremendous change. Using the sensitive human chorionic gonadotropin (HCG) test and transvaginal ultrasound scan has enabled its early diagnosis. Thus, most tubal pregnancies are now diagnosed before rupture of the fallopian tube, and only a small number of women require urgent

surgery and blood transfusions due to intraabdominal bleeding and hemorrhagic shock [2].

Primary ovarian ectopic pregnancy is a rare variant of extrauterine pregnancy. Its incidence ranges from 1:2100 to 1:60,000 pregnancies, placing ovarian pregnancy at 0.5–3% of all ectopic gestations [3–5]. The use of contraceptive intrauterine devices (IUD) was associated in the past with the occurrence of ovarian pregnancy [6–8]. However, this has been disproved by more recent studies based on statistical calculations, although IUDs reduce intrauterine implantation by 99.5% and tubal implantation by 95% [9].

The findings suggestive of ovarian pregnancy on 2D ultrasound technology, in the absence of a yolk sac or fetal heart motion, may have a similar appearance to ruptured corpus luteum, which emphasizes the need for better and more precise diagnostic tools. Comstock et al. [10] reported a case series in which they evaluated the ultrasonographic appearance of proven ovarian ectopic pregnancies. They showed a wide echogenic ring with an internal echolucent area as compared to a thin tubal ring with tubal pregnancies or corpus luteum cyst. Only occasionally was a yolk sac or fetal heart motion also identified. 3D ultrasound has recently been reported to distinguish ovarian pregnancy from corpus luteum cyst, which may improve detection [11].

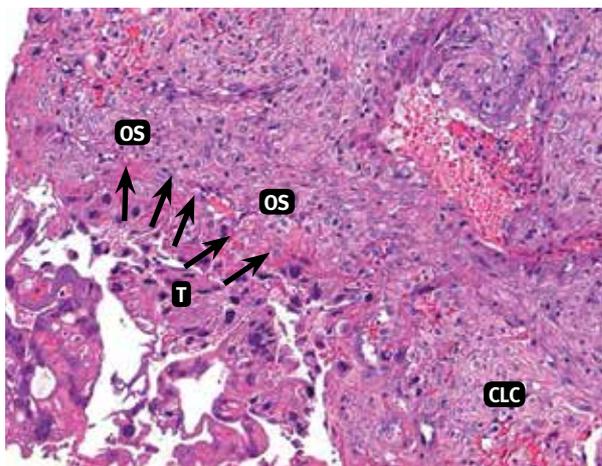
The delay in diagnosis of ovarian pregnancies has been attributed to the non-specific clinical presentation upon admission, while the massive intraabdominal bleeding has been explained by the fragility and hypervascularity of the ovarian tissue [6–8]. Patients with primary ovarian pregnancy mostly undergo surgery for suspected rupture of tubal ectopic pregnancy or hemorrhagic corpus luteum, and the final diagnosis is made intraoperatively [6].

The current study sought to assess whether the prevalence, clinical manifestation, treatment modalities and post-procedure outcome in women diagnosed with primary ovarian pregnancy has changed in our institute over the past four decades.

PATIENTS AND METHODS

The study group comprised 46 cases of ovarian ectopic pregnancy treated in our department from 1971 to 2013. All cases were diagnosed during three arbitrary time periods: 19 years

Figure 1. Histopathology examination of the specimen consistent with ectopic pregnancy located within the ovary. Trophoblastic cells (T) adjacent to ovarian stroma (arrows) (OS), showing a corpus luteum cyst (CLC) (hematoxylin & eosin, original magnification x100)



between 1971 and 1989 (first period, Raziel et al. [6]), 12 years between 1990 and 2001 (second period, Raziel et al. [8]), and 12 years between 2002 and 2013 (third period, Melcer et al. [12]). The seven cases from the third period were identified through search of a computerized database using ICD-9 codes.

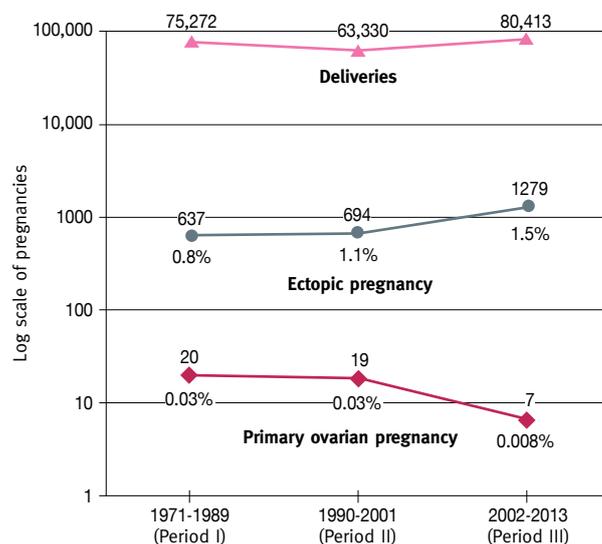
Intraoperative findings and histopathologic examination [Figure 1] fulfilled all four of Spiegelberg's criteria [13]: (i) an intact ipsilateral tube clearly separate from the ovary, (ii) a gestation occupying the normal position of the ovary, (iii) a gestational sac connected to the uterus by the utero-ovarian ligament, and (iv) ovarian tissue in the wall of the gestational sac.

Information on cases from the first two periods in the study was collected by reviewing existing databases available from our previous publications. Information on cases from the third period was obtained by retrospective review of their medical records. We collected information on demographics, obstetric and gynecologic history, clinical presentation, sonographic findings, operative procedure, postoperative care, and final pathology. Subsequently, we enquired about subsequent pregnancy outcomes by means of telephone interviews with women from the third study period. The study was approved by the local institutional review board (registration number 220-13). For the purpose of this study we compared the following parameters: admission hemoglobin (g/dl), estimated blood loss (ml), blood transfusion, and postoperative hospitalization (days).

STATISTICAL ANALYSIS

Statistical analysis was performed in the statistical laboratory at Tel Aviv University using SPSS software (SPSS Inc., version 15 Chicago, IL, USA). Continuous variables are presented as the

Figure 2. Time trends of deliveries, decreased primary ovarian pregnancy ($P = 0.009$) and increased ectopic pregnancy ($P < 0.001$) over three time periods in a single center. The percentages are related to total deliveries for each period



mean \pm standard deviation or as median (range). Frequencies are presented as percentages. For comparison of continuous variables, the analysis of variance (ANOVA) was used. The chi-square test was used to assess frequencies. P value < 0.05 was considered statistically significant.

RESULTS

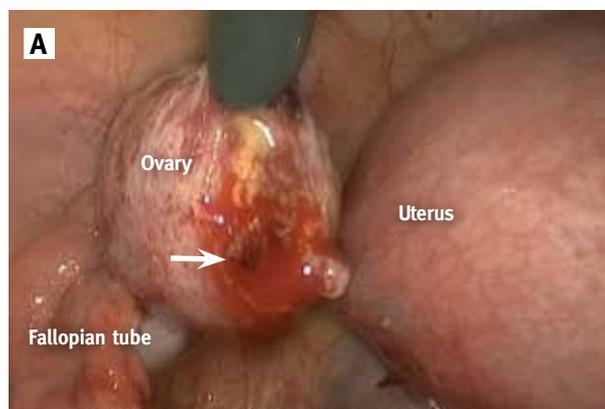
During the entire study period (1971–2013), 218,995 deliveries were recorded in our institute [Figure 2]. In addition, 2610 ectopic pregnancies (1.2%) were diagnosed. Of these, 46 were primary ovarian (1.8%). Overall, the number of deliveries increased during the study period and the rate of ectopic pregnancies almost doubled, from 0.8% in the first period to 1.5% in the third ($P < 0.001$) [Figure 2]. Contrarily, there was a significant fall in the rate of ovarian ectopic pregnancies, from 0.03% in the first period to 0.008% in the third ($P = 0.009$) [Figure 2]. The mean age of patients with a diagnosis of ovarian pregnancy increased by 4.2 years, from 27.9 ± 4.3 in the first time period to 32.1 ± 4.4 in the third ($P = 0.02$).

We found that 6 of 20 patients (30%), 4 of 19 patients (21%) and 5 of 7 patients (71.4%) in the first, second and third period respectively were admitted with hemodynamic shock. The rate of IUD use was extremely high, 18 of the 20 patients (90%), 13 of 19 patients (68.4%) and 3 of 7 patients (42.9%) in the first, second and third time period respectively ($P = 0.04$). In our patients who underwent sonographic assessment of the pelvis we found unspecific findings alerting

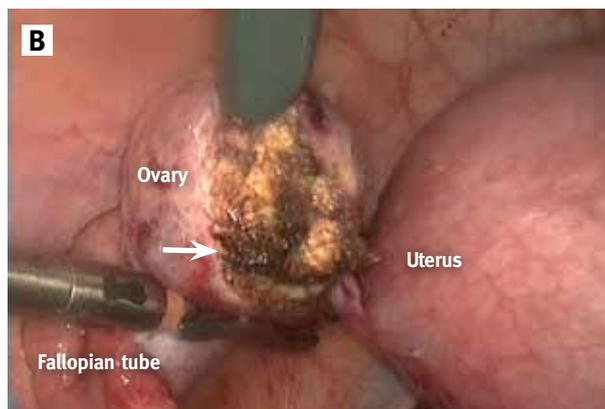
to ectopic pregnancy. This includes an empty uterine cavity or IUD in situ, complex mass, and free fluid in the pouch of Douglas. We did not encounter any case in which primary ovarian ectopic was sonographically diagnosed preoperatively.

Wedge resection by laparotomy was the treatment of choice until 1990, after which it was performed by laparoscopy ($P < 0.001$). Figure 3 presents the laparoscopic view of left primary

Figure 3. Laparoscopic view of ovarian pregnancy in the left ovary (arrow) and intact left fallopian tube



[A] Before wedge resection of ovarian pregnancy



[B] At completion of the surgical procedure

ovarian ectopic pregnancy. No case of persisting ovarian pregnancy after surgery was encountered.

Comparison of the laboratory findings of the 46 women with primary ovarian pregnancy between the three time periods is shown in Table 1. No significant difference was found between admission hemoglobin, estimated blood loss and blood transfusion. However a significant difference was found when we compared the postoperative hospitalization days (4.06 ± 1.4 vs. 2.0 ± 0.6 respectively, $P = 0.001$) in the second versus the third time period. No maternal mortality was encountered in all three groups.

All 48 patients were approached by telephone interview. Twenty used various methods of contraception; 17 patients conceived spontaneously and had uneventful intrauterine pregnancies, and one patient had a repeated ectopic tubal pregnancy.

DISCUSSION

To the best of our knowledge, this is the first detailed study to assess time trends over four decades of primary ovarian pregnancy diagnosed and treated in a single hospital. Our study has yielded several important observations that merit further discussion. A key observation was the increased number of deliveries followed by a parallel increase in the number of ectopic pregnancies. However, there was a decrease in the rate of ovarian pregnancy over the three time periods. High rates of IUD use, ranging from 90% to 42.9%, were found in the three periods examined, but overall the rate of IUD use decreased significantly over time. The significance of this finding is unclear since the rate of IUD use over time in our population is unknown.

The routine use of early ultrasound for diagnosis of ectopic pregnancy prompted medical treatment with methotrexate (MTX) in many selected cases. Therefore, it is likely that the frequency of ovarian pregnancies is underestimated. Some of the suspected tubal pregnancies, tubal abortion or the sonographic description of “complex mass” [14] – which are suitable for expectant management or MTX treatment without laparoscopic validation – may be early ovarian.

Our study demonstrates that patients with ovarian pregnancy commonly present with circulatory collapse and sig-

Table 1. Comparison of laboratory and surgical characteristics of the 46 women with primary ovarian pregnancy between the three time periods

	First time period (1971-1989) (n=20)		Second time period (1990-2001) (n=19)		Third time period (2002-2013) (n=7)		P value
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Admission hemoglobin (g/dl)	NK	NK	9.4 ± 2.2	6.4-12.9	9.8 ± 2.8	6.8-13	0.73*
Estimated blood loss (ml)	729.4 ± 602.6	100-2000	NK	NK	983.3 ± 470.8	400-1500	0.36*
Blood transfusion	2.2 ± 0.9	0-2	2.0 ± 0.6	0-2	1.7 ± 0.7	0-2	0.78*
Postoperative hospitalization (days)	NK	NK	4.06 ± 1.4	2-6	2.0 ± 0.6	1-3	0.001*

*ANOVA test NK = not known

nificant blood loss during surgery, leading to requirements for blood transfusion and longer hospitalization. Odejinmi et al. [15] recently reviewed 12 cases of primary ovarian ectopic pregnancy and showed similar results. The mean total blood loss was 730 ml and 5 of 12 patients were found to have hemoperitoneum \geq 500 ml. A large case series from Taiwan including 110 cases treated in a tertiary center over a 21 year period (from 1989 to 2009) also found high mean blood loss of 806.25 ml for patients operated by laparotomy and 583.33 ml for patients operated by laparoscopy [16].

Several case reports emphasize that despite the establishment of modern diagnostic methods, early and accurate diagnosis of primary ovarian ectopic pregnancy can be improved. Anecdotal case reports suggest that ovarian pregnancy may reach advanced gestation. One case report described an ovarian pregnancy diagnosed at cesarean section performed at 30 weeks gestation [17]. Another study described a case of heterotopic ovarian pregnancy reaching term [18]. Additional studies reported an ovarian pregnancy resulting in a surviving neonate [19], and an advanced ovarian pregnancy with retention of the dead fetus for more than a year [20].

In agreement with other studies investigating the surgical management of primary ovarian ectopic pregnancies [3,15,16,21], the majority of cases in our series in the second and third time periods underwent laparoscopy with resection of the primary ovarian ectopic pregnancy. This represents a shift from the traditional surgical approach when laparotomy was performed for most cases [7,8]. In view of the significant blood loss associated with ruptured ovarian pregnancy, it is still prudent to recommend prompt surgical intervention for cases of suspected ovarian ectopic pregnancy before rupture has occurred. This approach may be conducted either by laparoscopy or laparotomy, depending on the training and skill of the physician in charge and on the facilities available. Conservative treatment of non-ruptured ovarian pregnancy (by expectant management or MTX administration), although successful in several case reports [22], has not yet become the mainstay of treatment.

Despite the awareness for ectopic pregnancy, the combination of IUD in situ, empty uterine cavity, complex mass and positive pregnancy test should alert the physician to ovarian pregnancy. Therefore, in the absence of any specific findings like fetal pole in the ovary, this type of ectopic remains a sonographic challenge. This may lead to a delay in diagnosis followed by circulatory collapse, hemoperitoneum, and requirements for blood transfusion and longer hospitalization days. Because of the above difficulties the correct diagnosis is most frequently made intraoperatively and requires histopathologic confirmation.

In conclusion, additional diagnostic measurements are requested for early and correct diagnosis of primary ovarian pregnancy which will allow more rapid and efficient treatment, thus changing the cascade of events. Recent improvements in

ultrasound technology may lead to earlier and more accurate detection of ovarian pregnancies, possibly enabling non-invasive treatment modalities in the future.

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