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## **A clinico-histopathological study of ectopic pregnancy in a tertiary care hospital with special focus on histomorphology of fallopian tubes in tubal ectopic pregnancy**

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**Abstract**--Introduction: Ectopic pregnancy can present as an acute life-threatening emergency when it ruptures and accounts for about 10% of all maternal mortalities; therefore, it is imperative to diagnose the unruptured ectopic pregnancy such that timely intervention will prevent morbidity and mortality. The fallopian tube is the most common site for ectopic pregnancy (90-95%). With an increasing incidence of ectopic pregnancy worldwide, a histopathological study of the resected fallopian tubes becomes important to look for predisposing/associated findings such as acute salpingitis, chronic salpingitis and salpingitis isthmica nodosa (SIN). Objectives: The aim was to study the clinical presentation of ectopic pregnancy and its

association with various factors like age and gravida status. It also aims to study the histomorphology of the fallopian tubes with ectopic gestation and note the presence of predisposing factors such as acute salpingitis, chronic salpingitis and SIN. **Materials and Methods:** A total of 79 specimens of ectopic pregnancy received in Department of Pathology for a retrospective period of 2.5-years from January 2019 to May 2021 were reviewed. Histologic sections were studied for the presence of chorionic villi confirming the ectopic gestation and in cases of tubal ectopic pregnancy, the fallopian tubal wall was screened for features of acute salpingitis, chronic salpingitis, Salpingitis isthmica nodosa and any other related pathological findings. **Results:** Total 79 cases were included in the study. The age of the patients ranged from 18 to 40 years. Women with age 20-25yrs had highest incidence (39.24%) and with least below 20yrs (2.53%). Ectopic pregnancies were common in primigravida/nulliparous women (72.15%) than multiparous women. Right sided ectopic was more common. Site of ectopic: most common in fallopian tube-ampullary region (78.48%) followed by cornua (5.06%), isthmus (2.53%), ovarian ectopic (3.79%), adnexal (7.59%) and 1 case (1.26%) each of scar ectopic and rudimentary horn of uterus ectopic. Total 64 cases of tubal ectopic pregnancy were identified. Histomorphological study of these cases showed Chronic salpingitis in 76.56% followed by Acute salpingitis in 15.62% and SIN in 7.81%. **Conclusion:** The incidence of ectopic pregnancies in Nulliparous women are on the rise as evident by the study. Though the recent trend in the management of ectopic pregnancy is the use of a conservative surgical or medical line of management, salpingectomy was the treatment modality which was used in the present study. Histopathological examination of the resected fallopian tubal ectopics can provide an insight into the etiopathogenesis of ectopic pregnancy. In some cases, it can also aid in the treatment modality to prevent a recurrent ectopic.

**Keywords**--ectopic pregnancy, tubal ectopic pregnancy, chronic salpingitis, salpingitis isthmica nodosa.

## **Introduction**

An ectopic pregnancy occurs when a fertilized ovum implants outside the normal uterine cavity. It is the most important cause of maternal mortality and morbidity in the first trimester. It greatly endangers the life of the woman and also her future fertility by causing damage to the fallopian tubes and/or ovary. The incidence of ectopic pregnancy has been increasing worldwide. The incidence of ectopic pregnancy in developed countries is about 19.7/1000 pregnancies and that in India is 3.12/1000 pregnancies.<sup>1</sup> Risk factors like previous ectopic pregnancy, tubal corrective surgery, tubal sterilization, intrauterine devices, documented tubal pathology, infertility, assisted reproductive techniques, PID, smoking, prior abortions, multiple sexual partners and prior delivery have been implicated in the development of the ectopic pregnancy.<sup>2,3,4</sup> A knowledge of the associated risk factors helps identify women at higher risk in order to facilitate

early and more accurate diagnosis. The most common site for ectopic pregnancy is fallopian tubes (90–95%)<sup>1</sup>. Most risk factors are associated with risks of prior damage to the Fallopian tube. These factors include any previous pelvic or abdominal surgery, and pelvic infection. Chlamydia trachomatis has been linked to 30-50% of all ectopic pregnancies.<sup>2,4</sup>

Early diagnosis reduces the risk of tubal rupture and allows more conservative medical treatments to be employed.<sup>2,5</sup> Histopathological examination of the resected fallopian tube can give an insight into the etiopathogenesis of ectopic pregnancy. This retrospective analysis was done to study the clinic-histopathological aspects of ectopic pregnancy in a tertiary care hospital; special focus was given on histomorphology of fallopian tubes in ectopic pregnancy.

## **Materials and Methods**

The present study includes all the resected specimens of ectopic pregnancy irrespective of site and location with a clinical diagnosis of ectopic gestation received in the Department of Pathology, Medical College Baroda, Gujarat. A total of 79 specimens for a retrospective period of 2.5-years from January 2019 to May 2021 were reviewed. Clinical and demographic data were noted from the case files. Specimens were fixed in 10% formalin and processed routinely. Paraffin blocks were made and 4-6 micron sections were taken. These slides were stained with haematoxylin and eosin stain. Sections were studied for the presence of chorionic villi confirming the ectopic gestation. In case of tubal ectopic pregnancy (ampullary and isthmic), the fallopian tubal wall was screened for features of acute salpingitis, chronic salpingitis, Salpingitis isthmica nodosa, and any other related pathological findings. The following histological criteria was used for classification. Chronic salpingitis (CS) was suggested by the presence of lymphocytes and plasma cells in the lamina propria, thickening of the rugae, which were adherent to one another, and atrophy, fibrosis, blunting of the plicae and loss of cilia. Salpingitis isthmica nodosa (SIN) was defined as the microscopic presence of tubal epithelium within the myosalpinx or beneath the tubal serosa on a properly embedded tissue slide.

## **Results**

A total of 79 cases of ectopic gestation during the period of 2.5 years from January 2019 to May 2021 were included in the study. Along with clinical and demographic evaluation, retrospective analysis of the histomorphology of 64 cases of tubal gestation was also done. A majority of the patients (39.24%) belonged to the age group of 20-25 years. (Table 1). In 81.01% of cases, ectopic pregnancy was tubal (64 cases out of 79) and it was more common in right side (65.82%). A majority of the cases were ampullary pregnancies (78.48%) cornual pregnancy was seen in 5.06% and 2.53% were isthmal pregnancies while 7.59% of cases were of adnexal ectopic gestation. (Table 2). In the present study, 72.15% of cases of ectopic gestation were nulliparous and 27.85 % were multigravida. (Table 3). Maximum number of cases in present study group belonged to the age group of 20-25 years with parity status as nullipara, accounting for 26 cases where as 4 cases in the age group 20-25 had parity of one. There were only 4 nulliparous cases with ectopic pregnancy in the age group of >35 years. (Table 4).

85% of patients presented with abdominal pain as the chief complaint. 31.48% of patients presented with approximately 1.5 months of amenorrhea followed by 27.78% of cases presenting with approximately 2 months of amenorrhea and 12.96% of cases with 3 months of amenorrhea (Table 5). 54% of total cases presented with ruptured ectopic pregnancy with ampullary being the most common site. Right side fallopian tube was involved more frequently than left side in the current study. Microscopic examination revealed chorionic villi in the wall of the tube confirming the ectopic gestation [Figure 1]. Chronic salpingitis was seen in 49 cases (76.56%) and it was characterized by chronic inflammatory cells in the wall along with distortion of plicae in some cases (Table 6) [Figure 2]. SIN was seen in 05 cases (7.81%). SIN presents with nodular thickening of the fallopian tube and is microscopically characterized by the presence of tubal epithelial-lined glands surrounded by hypertrophied smooth muscle cells [Figure 3]. Acute salpingitis was seen in 10 cases (15.62%) and it was characterized by presence of acute inflammatory cells in the tubal wall [Figure 4].

## Discussion

Ectopic pregnancy may occur at any age from menarche to menopause. A study by Rose et al found maximum cases in age group of 21-30 years (43%) which corroborated with the present study (68.35%).<sup>6</sup> Other studies done by Samiya Multi, et al (75.4%) Panchal D, et al (71.66%) and Rashmi also showed maximum incidence of ectopic pregnancy in age group of 20-30 years.<sup>7,8</sup> As per the study done by A Gaddagi, et al (70.2%) most of the women in India marry at an early age and completes their family at an early age. This age corresponds to the age of peak sexual activity and reproduction.<sup>9</sup> In the present study, the maximum incidence of ectopic occurred in nulliparous women (72.15%). In the study by Rose et al, as parity increases there is a decrease in the incidence of ectopic pregnancy.<sup>6</sup> Munro Kerr and Eastman are of the opinion that there is no specific relation between parity and ectopic. The findings of the present study are in contrast to the studies done by Shraddha Shetty K, et al (83.9%) and Panchal D, et al (81.66%) which showed higher incidence of ectopic pregnancy in multigravida women probably due to previous miscarriages and infection resulting in tubal damage.<sup>8,10</sup> Pelvic Inflammatory Disease (PID) is an important factor predisposing to the development of ectopic pregnancy. PID following gonococcal, chlamydial and other bacterial infection cause 3.3-6 fold increased risk of ectopic pregnancy. Levin et al demonstrate the risk of ectopic pregnancy is increased in women with history of PID.<sup>11</sup> Many cases of chlamydia salpingitis are indolent may go unrecognized causing tubal damage and subsequent tubal pregnancy. A strong association between Chlamydia infection and tubal pregnancy has been established in several studies. So, a recent change in sex life can cause pelvic inflammation and tubal damage in younger age groups causing more incidence of ectopic pregnancy in young, nulliparous or low parity women.

No specific sign or symptom can be said to be pathognomonic of ectopic gestation. The clinical picture is dependent on several factors mostly the extent of time taken for disturbance to occur in ectopic gestation. The more extensive and rapid the disturbance, the clearer is the clinical picture. Hence, undisturbed ectopic gestation is likely to be missed in majority of the cases as the clinical features are vague. 85% of patients presented with abdominal pain as the chief complaint in

the present study along with complaints of amenorrhea. 31.48% of patients presented with approximately 1.5 months of amenorrhea followed by 27.78% of cases presenting with approximately 2 months of amenorrhea and 12.96% of cases with 3 months of amenorrhea. These findings are in corroboration with other studies like Rose et al<sup>6</sup> and Pendse et al<sup>12</sup>.

Ectopic pregnancy can occur at different sites such as fallopian tubes, ovary, and abdominal cavity. The most common site is the fallopian tube (90–95%). In the present study, 81.01% of cases had tubal ectopic pregnancy and it was more common in right side (65.82%) consistent with other studies<sup>13,14</sup>. The commonest site of location of the ectopic pregnancy in the current study was in the ampulla of the fallopian tube (78.48%). Ampullary part of the tube was commonly involved in most of the ectopic pregnancies in other studies<sup>15</sup>. Fallopian tubal pregnancy often presents as an acute medical emergency due to rupture of the fallopian tube. The wall of the fallopian tube becomes thinned out due to the invasion of trophoblastic cells and chorionic villi, which in turn is due to the limited ability of the endosalpingeal stroma to undergo decidualization. Unruptured ectopics are seen as irregular sausage-like dilatations of the tube, with a bluish discoloration caused by hematosalpinx. Ectopic tubal pregnancy is the most common cause of hematosalpinx<sup>16</sup>. In the present study 54% of total cases had presented with features of ruptured ectopic.

Chronic salpingitis due to chronic PID has been documented as one of the most important risk factors in the development of ectopic pregnancy. It is said that major proportion of salpingitis is the result of PID caused commonly by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The incidence of chronic salpingitis in fallopian tubal pregnancy has been variable (29–88%)<sup>3,16</sup>. Dubuisson<sup>17</sup> and Green<sup>16</sup> have reported a high incidence of chronic salpingitis of 89% and 88% in ectopic pregnancies, respectively. Microscopically, chronic salpingitis shows lymphocytes and plasma cells in the mucosa with or without plica distortion/adhesions. Tubal scarring and fibrous adhesions may also be noted. Sometimes, when it involves the fimbriae, due to the proximity of the ovary to it, tubo-ovarian adhesions can form. In chlamydial salpingitis, repeated episodes of inflammation are associated with accumulation of CD8 T-cells and tubal scarring. The current study showed the features of chronic salpingitis in 76.56% (49 out of 64) of cases.

One of the other causes for chronic salpingitis, especially in India, is genital TB. In India, the incidence of genital TB in patients undergoing surgery for acute ectopic pregnancy was as high as 35.29-40%<sup>18</sup>. TB is characterized by granulomatous inflammation. The earliest microscopic lesions are mucosal with the extension of granulomas into the muscularis and serosa. As the tubercles enlarge, they erode through the mucosa and discharge contents into the lumen. The mucosal inflammation leads to progressive scarring with plica distortion<sup>1</sup>. Even if tubercles are not present in the given sections, the presence of caseation, fibrosis, or calcification in a fallopian tube necessitates a more thorough study to rule out TB. The complications of tuberculous salpingitis are several. Alteration of tubal function and bilaterality of the disease lead to sterility. Since ectopic pregnancy is one of the most serious complications of PID, the identification of features of chronic salpingitis with subsequent treatment reduces the risk of a

recurrent ectopic. Hence, it is important to thoroughly examine the fallopian tube to identify the features of chronic salpingitis in all resected tubal ectopic specimens.

SIN is often bilateral, usually seen as a result of post inflammatory distortion of the fallopian tube with diverticula of tubal epithelium into the muscular layer<sup>1,3</sup>. Inflammatory tubal disease may be associated with SIN ipsilaterally or contralaterally. Grossly, it is characterized by one or more nodular swellings in the isthmus of the fallopian tube<sup>1</sup>. SIN is seen to occur in about 10–43% of tubal ectopics.<sup>3,16,19</sup> SIN was seen to be concomitant with chronic salpingitis in some studies<sup>3</sup>. In another study, SIN was noted in 7.4% of infertile women with tubal obstruction and 10% of women with ectopic tubal pregnancy. In the same study, SIN was present in both the tubes in 60% cases<sup>19</sup>. Several retrospective studies have demonstrated an association between SIN and other infectious lesions<sup>16,17</sup> Skibsted *et al.*, in their study of SIN in Danish women, concluded that women with SIN had a greater risk of tubal pregnancies as compared to women without SIN<sup>20</sup>. The most serious clinical and pathological complications of SIN are infertility and a strong association with ectopic pregnancy<sup>1,16</sup>. We came across 05 cases (7.81%) of SIN in this study. Acute salpingitis was diagnosed in 15.62% of cases (10 out of 64) and it was considered directly related to the presence of ovum implantation.

## **Conclusion**

The incidence of ectopic pregnancies in Nulliparous women are on the rise as evident by the study. Though the recent trend in the management of ectopic pregnancy is the use of a conservative surgical or medical line of management, salpingectomy was the treatment modality which was used in the present study. In conclusion, our results suggest that chronic salpingitis and SIN are of important role in the etiology of ectopic pregnancy and SIN is significantly associated with chronic tubal pathologies. Histopathological examination of the resected fallopian tubal ectopics can provide an insight into the etiopathogenesis of ectopic pregnancy. In some cases, it can also aid in the treatment modality to prevent a recurrent ectopic.

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None

## **Conflicts of interest**

There are no conflicts of interest.

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## Figures

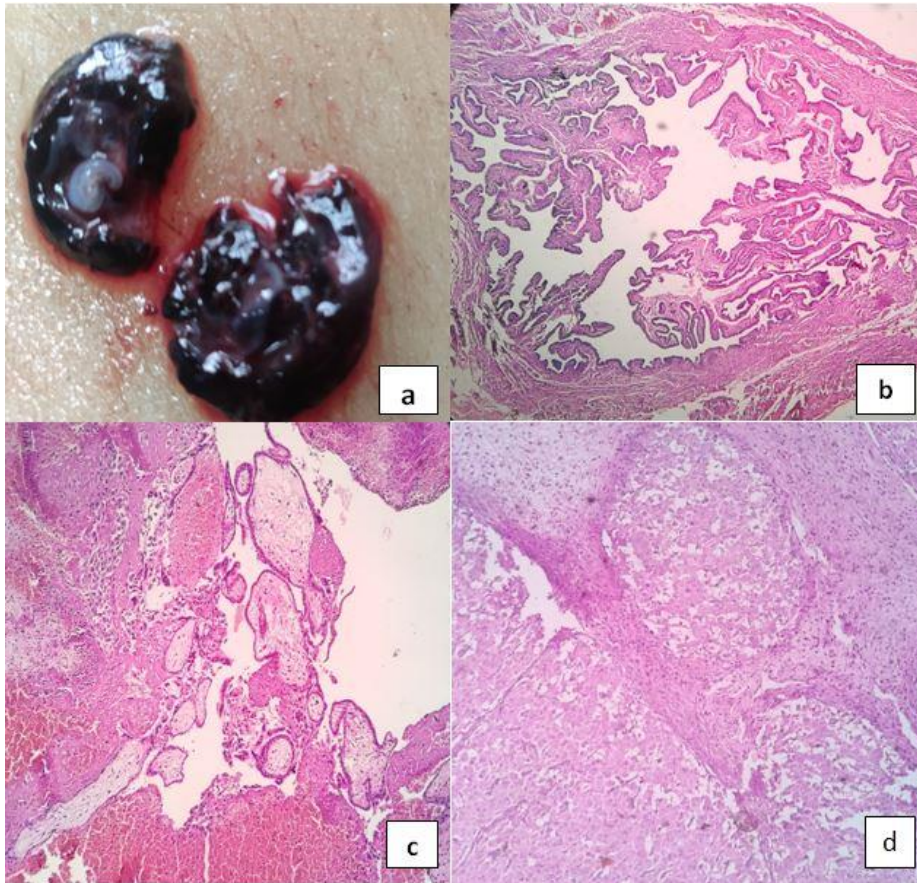


Figure 1: a) Gross specimen of a tubal mass showing hemorrhagic cut surface along with fetal parts signifying ectopic pregnancy; b) Lining epithelium of fallopian tube (Hematoxylin and Eosin x100); c and d) Chorionic villi and trophoblasts are seen along with hemorrhagic areas which confirms the diagnosis of tubal ectopic pregnancy. (Hematoxylin and Eosin x100)

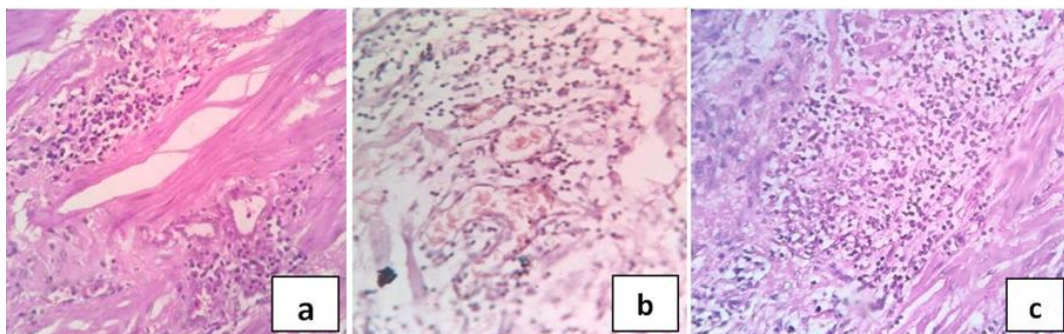


Figure 2. a, b and c) Sections from a case of tubal ectopic pregnancy showing presence of dense lymphocytic population which confirms the changes of Chronic Salpingitis. (Hematoxylin and Eosin x400)

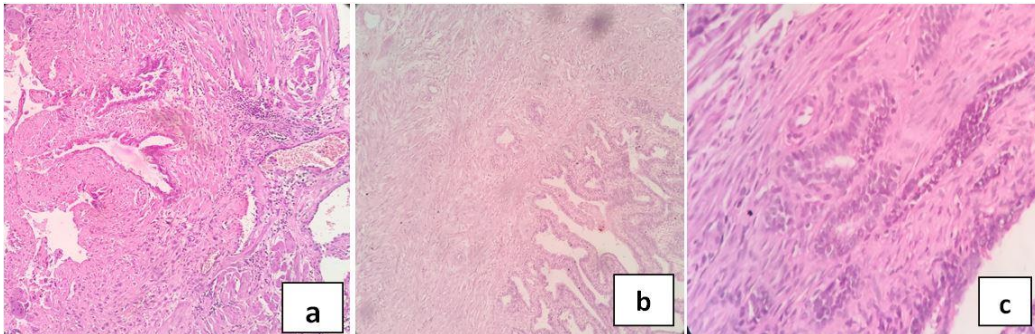


Figure 3. a, b and c) Sections from a case of tubal ectopic pregnancy showing presence of tubal epithelial-lined glands surrounded by hypertrophied smooth muscle cells confirming diagnosis of Salpingitis Isthmica Nodosa (SIN) (a,b: Hematoxylin and Eosin x100; c: Hematoxylin and Eosin x400)

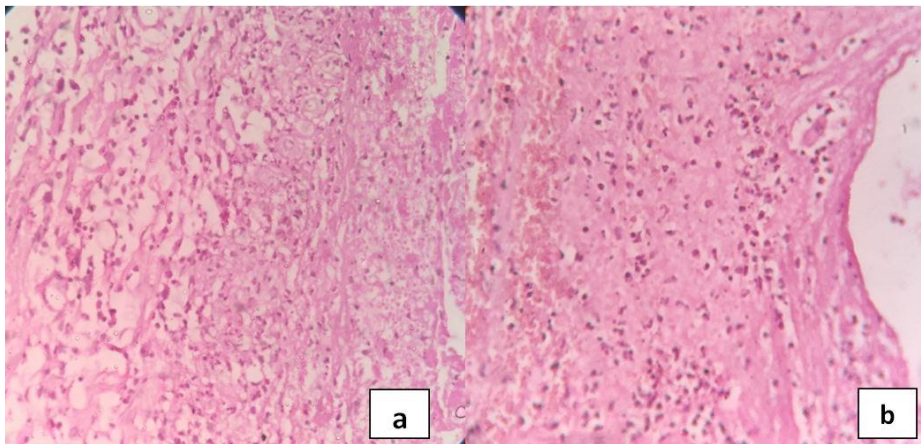


Figure 4. a and b) Sections from a case of tubal ectopic pregnancy showing presence of abundant neutrophils which confirms the changes of Acute Salpingitis. (Hematoxylin and Eosin x400)

## Tables

Age (years)	Number	Percentage
<20	2	2.53%
20-25	31	39.24%
26-30	23	29.11%
31-35	16	20.25%
>35	7	8.86%

Table 2  
Site of ectopic pregnancy

Site of ectopic	Number	Percentage
Ampulla	62	78.48%
Cornual	4	5.06%
Isthmus	2	2.53%
Ovarian	3	3.79%
Adnexal	6	7.59%
Scar ectopic	1	1.26%
Rudimentary	1	1.26%

Table 3  
Distribution of cases based on Parity

Parity	Number	Percentage
Nulliparous	57	72.15%
1	10	12.66%
2	8	10.13%
3	4	5.06%

Table 4  
Correlation of sample by age and parity

Age (years)	Nullipara	1	2	3	Total
<20	2(100%)	0	0	0	2
20-25	26(83.87%)	4(12.9%)	1(3.22%)	0	31
26-30	12(52.17%)	5(21.74%)	4(17.39%)	2(8.69%)	23
31-35	13(81.25%)	1(6.25%)	1(6.25%)	1(6.25%)	16
>35	4(57.14%)	0	2(28.57%)	1(14.28%)	7

Table 5  
Distribution of cases according to period of amenorrhea

Period of Amenorrhea(months)	Number	Percentage
0.5 (2 weeks)	5	9.25%
1	6	11.11%
1.5	17	31.48%
2	15	27.78%
2.5	2	3.70%
3	7	12.96%
>3	2	3.70%
	Total: 54	

Table 6 Distribution of cases according to histomorphological finding in fallopian tube in tubal ectopic pregnancy		
Histomorphological feature of Fallopian tube	Number	Percentage
Acute Salpingitis	10	15.62%
Chronic Salpingitis	49	76.56%
Salpingitis Isthmica Nodosa	05	7.81%