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Unexplained infertility; How far laparoscopy can disclose the causes

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Abstract
Background: Unexplained Infertility is a complex medical disorder that requires the evaluation and treatment of a couple rather than an individual in which the three standard fertility screening tests looking normal.
Objective: To identify the underlying causes of infertility in women suffering from unexplained infertility via using laparoscopy.
Patients and Method: A prospective clinical observation study conducted at Al-Elwyia Maternity Teaching hospital at Obstetrics and Gynecology department during the period from the first of February 2019 to the first of August 2019.
Results: Fifty women with unexplained infertility were included in the study, their main age group (46.0%) were between (25-29) years and (70.0%) of them are with primary infertility. Their mean duration of infertility was 55± 29 (months). (98%) were presented with patent tubes and only one (2.0%) patient showed one blocked tube by hysterosalpingography. Evidence of pelvic pathology was seen in (76.0%) of the patients and endometriosis constituted about (68.4%) of pelvic pathology while simple peri tubal adhesion was found in12/38 patients (31.6%).
Conclusion: The main pathology seen in women with unexplained infertility was pelvic endometriosis in 26/38 patients, followed by simple peri tubal adhesion.

Keywords: Unexplained infertility, laparoscopy, peri tubal adhesion, pelvic endometriosis

Introduction
Unexplained infertility is a complex medical disorder that requires the evaluation and treatment of a couple rather than an individual. Infertility is defined as failure to conceive after regular unprotected sexual intercourse for one year [1]. If the female partner is 35 year of age or older, evaluation should be initiated after 6 months of unprotected intercourse. Fecundability, or the ability to achieve pregnancy in one menstrual cycle, is a more accurate measurement to evaluate fertility potential. The fecundity rate in a normal couple who has had unprotected intercourse is approximately 20% to 25% for the first 3 months, followed by 15% during the next 9 months [2].

Prevalence
The prevalence of infertility in the general population is approximately 14%, affecting about 1 in 7 couples. Causes of infertility include ovulatory disorders, tubal damage, male factors, and uterine or peritoneal problems. Traditionally, after excluding common causes of infertility using standard fertility tests, which include semen analysis, assessment of ovulation, and tubal patency testing. These tests have been selected as standard fertility tests because they were found to have definitive correlation with pregnancy [3].
The diagnosis of unexplained infertility is made when a cause is not identified after the completion of standard fertility investigations. It accounts for nearly 40%of female infertility and 8% to 28%of infertility in couples. The reported incidence of unexplained infertility varies according to the age and selection criteria in the study population [4]. Many couples with a provisional diagnosis of unexplained infertility will subsequently conceive spontaneously; the spontaneous pregnancy rate in couples with unexplained infertility has been reported as 2%to 4% per menstrual cycle. Women's age is the most important prognostic factor for successful spontaneous conception with lower conception rates after the age of 30 years. After 12 months of unsuccessful attempts, 50% will conceive in the following 12 months and another 12% after 24 months. (Box1) [3, 4].

Box 1: Causes of female unexplained infertility.

- Endometriosis
- Undiagnosed tubal factor
- Premature ovarian aging
- Immune infertility
- Oxidative stress
- Poor oocyte quality
- Uterine cavity abnormalities:
  - Endometrial synechiae
  - Endometrial polyps
  - Chronic endometritis

Laparoscopy

Laparoscopy is a minimally invasive surgical technique that provides a panoramic and magnified view of the pelvic organs and peritoneal surfaces and allows surgery at the time of diagnosis [5]. Historically, only diagnostic procedures were performed with the laparoscope. In the last decade, use of the laparoscope has expanded. Now various reproductive disorders are diagnosed and treated primarily with the laparoscope including pelvic adhesions, endometriosis, and disorders of the fallopian tubes. In response to the significant advances in endoscopy, today's gynecologic surgeons can integrate operative laparoscopy into daily practice and in many situations. Infertility is a major health issue with multifactorial etiology. None of the laboratory findings alone is sufficient in diagnosing infertility. Laparoscopy provides important and essential information helpful in the investigation and management of infertility [6].

Laparoscopy is generally regarded as the most reliable tool in the diagnosis of tubal pathology and other intra-abdominal causes of infertility. Where there is no suggestive clinical signs and symptoms, laparoscopy offers an excellent means through direct visualization. Diagnostic laparoscopy (DLS) is generally accepted as the most accurate procedure to detect tubal pathology and endometriosis but it is still a matter of debate whether laparoscopy should be routinely done in the infertility work-up. There are several noninvasive and cost-effective tools to evaluate or predict tubal pathology. Several studies describe the accuracy of Chlamydia antibody testing (CAT) and hysterosalpingography (HSG) with diagnostic laparoscopy as gold standard but alone no one tool is conclusive. (6) Hysterosalpingography has been classically used for decades for the evaluation of tubo-peritoneal infertility. Based on symptoms suggestive of previous pelvic inflammatory disease (PID), a history of abnormal vaginal discharge and a previous diagnosis of a lower genital tract infection, the positive predictive value of thorough history taking, was only 56%, 59%, and 35%, respectively, in predicting tubo-peritoneal infertility in several studies [7].

Laparoscopy still reveals tubal pathology or endometriosis in 35-68% of cases, even after normal HSG and in patients with no suggestive history. Many women with pelvic endometriosis however are asymptomatic. Lack of satisfactory non-invasive tests for endometriosis has made laparoscopy the gold standard for diagnosis. Laparoscopy also has therapeutic role in endometriosis [8].

The Role of Laparoscopy in the Infertility Evaluation

The role of laparoscopy in the investigation of infertility has changed over the past decade. Whereas laparoscopy used to be part of the basic infertility workup, it is now reserved for selected cases. Given that it allows direct visual examination of the pelvic reproductive anatomy, it is the test of choice to identify otherwise unrecognized peritoneal factors that influence fertility, specifically endometriosis and pelvic adhesions. According to the guidelines of the ASRM, laparoscopy should be performed in women with unexplained infertility or signs and symptoms of endometriosis or in whom reversible adhesive tubal disease is suspected [9]. However, the role of laparoscopy as a standard approach to the management of infertility remains controversial for several reasons. Although women with infertility have an increased prevalence of endometriosis (estimated at greater than 30%), it is difficult to predict which patients are likely to benefit from surgery. Furthermore, prospective randomized studies exploring the effects of surgically corrected endometriosis on fecundity have been limited, are sometimes contradictory, and at best have demonstrated a modest effect. Modern fertility treatments, especially in vitro fertilization (IVF), result in marked improvements in fecundity; it is unclear whether these treatments are compromised by unrecognized endometriosis. Consequently, patients increasingly forego surgery, particularly if they are otherwise asymptomatic and their initial diagnostic studies (i.e., hysterosalpingogram) are normal. Theoretically, there are potential benefits to routinely performing laparoscopy in infertile women [10].

First, it is possible to avoid fertility treatments and their direct as well as indirect financial and social costs such as multiple gestation pregnancy.

Second, intraoperative findings that include Multiple red spots of endometriotic lesion, whit scaring inflammation in the Pouch of Douglas and uterosacral ligament, brown black lesion on the ovarian surface, ovarian endometriomas, Pelvic and Peritubal adhesion can guide postsurgical management, circumventing treatments that are of low benefit and costly.

Third, surgically correcting endometriosis may enhance response to fertility treatments or mitigate the effects of comorbidities such as pelvic pain [10]. The complexity of deciding if and when laparoscopy should be performed to diagnose and treat endometriosis among infertile women is highlighted by an opinion from the Practice Committee of the American Society of Reproductive Medicine: ‘‘the treatment of endometriosis. Raises a number of complex clinical questions that do not have simple answers. There are few infertility problems requiring greater clinical acumen.’’ The committee suggests, ‘‘Laparoscopy should be seriously considered before applying aggressive empirical treatments involving significant cost and/or potential risks’’ [11].

The benefits of laparoscopy

- More accurate diagnosis.
- No stitches.
- Therapeutic benefit
- Shorter recovery time
- Fewer post-op complications less scarring.

Aim of the study: To identify the underlying causes of infertility in women suffering from unexplained infertility via using laparoscopy.

Patients and method

Study design and setting: An observation study conducted at Al-Elwyia Maternity Teaching hospital at Obstetrics and Gynecology department during the period from the first of February 2019 to the first of August 2019. Patients included in the study were diagnosed to have unexplained infertility (normal

ovulation, patent tubes, normal seminal fluid analysis) according to their medical reports and previous assessment by the supervisor of the current study, who is a consultant gynecologist. On admission, further assessment of the patient was done by full history taken and examination. The questionnaire paper included the following data: age, type and duration of infertility, menstrual patterns, presence of dyspareunia, dysmenorrhea, and other pelvic pain, and their past medical or past surgical history, current medication regime. Examination was concentrated on endocrinological evidence of abnormality i.e hirsutism, acne, body weight (obesity), galactorrhea, thyroid gland assessment for presence of any swelling or mass. A verbal and written consents was taken from the participants after explain the idea of the research.

Inclusion criteria: Patients with unexplained infertility Normal ovulation, normal hysterosalpingography or at least one patent tube, and normal seminal fluid analysis

Exclusion criteria: Presence of identify cause of infertility Evidence of PCOS or other endocrine disease (thyroid disease), male factor infertile, and abnormal hysterosalpingography i.e (blocked tubes) The patients then subjected to diagnostic laparoscopy to identify the underlying causes of their problem during follicular phase of cycle.

Intra operative finding: Using laparoscopy (storz) set up under general anesthesia, using modified semi lithotomy position, under aseptic technique port entry using umbilical region for main camera and two secondary port at midline suprapubic and right mid-clavicular line, inflation of the abdominal cavity by using CO2 up to 15 mmHg, pelvic cavity then visualization for any pathology i.e features of endometriosis, pelvic or peri tubal adhesion. Some cases normal pelvic were seen. Dye test using methelin blue to visualized tubes patency and the ovaries were assessed for any pathology. The finding was compared with hysterosalpingography and then reported on the questionnaire formula.

Statistical analysis: All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 21 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables and t-test was used to compare between two means. One way ANOVA analysis was used to compare between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

Results

Table 1 show that there is a significant difference were found between age of patients and duration regarding the type of infertility ($P<0.05$)

Table 1: Duration of age and Infertility according to type.

	Primary (n=35)	**Secondary n=(15)**	**P value**
	Mean±SD	Mean±SD	
Age	27± 4	30±5	0.02
Duration (Mean±SD)/ Years	5.0±2.7	3.6±1.1	0.05

Table 2 show that by using the Hystrosalpingography we found that 97.1%) of the primary infertility were with patent tubes and all secondary infertility 15 (100.0%) present with patent tubes and only 1 (2,9%) of primary infertility presented with block tube.

Table 2: Hystrosalpingography of the tube according to type of infertility

Variable		**Type of infertility**			
		Primary		Secondary	
		No.	%	No.	%
Hystero-salpingography	Patent tubes	34	97.1	15	100
	Block tube	1	2.9	0	0

Laparoscopic finding of the patients shows that, abnormal pelvic were found in 38 (76.0%) of the patients and 12 (24.0%) of the patients present with normal pelvic. Endometriosis were found in 26/38 (68.4%) of patients with abnormal pelvis when minimal found in 9/26 (34.6%) of the patients while 11/26 (42.3%) were with mild endometriosis, moderate endometriosis in 4/26 (15.4%), and sever in 2/26 (7.7%). Adhesion was found in 12/38 patients (31.6%), when 8/12 (66.7%) unilateral and 4/12 (33.3%) were bilateral adhesion. For tubal patency, it was found that 45 (90.0%) were present with bilateral patency and only 5 (10.0%) were unilateral (table 3).

Table 3: Laparoscopic finding of the studied group

Laparoscopic finding		**No.**	**%**
Pelvic	Normal	12	24.0
	Abnormal	38	76.0
Total		50	100.0
Endometriosis (n=26)	Minimal	9	34.6
	Mild	11	42.3
	Moderate	4	15.4
	Sever	2	7.7
Total		26	100.0
Peritubal adhesions (n=12)	Unilateral	8	66.7
	Bilateral	4	33.3
Total		12	100.0
No adhesion		38	76.0
Tubal patency	Unilateral	5	10.0
	Bilateral patent	45	90.0
Total		50	100.0

For the relation between laparoscopic finding and type of infertility, it was found that there is no significant association between normal pelvic, endometriosis, peritubal adhesion, and Tubal patency with type of infertility (table 4).

Table 4: Association between laparoscopic finding and type of infertility

Laparoscopic finding		**Type of infertility**				**P value**
		Primary (n=35)		**Secondary (n=15)**		
		No.	%	No.	%	
normal pelvic	Normal	9	75.0	3	25.0	0.6 Ns
	Abnormal	26	68.4	12	31.6	
Peritubal adhesion (n=12)	Unilateral	6	75.0	2	25.0	0.1 Ns
	Bilateral	1	25.0	3	75.0	
No adhesion		28	63.0	10	37.0	
Endometriosis (n=26)	Minimal	6	66.7	3	33.3	0.1 Ns
	Mild	9	81.8	2	18.2	
	Moderate	3	75.0	1	25.0	
	Sever	0	-	2	100.0	
Tubal patency	Unilateral	2	40.0	3	60.0	0.3 Ns
	Bilateral	33	73.3	12	26.7	

Discussion

Laparoscopy is considered as a gold standard in the diagnosis of endometriosis and should be offered to couples with UI prior to embarking on assisted reproductive techniques. Women diagnosed with mild endometriosis may be offered surgical removal of the endometriosis and this approach has been reported to improve postoperative pregnancies. The mean duration of the infertility was found to be (55± 29 months=4.6±2.4 years) which is in agreement with Kanda Y, *et al* study that reported the mean duration of infertility was (5.0 ± 2.67) years [12]. Tubal disease is an important cause of infertility and should be specifically excluded. The methods for evaluating tubal patency are complementary and not mutually exclusive [13]. The current study shows that abnormal pathology in (76%) were found in women with unexplained infertility that underwent laparoscopy. Laparoscopy is extremely useful in decision making while dealing with infertility of prolonged duration and older women. In a retrospective study of 495 infertile women with unexplained infertility, laparoscopy before starting treatment revealed a significant incidence of abnormalities resulting a changed in decision. Similarly, when patients with unexplained infertility following standard infertility screening tests underwent diagnostic laparoscopy, 21-68% of these patients were found to have pathologic abnormalities which included endometriosis and tubal disease. [14].

Meuleman C *et al*, reported that endometriosis is found in 4.5%-82.0% of women with chronic pelvic pain, and in 2.1%-78.0% of infertile women [15]. The current study showed that pelvic pathology by laparoscopy were found in 76% of the studied group. Which is in agreement with that mentioned by Tsuji I *et al*, which reported the pelvic pathology was present in (80.7%). [16].

Sebastião F *et al*, reported that endometriosis was found in 181 (76.4) of the infertile patients [17]. In Begum J, study found that pelvic pathology by laparoscopy was confirmed in 54.5% of cases, moreover he found tubal block was the most common pathology (40%), followed by pelvic inflammatory disease (18.5%). Ovarian pathology comprised 8.1% whereas pelvic endometriosis 4.4% and distorted uterus was also 4.4% of infertile cases diagnosed by laparoscopy [18]. While in our study the most common finding was endometriosis, when 26/38 of the patients with unexplained infertility (primary or secondary) then simple peritubal adhesion in 12/38 Tubal and peritoneal pathology account for the primary diagnosis in approximately 30 to 35% of infertile couples [19]. The gold standard technique for diagnosing these disorders is laparoscopy, which is a better predictor of future spontaneous pregnancy in infertile couples with unexplained infertility [20]. Jayakrishnan *et al*., [19] from India detected pelvic pathology in 26.8% cases of infertile patients by laparoscopic evaluation. In addition, endometriosis and adnexal adhesions were the two major abnormalities found among infertile patients in different studies similar to our findings [21]. In contrast to the Study by Godinjak *et al*., [20] the prevalence of adhesions found in the current study is consistent with the prevalence of 5.5%- 41.0% reported by others studies [21, 22]. In previous studies, diagnostic laparoscopy was done for unexplained infertility shown that pathologic abnormalities found in 75%-80% of the infertile patients, in which endometriosis was identified in 30%-80% of the cases and peritubal adhesions were recognized in 29%-41% of the patients. [23] There are no significant differences were found regarding the relation between laparoscopic findings and type of infertility, which is same that revealed by Begum J, in his study that included 135 patients using combined hysterolaparoscopy to evaluate female infertility [18].

Our results at laparoscopy and hystrosalpingography had shown bilateral tubal patency in 49 (98%), and unilateral tubal block in 1 (2%) of infertile patients. In one study at laparoscopy, carried by Godinjak Z, found that bilateral tubal patency was demonstrated in 86.67%, bilateral tubal block in 5% and unilateral block in 8.33% of patients [20]. Nayak KP *et al*. got nearly equal prevalence of tubal block in primary infertility patients (40.9%) and secondary infertility patients (38.2%) [23].

Conclusion

The main pathology seen in women with unexplained infertility was pelvic endometriosis followed by simple peritubal adhesion.

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