Is hysterolaparoscopy a real theranostic approach for anatomical barriers in female fertility? A future argument

Namita Agrawal*, Poonam Yadav, S. Fayyaz, Brinderjeet Kaur

Department of Obstetrics and Gynecology, Santokba Durlabhji Memorial Hospital and Research Centre (SDMH), Jaipur Rajasthan, India

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*Correspondence:
Dr. Namita Agrawal,
E-mail: namitaagarwalsms@gmail.com

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ABSTRACT
Background: Hysterolaparoscopy is a modality that provides the real time abdomino-pelvic view during diagnosis in infertile female patients and any pathology is noticed can be tackled at the same time. So we investigate the theranostic application of hysterolaparoscopy in structural causes of female infertility in present study.

Methods: Authors prospectively evaluate 157 female patients (mean age 27.7 years) diagnosed as infertile, underwent hysterolaparoscopy during diagnostic work-up. All the enlisted patients fulfilled the criteria of infertility. The noticed anatomical abnormalities in the hysterolaparoscopy were tackled at the same time if possible.

Results: Of the 157 infertile female patients, 93 (~59.2%) were of primary infertility and remaining 64 (~41.8%) were secondary infertility patients. Hysterolaparoscopy showed abnormalities in 125/157 (~85.0%) patients. The detected hysterolaparoscopic abnormalities were distributed in 77/93 (~82.8%) primary and 48/64 (~75.0%) secondary infertility patients. Of the 125 patients with abnormal hysterolaparoscopic findings, 121 (~96.8%) experienced for active therapeutic interventions. All of the 48 secondary infertility patients with hysterolaparoscopic abnormalities experienced for active hysterolaparoscopic interventions. Of 77 patients with hysterolaparoscopic abnormality in primary infertility group, 73 (~94.8%) experienced active intervention. Only four patients with streak ovaries and hypoplastic uterus, few tiny fibroids and adenomyosis did not undergo for active hysterolaparoscopic intervention.

Conclusions: Authors concluded that hysterolaparoscopy has a better theranostic approach for the anatomical barriers of female fertility so it can be performed in the initial phases of the infertility diagnostic work-up.

Keywords: Anatomical barriers, Female fertility, Hysterolaparoscopy, Theranostic

INTRODUCTION
The future of medicine is found in the personalised medicine’ (PM), that’s aim is to deliver the right treatment at the right time to the right patient.1,2 So the concept of “theranostics” was coined to define ongoing efforts in clinics to develop more specific, individualized therapies for various diseases, and to combine diagnostic and therapeutic capabilities into a single agent/modality.3 The rationale of the theranostic arises from the fact that diseases are immensely heterogeneous and existing treatments are effective only for limited patient subpopulations. Theranostics cover a wide range of topics, which includes predictive medicine, personalized medicine, integrated medicine, and pharmacodiagnosics.3-5 The fertility is classified in various ways and it can be classified on anatomical and functional basis. For female infertile patient’s, various abdomino-pelvic anatomical causes are responsible for infertility. The common anatomical causes of female infertility are ovarian cyst/tumor (lead to ovulation dysfunction), tubal damage, endometriosis, and
congenital (septate uterus) /acquired (myomas and synechiae) uterine anomalies. In the anatomical causes, surgical intervention plays a significant role to improve the fertility outcome. Most of abdomino-pelvic pathologies are required specific treatments to the individualized pathologies. The endoscopic methods such as, laparoscopy and hysteroscopy are commonly used in an evaluation of infertility and pelvic pain. Laparoscopy is a method of direct visualization of abdomen, pelvis and pelvic genital organs (ovaries, fallopian tubes, and uterus). Another endoscopic method, hysteroscopy is used for direct visualization of uterine cavity and bilateral ostea. It also makes identification and correct localization of the possible intrauterine pathologies reasonably easier. These endoscopic methods have capabilities to diagnose and to tackle the abdominopelvic pathologies simultaneously at the same sitting. So authors want to investigate its theranostic application and effectiveness in infertile woman.

**METHODS**

The present study was prospective analytic study and carried out between March 2016 to May 2017 at the Department of Obstetrics and Gynaecology at Santokba Durlabhji Memorial Hospital, Jaipur (Tertiary Care Centre).

**Inclusion criteria**

- Infertile female patients with age 19-35years.
- Regular and irregular menstrual cycle,
- Couple, who did not conceive even after at least one-year of unprotected regular sexual intercourse
- Normal partner semenogram
- Investigations
- Hemoglobin, complete blood count (CBC), Erythrocyte sedimentation rate (ESR), Random blood sugar, thyroid function test- within normal limit
- Ovulatory function, husband semen analysis, hormonal profile (TSH/FSH/LH/Prolactin) and APLA (anti phosphor lipid antibody) levels (if available and only in secondary infertility) - within normal limit.

**Exclusion criteria**

- Age <19year; >35 year
- Abnormal husband Semen analysis
- Abnormal Hormonal profile
- Active genitourinary infection
- Any treatment, chronic illness and MPA (Medroxy progesterone acetate) contraception that imparts a negative effect on fertility.

Infertile female patients, age between 19-35 years were registered to participate in the study after taking the informed and written consent. After detailed history (together as well as separately) and clinical examination (general, systemic and gynecological examination), routine investigations were performed. Pelvic ultrasonography findings were recorded in all enlisted patients. After considering the exclusion criteria and contraindications of the operative procedure, hysteroscopy and laparoscopy were concurrently performed at SDMH, Jaipur, Rajasthan. The uterus, anterior and posterior cul-de-sacs, fallopian tubes, ovaries, ovarian fossae, pelvic peritoneum, appendix and liver surface were examined during the procedure, if some abnormalities were seen and it was noted down as shown in Table 1 and 2. Chromopertubation (CPT) was performed in all cases.

| Ovarian Findings | Normal | Cystic (Single, polycystic and chocolate cyst) | Adhesions | Endometriotic | Streak |
|------------------|--------|-----------------------------------------------|-----------|---------------|-------|
| Fallopian Tube Findings | Healthy and mobile | Dilated and tortuous | Adherent | Endometriotic patches | Hidden fimbrial end |
| Uterine Findings | Normal | Bulky (Fibroid and adenomyosis) | Endometriotic patches | Tubercle or white patches | Adherent | Hypoplastic or distorted shape | Acutely retroversion |
| Adhesions | Absent | Flimsy adhesions | Dense adhesions |
| Fluid in POD | No fluid | Clear fluid | Hemorrhagic fluid | Caseous material |

Therapeutic interventions were performed at the same sitting, if required. These included ovarian drilling, adhesiolysis, ablation of endometriotic spots, cystectomy, synechiolysis, septum resection, polypectomy and cannulation. After offering the successful treatment, Patient’s were advised for regular sexual activity.
Approval of the institutional ethical committee was obtained for this prospective study. In view of the prospective study design, written informed consent was obtained.

Table 2: Categorization of findings of hysteroscopy and CPT (Chromopertubation) in infertility patients.

| Hysteroscopic findings | Uterine cavity | Small size | Hypertrophied endometrium | Septum (Complete or incomplete) | Polyp or fibroid | Tubercle or white patches |
|------------------------|----------------|------------|---------------------------|---------------------------------|-----------------|--------------------------|
| Both ostal end         | Well visualized| Not visualized| Stenosis                  | Osteal webbing                  |                 |                          |
| Cervix                 | Normal         | Abnormal    |                           |                                 |                 |                          |
| External os and internal os | Normal      | Abnormal    |                           |                                 |                 |                          |
| CPT findings           |                |            |                           |                                 |                 |                          |
| CPT findings of fallopian tubes | Bilateral spill present | Unilateral blockage | Bilateral blockage | | |

Statistical analysis

All enlisted patients were divided into two subgroups, primary and secondary infertility and the detected pathologies and treatment in each group during the hysterolaparoscopic procedure were noted. The analysis between the two groups and continuous variables were summarized as mean and standard deviation, whereas nominal/categorical variables were summarized as proportions. Parametric tests [Student t test] were used for analysis of continuous variables while Chi-square was used for nominal/ categorical variables. ‘p’ value <0.05 was considered as significant. IBM-SPSS version 22.0 software was used for all statistical analysis.

RESULTS

157 female patients with the complained of infertility were included in the present study. The mean age of patients was 27.7 years (range of 19-35years).

All enlisted patients fulfilled the inclusion criteria of the present study. On the basis of obstetric history, patients were divided in primary and secondary infertility. The characteristics of all patients are given in Table 3.

After the detail history, clinical examination and biochemical evaluation, all patients underwent the pelvic ultrasound. The abnormities detected in the USG of primary and secondary infertile patients were noted down.

Hysterolaparoscopic findings (diagnostic)

After the initial evaluation, all patients underwent hysterolaparoscopy. Out of 157 patients, abnormalities were detected in 125/157 (79.6%) patients during Hysterolaparoscopy and underwent various therapeutic interventions according to the detected abnormalities.

Independently the abnormalities detected in the primary and secondary infertile are tabulated in Table 2 and 3.

Table 3: Characteristics of infertility patients (Age, BMI).

| Infertility (Total number of patients) | 157 |
|---------------------------------------|-----|
| Age (In years)                        | Mean±standard deviation 27.72±3.82 |
| BMI (Kg/M²)                           | Mean±standard deviation 21.80±3.03 |
| Primary infertility (Number of patients) | 93/157 (59.2%) |
| Age (In years)                        | Mean±standard deviation 26.59±3.23 |
| BMI (Kg/M²)                           | Mean±standard deviation 21.8±2.62 |
| Secondary infertility (Number of patients) | 64/157 |
| Age (In years)                        | Mean±standard deviation 29.35±4.04 |
| BMI (Kg/M²)                           | Mean±standard deviation 21.7±2.62 |

There was no statistically significant difference between primary and secondary infertile patients for the laproscopic abnormalities (p=0.404).

While, the hysteroscopic abnormalities in primary infertile patients were significantly higher (p<0.05) from the secondary infertile patients. These abnormal findings in the laparoscopy and hysterectomy are summarized in Table 4 and 5 respectively.
Table 4: Summary of the abnormalities detected in the laparoscopic examination in primary and secondary infertility patients.

| Laparoscopic organ abnormality | Primary infertility | Secondary infertility | Sub-categorization of abnormalities | Primary infertility | Secondary infertility |
|-------------------------------|---------------------|-----------------------|------------------------------------|---------------------|-----------------------|
| Ovarian abnormalities         | 54/93 (58.4%)       | 24/64 (37.5%)         | Cystic abnormality (Polycystic, single cystic) | 38/54 (70.4%)       | 18/24 (75%)           |
| Adherent                      | 9                   | 5                     | Endometriotic                      | 6                   | 1                     |
| Streak                        | 1                   | 0                     |                                    |                     |                       |
| Fallopian tube abnormalities  | 20/93 (21.5%)       | 14/64 (21.8%)         | Adherent                           | 10/20 (50%)         | 9/14 (64.3%)          |
| Dilated and tortuous          | 8                   | 2                     | Endometriotic patches              | 1                   | 1                     |
| Hidden fimbrial end           | 1                   | 2                     |                                    |                     |                       |
| Uterine abnormalities         | 20/93 (21.5%)       | 10/64 (15.6%)         | Bulky uterus                       | 7/20 (35%)          | 4/10 (40%)            |
| Fibroid / adenomyosis         | 3                   | 2                     | Endometriotic patches              | 3                   | 2                     |
| Tubercle                      | 4                   | 0                     |                                    |                     |                       |
| Adherent and congested       | 3                   | 2                     | Hypoplasty uterus                  | 2                   | 0                     |
| Acutely retroverted uterus    | 1                   | 2                     |                                    |                     |                       |
| Adhesions                     | 20/93 (21.5%)       | 17/64 (26.6%)         | Flimsy adhesions                   | 9/20 (45%)          | 12/17 (70.6%)         |
| Dense adhesions               | 11/20 (55%)         | 5/17 (29.4%)          |                                    |                     |                       |
| POD abnormalities             | 33/93 (35.5%)       | 15/64 (23.4%)         | Clear fluid                        | 22/33 (66.7%)       | 12/15 (80%)           |
| Hemorrhagic fluid             | 8                   | 1                     |                                    |                     |                       |
| Caseous material              | 3                   | 2                     |                                    |                     |                       |

Table 5: Summary of the abnormalities detected in the hysteroscopic examination in primary and secondary infertility patients.

| Hysteroscopic organ abnormality | Hysteroscopic abnormalities in primary infertility | Sub-categorization of hysteroscopic abnormalities in primary infertility | Patients number | Hysteroscopic abnormalities in secondary infertility | Sub-categorization of hysteroscopic abnormalities in secondary infertility | Patient number |
|--------------------------------|---------------------------------------------------|------------------------------------------------------------------------|-----------------|---------------------------------------------------|------------------------------------------------------------------------|----------------|
| Cervix (external and internal os), Uterine cavity and osteal web abnormality | 18/93 (19.4%) | Hypertrophied endometrium                                             | 3               | Hypertrophied endometrium in Bicornuate uterus and cervical stenosis | 1                        |                        |
|                                 |                      | Uterine septum                                                      | 6               | Uterine septum                                    | 2                        |                        |
|                                 |                      | Cervical stenosis                                                  | 2               | Uterine poly/p fibroid                            | 1                        |                        |
|                                 |                      | Uterine polyp/fibroid                                              | 2               | Tubercles/white patches                           | 1                        |                        |
|                                 |                      | Synechie                                                          | 1               | Tubercles/white patches and uterine septum        | 1                        |                        |
|                                 |                      | Tubercles                                                         | 1               |                                                       |                          |                        |
|                                 |                      | Osteal webbing                                                     | 1               | Osteal webbing                                    | 1                        |                        |
|                                 |                      | Tubercle and osteal webbing                                       | 1               | Osteal webbing and uterine septum                 | 1                        |                        |
|                                 |                      | Vaginal septum                                                    | 1               |                                                       |                          |                        |

Hysterolaparoscopic interventions

Out of 157 patients, abnormalities were detected in 125 patients (~79.6%) during hysterolaparoscopic examination. Out of these 125 patients, 121 (~96.8%) underwent therapeutic interventions in form of ovarian drilling (Figure 1), adhesiolysis, Successful cannulation, fluid drainage, fulguration of white patches, septum resection and chocolate cystectomy. Separately in primary infertile patients, out of 77 patients with abnormal hysterolaparoscopic findings, 73 underwent various therapeutic interventions. While in secondary
infertility, 48 patients had abnormal hysterolaparoscopic findings and all underwent therapeutic interventions.

![Figure 1: a, b) Bilateral polycystic ovarian disease. c, d) hysterolaparoscopy: variable sized cystic lesions in the both ovaries.](image)

Out of 125, 4 patients with abnormal hysterolaparoscopic findings were not underwent active intervention. These patients have streak ovaries and hypoplastic uterus, few small fibroids and adenomyosis in 1, 1 and 2 patients respectively.

In all hysterolaparoscopic patients, during and after the procedure no major surgical and anesthetic complications were reported. Few patients were reported with mild abdominal pain and low-grade fever of short duration.

DISCUSSION

Hysterolaparoscopy is used for both diagnostic and therapeutic purpose in various abdominopelvic pathologies. In the present study, we assessed the role of hysterolaparoscopy as a theranostic approach in the infertile patients.

According to the literature, detection rate of pelvic abnormalities with the help of hysterolaparoscopy in infertile patients varies from 30-90%. Hysterolaparoscopy mediated pelvic abnormalities were detected in 87% patients by Jayakrishnan et al, 36% by Firmal et al and 26-30% by Nayak et al. In present study, we detected pelvic abnormalities in ~79.6% female infertile patients.

Of 125 patients with abnormal hysterolaparoscopic findings, we performed the active hysterolaparoscopic intervention in the 121 patients (~96.8%). The most common intervention executed in present study was ovarian drilling in 47 patients (isolated or combined with other intervention) comparable to Puri et al. In present study, through help of hysterolaparoscopy we treated the abdomino pelvic pathologies in 96.8% patients without damaging other parts of the reproductive system. Only in four patients (~3.2%) we could not perform the active intervention due to streak ovaries & hypoplastic uterus, few tiny fibroids and adenomyosis in 1, 1 and 2 patients respectively. So, it appears hysterolaparoscopy is really a theranostic approach in female infertile patients. To the best of my knowledge, there is no comparable study in the published literature, which provides the exact percentage targeted theranostic approach of hysterolaparoscopy in the infertile female patients.

In all recruited patients, no major surgical and anesthetic complications were reported during and after the procedure. Therefore, hysterolaparoscopy is a safe theranostic approach in the infertile female patients.

The major limitation of present study was that we did not interpret our results in form of pregnancy outcome. The other limitation is, this was a single center study so inter-operator variability can lead to discrepancy in outcomes.

CONCLUSION

Hysterolaparoscopy is a treasured modality for simultaneous diagnosis and treatment of different structural abdomino-pelvic pathologies.

Hysterolaparoscopy should be recommended in the initial phases of the work-up in female infertility patients.

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