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4D-HyCoSy performed in a reproductive center: retrospective analysis of pain perception, complications and spontaneous pregnancy rate after the technique

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Abstract. – OBJECTIVE: Nowadays 4D hysterosalpingocontrast sonography (4D-HyCoSy) represents a primary technique in the evaluation of tubal impairment, with a low rate of pain referred and complications related, but its role in increasing the chance of spontaneous clinical pregnancy in women in childbearing age is still debated.

PATIENTS AND METHODS: Retrospective study of 359 women performed 4D-HyCoSy at Reproductive Physiopathology and Andrology Unit, Sandro Pertini Hospital, Rome, during the period 2018-2020. Inclusion criteria: women attending our IVF (*in vitro* fertilization) center with at least 1 year of infertility. Exclusion criteria: female age over 43 years, previously known severe tubal infertility, suspected anovulation, and semen abnormalities. Primary outcome: evaluation of tubal patency, complications related to technique, and pain perception evaluated thanks to a 10-cm visual analogue scale (VAS) Scale. Secondary outcomes: clinical pregnancy rate (PR) after the technique confronted between the group of women with bilateral tubal patency (group A) with the group of monolateral tubal patency (group B) within 30 days and between 30-180 days, and 180 days-1 year from the exam. Time to pregnancy (TTP) and other obstetrical outcomes were evaluated too.

RESULTS: The average age of the study's population was 33.3 years. Mean duration of infertility was 2.1 years. Complication rate was 6.4%, and in any case the use of ephedrine was required. 182 (50.6%) women reported absence of pain during the exam (VAS scale value 0) and 131 (36.5%), reported mild pain experience (VAS scale value between 1-4). Spontaneous pregnancy rate was of 29.3% in group A and 30.3% in group B; time to pregnancy was 32 ± 14.7 days in group A and 35 ± 13.1 days in group B. The insurgence of a spontaneous pregnancy was significantly lower for both 4D-HyCosy sub-groups after 30 days following technique respect to 30-180 days and 180 days-1 year following the technique (both *p*-value < 0.001).

CONCLUSIONS: We confirm that 4D-HyCoSy is a safe and user-friendly technique, used as first line assessment of tubal patency of women afferent to a reproductive center. We also reported a positive impact on spontaneous pregnancy rate in women performing 4D-HyCoSy, emphasized within the first following month. This mandatory technique for tubal investigation, has not only a function in the diagnostic assessment of female infertility, but also has a therapeutic role, in young women who desire a pregnancy, avoiding, in some cases, the need of IVF treatments and clinical risks linked, while saving medical and monetary resources.

Key Words:
Hysterosalpingo contrast sonography, Fallopian tube patency, Pregnancy rate, Time to pregnancy.

Introduction

Infertility is a couple's reproductive health problem defined by World Health Organization (WHO) as the inability to achieve a spontaneous pregnancy after at least one year of unprotected, regular sexual intercourses[1]. To date, it is estimated that infertility affects between 8 and 12% of reproductive-aged couples worldwide, and

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almost 1/7 heterosexual couples in Italy, with around 77.000 couples that every year refer to one of more 360 Italian reproductive centres[2,3].

In several cases, etiology of infertility is unexplained (25%) or can be caused by male factors, but in one-third of the cases it is caused by female factors. Tubal and uterine cavity diseases commonly compromise female fertility: approximately 25% of women have congenital or acquired morphological uterine abnormalities that can lead to a delay in conception[4].

Tubal damage is also a common cause of infertility: it can be a result of pelvic inflammatory and infective disease, endometriosis, pelvic surgery, ectopic pregnancy, or septic abortion. For this reason, an accurate examination of tubal patency and uterine cavity morphology is essential in the diagnostic workup of an infertile couple who desires a pregnancy[5,6].

The ideal technique for investigating uterine cavity and tubal status should be safe, accurate, easy to perform, inexpensive, and well-accepted by infertile women[7,8].

Nowadays, hysteroscopy, laparoscopy with chromopertubation and Rx-Hysterosalpingography (RX-HSG) are widely accepted procedures for the assessment of tubal patency and uterine cavity[9,10].

In specific Rx-Hysterosalpingography (RX-HSG) shows some limitations: it involves ionizing radiations and the direct injection of iodinated contrast agent into the uterine cavity, that can cause toxic reactions, without providing information about the ovaries or the external profile of the uterus.

Laparoscopy with chromopertubation is considered an excellent technique for tubal evaluation, whether for endometrial cavity hysteroscopy is considered the gold-standard technique, respectively. On the other hand, Laparoscopic approach has the disadvantage to be expensive, related to surgical waiting list and surgical risks, as well as anesthesia risks[11].

Therefore, nowadays transvaginal sonography (TVS) is a widely and accurate technique, used to diagnose various uterine and pelvic conditions linked to infertility, as well as hysteroscopy. Unfortunately, both techniques have no role in evaluating tubal status.

Hysterosalpingo contrast sonography (HyCoSy) is an ultrasound=based imaging technique that allows an accurate evaluation of tubal conditions, through a dynamic acquisition of real time images and, at the same time, it permits to study uterine and ovaries status. The concordance between HyCoSy and HSG was 89.6% in the diagnosis of tubal patency, and HyCoSy has proved to be as reliable as laparoscopic techniques in the assessment of tubal patency and uterine morphology, by overcoming such major drawbacks as hospitalization, radiation exposure, anesthesia, and use of iodinated contrast media[12,13]. Moreover, HyCoSy is less invasive and cheaper, in particular, if performed with air and saline as contrast media, compared with laparoscopy and RX-HSG, and gives information on uterine cavity and ovarian morphology, particularly with the 3-4 Dimension ultrasound machine equipment that permits an instant volume rendering . It can be performed by all the reproductive medicine specialist, after a short learning curve, as first step for evaluating infertile women attending a reproductive center.

Indeed, nowadays 4D-HyCoSy investigation is considered safe, well tolerated, rapid, easy to perform and inexpensive[14]. Therefore, several studies demonstrate an increase of spontaneous pregnancy after HyCoSy, but, until now, this aspect is still controversial and debated[15]. The aim of this study is to evaluate retrospective data of women that performed 4D-HyCoSy, afferent our reproductive center, in specific evaluating complications, pain perception and spontaneous pregnancy rate after the technique.

Patients and Methods

Between January 2018 and July 2020, 367 infertile women, with at least 1 year of infertility, underwent 4D-HyCoSy at Physiopathology of Reproduction and Andrology Unit, Sandro Pertini Hospital, Rome, to evaluate tubal patency and uterine cavity morphology. Exclusion criteria for the procedure were: age > 43 years, vulvovaginal or acute pelvic infections (verified by cervico-vaginal swab), an ongoing pregnancy, a diagnosis of hydrosalpinx at TVS, irregular menstrual cycles, suspected anovulation and semen abnormalities, according to WHO classification[16]. All procedures were performed by same specialist (FAB) in reproductive medicine with a long expertise in TVS using a standardized predefined technique. All patients gave their informed consent after reading precise information about the aims of the procedure and the possible side effects and complications. All the examinations were performed in the proliferative phase of the menstrual cycle, between the 6th and the 14th day of menstrual cy-

cle. No atropine or analgesia (before the procedure) was administered, and cervical swabs were recommended before the examination, without antibiotic prophylaxis given. The entire procedure lasted no more than 20 minutes.

All women performing 4D-HyCoSy were invited, from the following days after the technique to have free sexual intercourse with their partners.

This retrospective study was conducted following the Ethical Principles of the Helsinki Declaration and the national laws[17].

Technique Performance

Before the examination, all patients were advised that distension of the uterine cavity by air and saline might cause mild pelvic discomfort and that they could stop the procedure at any time. 4D-HyCoSy was performed through a TVS, performed with a Samsung HS80 ultrasound machine (Samsung, Seoul, South Korea), equipped with a 5.0-8.0 MHz vaginal probe with 3D/4D software equipment. The TVS evaluation, performed with patients examined in the lithotomy position, identified uterine or adnexal pathology, and locate the interstitial part of the salpinges and the ovaries. After the preliminary ultrasound evaluation 4D-HyCoSy were conducted according to the standard technique: Visualization of the cervix, thanks to a speculum, and subsequent disinfection with iodized polyvidone. Then, a catheter (Cook® Silicone Balloon HSG Catheter -Bloomington, Indiana, USA) was inserted into the cervix. To fix the catheter, a distal balloon was slowly filled with 2 mL of air. After removal of the speculum, a plastic syringe was attached to the catheter with 10 ml of air and 10 mL of sterile saline solution. A salpinx was considered not occluded if liberal flow of air bubbles was seen for at least 8-10 seconds through its interstitial part, after injecting air and saline as contrast media seen as hyperechogenic dots. To check for eventual intracavitary pathologies, such as polyps, myomas, which could have been missed by simple TVS without fluid contrast, after the tubal investigation, a few amounts of saline solution was injected to separate the two endometrial layer and view the endometrial profile. At the end of the procedure, the catheter was removed, and all patients were monitored in our visiting room for at least 20 minutes and, if needed, potential late side effects, such as vasovagal reactions were treated by the dedicated physician and nursing staff of the operating unit where the examination took place.

Primary Outcomes of the Study

Evaluation of the tubal patency and eventually uterine findings (polyps, myomas, synechiae), and evaluation of tolerability and complications of HyCoSy as mild symptoms (pallor, nausea, sudation, yawning, hypotension, epigastric discomfort, bradycardia) or severe symptoms (vomit, confusion, syncope) was done. Pain experience wad evaluated through a 10 cm Visual Analog Scale (VAS) scale: 0 indicated no pain at all and 10 corresponded to extreme pain. We considered "mild" pelvic pain a score from 1 to 4, "moderate" from 5 to 7, and "severe" from 8 to 10.

Secondary outcomes

Spontaneous pregnancy rate and time to pregnancy (TTP), in the sub-group of women with bilateral tubal patency (group A) and the sub-group of women with monolateral tubal patency (group B) was calculated. The occurrence of a spontaneous pregnancy was evaluated within the 30 days following the technique and between 30 and with 180 days and 180 days-1 year from the technique. Obstetrical outcomes (clinical pregnancy, miscarriage, ectopic pregnancy, spontaneous deliveries, or caesarean sections) were evaluated in both groups too.

In particular, to assess pain experience and evaluating the secondary outcomes, all the women were interview by telephone, at least after 9 months from 4D-HyCoSy and asked by the clinician to give an estimation of the pain felt during the procedure using VAS scale and asked regarding an insurgence and the time of a spontaneous pregnancy.

Statistical Analysis

Statistical analysis was performed using unpaired test when comparing groups, with the results expressed as mean ± standard deviation (SD), median, percentage. All analyses were performed using the SAS software (release 9.4). A p-value ≤ 0.05 is considered statistically significant.

Results

367 women requiring 4D-HyCoSy were evaluate during the studying period, before a preliminary cervical vaginal swab performed. The procedure was not completed in 8 women (2.17 %) because of cervical stenosis or uterine flexion that prevented the insertion of the catheter (4 patients, 1.08%), inadequate compliance and intolerance to

speculum positioning (2 patients, 0.57%). In 359 patients, the procedure was completed. The characteristics of the population that performed the procedure are given in Table I.

We evaluated results of the procedure, in terms of tubal patency and finding of intrauterine pathologies, and results of pain evaluation using the VAS scale (we evaluated "absent" pelvic pain to be a score as 0 VAS, "mild" pelvic pain to be a score from 1 to 4 VAS, "moderate" from 5 to 7 VAS, and "severe" from 8 to 10 VAS) and the compliance immediately after the procedure. All those results are reported in Table II.

All women diagnosed with polyps (16 women) submucosal myomas (10 women) or other uterine abnormalities (9 women), were directed to an hysteroscopic exam. After 4D-HyCoSY, all the patients diagnosed with bilateral tubal occlusion (24 women) were directed to IVF (*in vitro* fertilization) treatments.

Regarding results in terms of complications, it is interesting to underline that in 336 (93.6%) patients we did not report complications. Only in 23 (6.4%) patients we reported complications: a moderate, self-limiting vasovagal reaction (manifesting as nausea, pallor, sweating bradycardia, and hypotension) was felt by 20 out of 329 patients (5.57%), and a severe vasovagal reaction (represented by vomit, confusion) was reported in 3 (0.83%) women. All women reporting moderate/severe symptoms, were looked after in our ambulatory room with the constant presence of medical and nursing staff, monitoring vital signs, at least 30 min, and in all cases without use of drugs as ephedrine and no needed of recovery. No one of our patients reported an episode of syncope, of intra and post-procedural hemorrhage and of fever or peritonitis.

Table I. Demographics characteristics of women performed 4D-HyCoSy.

Characteristics of population (n = 359)	Patients
AGE years (SD)	33.3 ± 2.8
BMI kg/m^2 (SD)	23.9 ± 2.73
Duration of infertility years mean (SD)	2.1 ± 1.9
AMH (ng/ml) mean (SD)	2.04 ± 0.9
FSH (mIU/ml) mean (SD)	7.3 ± 1.8
Previous miscarriage (number) (SD)	0.8 ± 2.01
Present smoking n (%)	95 (26.46%)
Primary Infertility n (%)	202 (56.26%)
Secondary infertility n (%)	137 (38.16%)
Previous uterine interventions n (%)	34 (9.47%)

In 359 patients, as previously reported, the procedure was completed. Excluding patients with bilateral tubal obstruction (n. 25, 6.9%) and uterine pathologies found (No. 34, 9.94% including polyps, submucosal myomas and other abnormalities, such as endometriosis or synechiae), the remaining 300 patients presented monolateral or bilateral tubal patency:

In particular, women with bilateral patency (n. 201, 55.98%) were defined as group A and women with unilateral tubal patency (n. 99, 27.57%) were defined group B. Those two groups, similar for all demographics characteristics, as age, BMI, years of infertility and AMH values, were retrospectively analyzed. Spontaneous pregnancy rate, time to pregnancy and other obstetrical outcomes, were evaluated and confronted between those two groups. All results were comparable between two groups and are reported in Table III.

It is important to point out that the occurrence of a spontaneous pregnancy (SP), after 4D-HyCoSy, resulted statistically significative higher within the first month after the technique, compared to the subsequent 30-180 days after, in both groups (34 *vs.* 14 events, p-value < 0.001, in group A and 20 *vs.* 6 events, $p < 0.001$, in group B), and is statistically significative also comparing SP within the first month confronted to 180 days-1 year in both groups (34 *vs.*10 events, p-value < 0.001 in group A, and 20 *vs.* 4 events, $p < 0.001$, in group B. Those results are represented in Figure 1.

Discussion

4D-HyCoSy has the advantage to be a real-time, dynamic, user-friendly, and well tolerated technique, and can represent the gold standard assessment tool for evaluation of tubal patency, in women in childbearing age afferent to a reproductive centre[18].

Regarding pain perception, we reported an extremely low level of pain referred from our patients experiencing 4D-HyCoSy, measured by VAS scale. In 182 women of 359 studied, we registered an absence of pain referred and only in 20 women, we reported an intense experience of pain, with only 11 women (3,06 %) required a post procedural analgesic assumption. Pain experience was referred from our sample of women as uterine cramping or dysmenorrhea-like discomfort. Those symptoms can be due to uterine distension after saline solution infusion, because of the mechanical distension of the uterine walls

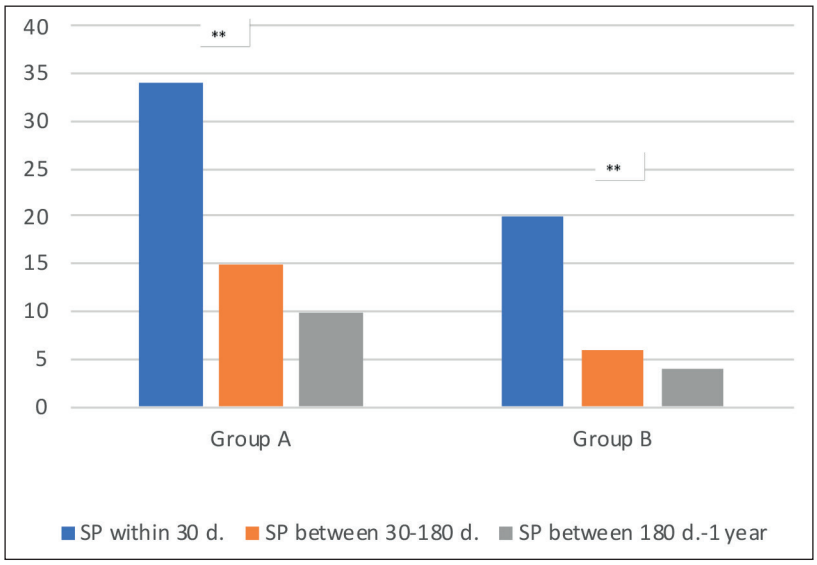

Figure 1. Spontaneous pregnancy within 30 days versus 30-180 days after 4D-HyCoSy. Abbreviations: Group A: Bilateral patency, Group B: Monolateral patency, SP: spontenuous pregnancy, d: days, **: Statistically significative.

could cause the release of local prostaglandins, resulting in uterine cramps. It is important to underline that we did not administer antispasmodic drug to our patients, according to a recent study which demonstrated that a preventive administration of antispasmodic drug, does not decrease pain during 4D-HyCoSy by affecting uterine contractions[19].

However, in our sample we reported an extremely low level of pain referred; this could be explained because most of our patients have both tubal patency, or unilateral tubal patency and because having an experienced and dedicated physician perform this examination allows a better standardization of the procedure among patients. Moreover, our dedicated physician always inflating the distal balloon slowly to a maximum of 2 mL of air to fix the catheter, to avoid a painful reaction from the patient, given from the rapid swelling of the same balloon, and limiting an eventual insurgence of vasovagal reactions at the same time. Our results regarding pain experience, are consistent with those of Savelli et al[20], Li et al[21], and Socolov et al [22].

Regarding complications, we reported an extremely low rate of complications, according to recent work in literature, as reported from Savelli et al[20] and Marci et al[23]. Our work confirms that 4D-HyCoSy did not lead to severe complications immediately after the technique, that might require the use of ephedrine, or long-term complications, such as pelvic infections and pelvic peritonitis, that might require antibiotics treatment and hospitalization, respectively. For sure, the cervico-vaginal swab check, required before the examination, was a useful tool, to avoid the ascent of germs through the female genital tract led to the injection of the contrast fluid. We highly recommend performing this propaedeutic exam before doing 4D-HyCoSy, and to treat cervico-vaginal infections detected by cervico-vaginal swabs.

Moreover, through 4D-HyCoSy, we were able to diagnose misrecognized uterine pathologies (such as endometrial polyps or submucosae's myomas) in 34 of our patients, that were directed to an hysteroscopic exam. The saline infusion injection, stretching the otherwise virtual uterine cavity, helped us to diagnosis those uterine findings, that could be undiagnosed with the only TVS scan without contrast media infusion. Moreover, the use of four-dimensional ultrasound equipment emphasizes the capacity to detect uterine internal findings, in particular abnormalities of the uterine fundus, such as malformation, with the help of contrast media as saline infusion[24,25]. Indeed, this technique has greater accuracy than the transvaginal ultrasound alone, in diagnosing uterine neoformations or synechiae[12], especially if performed by a dedicated and expert operator assisted by an advanced ultrasound machine equipped with a volume rendering technology for accurate measurements. So, we highly recommend performing a 4D-HyCoSy, as first step of evaluation of uterine status and morphology, in women afferent to

Table II. Clinical results of 4D-HyCoSy in terms of tubal patency, complications, and pain perception.

Clinical Results	Patients (n = 359)
Tubal patency and other uterine findings	
Bilateral patency No. (%)	211 (58.8%)
Monolateral occlusion No. (%)	123 (34.3%)
Bilateral occlusion No. (%)	25 (6.9 %)
Other Uterine pathologies	
Polyps No. (%)	16 (4.45%)
Submucsoal myomas No. (%)	10 (2.78%)
Other abnormalities (endometriosis, synechiae) No. (%)	9 (2.51%)
Complications	
No complications No. (%)	336 (93.6%)
Mild/moderate Vaso-vagal reaction No. (%)	20 (5.57%)
Severe Vaso-vagal reaction No. (%)	3 (0.83%)
Need for use of therapy and other related issues	
Required Ephedrine – No. (%)	0 (0%)
Required analgesic drug – No. (%)	11 (3.06%)
Required recovery – No. (%)	0 (0 %)
Hemorrhage – No. (%)	0 (0 %)
Fever or Pelvic Inflammatory Disease/peritonitis – No. (%)	0 (0 %)
Pain Perception	
Absent – Vas scale 0 No. (%)	182 (50.6%)
Mild – Vas scale 1 - 4 No. (%)	131 (36.5%)
Moderate – Vas scale 5 - 7 No. (%)	26 (7.24%)
Severe – Vas scale 8 - 10 No. (%)	20 (5.57%)

a reproductive center.

Regarding spontaneous pregnancy impact, we reported a positive impact on the insurgence of a spontaneous pregnancy. In our sample we reported a mean time to pregnancy of 32 and 35 days, respectively, in group A and B of our sample of women studied. This outcome is significantly lower than studies in the literature that demonstrate the mean of "conception time" of 75 days, 5.3 months and 8.8 months[26-28]. This difference can be due to the evident prevalence in our study group of patients with bilateral tubal patency, compared to monolateral tubal occlusion. Indeed, women with the occlusion of one tube, might need more time of conception and, thus, they remain pregnant spontaneously.

Although this difference in time to conception, our results are in line with a positive impact on spontaneous pregnancy as reported in those recent studies in literature, as in the Chunyan et al[27], in which PR was 19.44% within 180 days after 4D-HyCoSy and it was significantly higher in the first 30 days (6.35%) (p <0.01). Authors reported that PR was highest, with a rate of 32.01% in the group of bilateral tubal patency, followed by the PR of monolateral patency (15.04%) (p <.01).

Therefore, we noticed a higher value of spontaneous pregnancy rate (PR) within the first month (30 days) after the technique, of 50.6% in group A and of 66.6% in group B, compared to 30-180 days and 180 days-1 year subsequent the exam. Those results are consistent too with the study

Table III. Demographics characteristics and clinical outcomes in bilateral tubal patency and monolateral tubal patency groups.

Clinical outcomes	Bilateral tubal patency "group A" (n = 201)	Monolateral tubal patency "group B" (n = 99)	*p*-value
Spontenuous pregnancy No. (%)	59 (29.3%)	30 (30.3%)	0.51
Clinical Pregnancy No. (%)	44 (74%)	25 (83.3%)	0.73
Miscarriage No. (%)	12 (6.4%)	4 (13.3%)	0.43
Ectopic Pregnancy No. (%)	3 (1.5%)	1 (3.3%)	0.34
Live birth No. (%)	31 (52.5%)	21 (70%)	0.91
Spontaneous delivery No. (%)	18 (58.1%)	15 (71.1%)	0.82
Cesarean sections No. (%)	13 (41.9%)	6 (28.8%)	0.27
Time to pregnancy (days) mean ± DS	32 ± 14.7	35 ± 13.1	0.83
Spontaneous pregnancy within 30 days No. (%)	34 (57.6%)	20 (66.6%)	0.21
Spontaneous pregnancy between 30- 180 days No. (%)	15 (25.4%)	6 (20%)	0.81
Spontaneous pregnancy between 180 days-1 year No. (%)	10 (16.9%)	4 (13.3%)	0.75

Note and abbreviations: Clinical pregnancy: Ongoing pregnancy more than 12 weeks; Miscarriage: End of pregnancy < 12 weeks.

of Giugliano et al[26], that shows PR significantly higher in the first 30 days (45%) compared to other the months of observation.

It is important to underline that all male partners of our sample presented normal semen analysis, according to WHO definition, and all women included presented a regular menstrual cycle and ovulatory cycle, and normal values of FSH and AMH hormone. Those aspect can focus our obstetrical results on tubal status of our sample of women. However, the positive effect of tubal examinations on PR is still unknown, but probably is due to a mechanical action of the fluid used as contrast agent. The passage of liquid used, as saline infusion, through tubal lumen removes the buildup of material inside the tubes, that follows previous and usually misdiagnosed inflammatory processes. At the same time, the contrast media removes micro-adhesions, thickened mucus plugs, and expands tubal stenosis and convolutions, that can negatively impact on fecundation. This positive effect seems to be immediate and intricately linked to time elapsed from the procedure, as demonstrated from our results of a higher PR within the first month since the technique.

This positive impact can allow, in young women with tubal problems, to obtain a spontaneous, and usually long and strong desired, pregnancy, avoiding the waiting list for doing IVF techniques in a reproductive center. At the same time, it permits to avoid clinical risks linked to IVF treatments, as ovarian hyperstimulation syndrome (OHSS), that occurs in up to 30% of IVF cycles and carries a high morbidity[29]. Therefore, the achievement of a natural spontaneous pregnancy represents an evident save of money for the national health system and for couple saving. Indeed, HyCoSy has an estimated cost of only 30-55 Euros for the disposable material, as reported from Savelli et al[20], compared to higher costs of first and second level IVF techniques.

The limitations of our study were the retrospective design, the lack of randomization, and the little sample of women included. As a consequence, further randomized studies, with a bigger sample of women included, are needed to validate our results.

Conclusions

Our results confirm a positive impact on spontaneous pregnancy rate especially within first month after 4D-HyCoSy, respect to 3 months and 1 year subsequent the technique.

We confirm that 4D-HyCoSy is non-invasive, inexpensive, well-accepted, safe, and easy to perform by the all the gynecologist. This technique represents a mandatory first-level evaluation of tubal patency and uterine cavity morphology in infertile patients and seems to represent a therapeutic useful option, in young women who desire pregnancy with and without tubal impairment. Women accessing to a fertility center and performing this technique, obtaining a subsequent spontaneous pregnancy, could reduce overtreatment and clinical risks of IVF treatments, while saving medical and monetary resources.

Author's Contributions

Francesco Antonio Bisogni (FAB) and Francesco Galanti (FG) have contributed equally to the writing, review, and editing of the manuscript. All other authors have given a contribution to the realization of this study. All the authors have read and agreed to the current published version of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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