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Technical Note

A novel concept for female infertility exploration: the Fertiliscan©, a dedicated all-in-one 3D ultrasound exploration

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ABSTRACT

The investigation of the probable cause of infertility is mandatory to propose an accurate therapeutic option to the infertile couple i.e. good chance of pregnancy. Usually, this investigation in woman includes at least hormonal dosages to estimate the ovarian function and reserve, a pelvic ultrasound scan and a hystero-salpingography to determine tubal patency. We introduce a unique investigation based on the realization of a high quality 3D ultrasound scan that involves the assessment of tubal patency. It is called Fertiliscan as opposed to the standard pelvic scan. The Fertiliscan assesses both the anatomy and the function of the uterus, the ovaries as well as the tubes. It includes a hystero-sonography for the analysis of the uterine cavity and with respect to tubal patency, a hysterosalpingo-foam-sonogography (Hyfosy). The investigation is woman-friendly, cheaper and shorter. It allows a fast track to a treatment if needed and shortens "time to pregnancy" for the couple.

The investigation of the probable cause of infertility is mandatory before medically assisted reproduction (MAR). The purpose of investigation, which includes a semen analysis for the male partner, is to propose an accurate therapeutic option to the infertile couple, i.e. good chance of pregnancy. Usually, this investigation in woman includes at least hormonal dosages, a pelvic ultrasound scan and a hystero-salpingography (HSG). This process is long for infertile couples, 13 weeks on average [1], but necessary to determine the optimal MAR treatment for a given couple. The exploration of infertile women is both anatomical and functional to evaluate ovulatory status, uterine cavity ability and tubal patency.

Uterine exploration

Only 50% of infertile women have strictly normal uterine cavity and 44% have abnormalities reducing the chances of implantation (polyps, leiomyoma, adenomyosis, synechiae, . . .) [2]. Among this subgroup of women, 15% need a surgery before conception. The gold standard for uterine cavity exploration is an hysteroscopy. It diagnoses the presence of any congenital or acquired abnormalities, and it is the only exploration to judge the visual aspect of the endometrium (diagnosis of endometritis). But it does not explore the whole myometrium. Besides, it is usually less available than ultrasound scan (US) and in absence of office hysteroscopy, the patient will sometimes undergo general anesthesia, which is a more invasive and costly procedure. The alternative is the saline infusion sonography or hysterosonography (Hysono). It consists of US with a vaginal probe, with saline infusion in the uterine cavity to enhance the contrast and separate the edges of the cavity. Hysono has good accuracy for the diagnosis of congenital and acquired uterine abnormalities, and it also determinates their impact on the myometrium and the whole uterus. Hysono has high sensibility (0.88 IC95%[0.85–0.90]) and very high specificity (0.94 IC95% [0.93–0.96]), comparable with hysteroscopy [3]. It can be used as a screening tool for subfertile patients for the diagnosis of uterine polyps, submucous myomas, uterine malformations and intra-uterine adhesions. It also has a higher tolerance with a mean score at analogic pain evaluation lower than with hysteroscopy, 1.6 vs 3.2 ($p < 0.05$) respectively [4]. The learning curve is fast, it is less costly than hysteroscopy and more convenient for patient, as the ultrasound scan also explore the whole uterus and ovaries, and may also detect sign of endometriosis.

Tubal exploration

The tubal exploration is a core element of the infertility workup because tubal patency is a limiting factor for MAR treatment. In a general population of infertile women, 71% of them have functional tubes, but 12,5% have hydrosalpinges

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requiring a first line surgery before infertility treatment and 10% have tubal bilateral occlusion requiring *in vitro* fertilization (IVF) [1]. The gold standard of tubal investigation is the laparoscopy but this is an invasive and expensive techniques requiring technical facilities and general anesthesia. It is barely used as a first line and it is routinely replaced by hysterosalpingography (HSG). The advantages of HSG are its low cost, it explores both uterine and tubes morphology and tubal patency with the peritoneal cavity diffusion. It allows a selective catheterization for restoration of patency in case of proximal obstruction. HSG has itself some disavantadges: exposure to X-ray irradiation (5 mGray) and risk of iodine allergy, need for technical facilities, risk of infectious complication (1%) [5]. HSG is also frequently a source of discomfort for the women as it is perceived painful. Since the 90's, tubal testing by transvaginal US have been developed, first with the visualization of the passage of different sonographic positive contrast through the tubes (hysterosalpingo-contrast-sonography, Hycosy) [6] and currently with the use of a new gel (hysterosalpingo-foam-sonography, Hyfosy) [7] that ensure a better sensibility and specificity [8]. Air is a key element to create an hyperechogenic contrast within ultrasound. The gel produced a foam giving a steady contrast lasting more than 10' with fluent texture which easily go through the tubes. Its innocuity and well tolerance [9] as well as shorter learning curve have been reported. The learning curve of a fellow trained in pelvic ultrasound was estimated to five Hyfosy (personal data, unpublished). Compared to Hycosy, Hyfosy has better sensibility [5] and compared with HSG, Hyfosy is faster (5' vs 12.5'), well tolerated (analogic pain evaluation 1.7 vs 3.7) [10], with no risk of allergy, and lower reported risk of infection (0.1%) [5]. In a recent prospective study [11], 132 women, among whom prevalence of tubal occlusion was 6%, had tubal evaluation successively with Hycosy then Hyfosy then laparoscopy as gold standard. Overall the accuracy of Hyfosy was very high (93.7%). The positive predictive value was 48%, meaning that when a tube appeared to be occluded, there is only one chance out of two that it is really occluded. It needed to be controlled either with a second Hyfosy or with laparoscopy, or even better when available, a less invasive procedure such as transvaginal laparoscopy (Fertiloscopy) [12], depending on the medical history of the patient. However, the sensibility and specificity of Hyfosy were very high, 87% and 94% respectively, with a negative predictive value of 99%, meaning that when the tube appeared to be potent with Hyfosy, it was confirmed with laparoscopy, meaning that Hyfosy is a very good screening test. Furthermore, as a result of Hyfosy have been shown to enhance spontaneous chance of pregnancy [13]. However, Hyfosy is still little practiced due to low availability of medical training, recent distribution of the hyper echogenic foam used to performed the test and poor or no economic valuation for the practitioners.

Ovarian exploration

The ovarian exploration is the third part of the infertility workup. Completed with physical examination, it determines if the women has ovulatory menstrual cycle and if not, the expected type and cause of anovulation or dysovulation. The two more frequent cause of ovulation dysfunction are the polycystic ovary syndrome and ovarian insufficiency. The ovarian induction/stimulation agents must be adapted according to these conditions. The ovarian exploration evaluate as well the ovarian reserve which is fundamental to predict the ovarian response to stimulation [14] and to give a prognosis on the decline of the fertility potential [15]. The evaluation of the ovarian reserve can be equally estimated either with the dosage of AMH or the measurement of antral follicle count (AFC) by ultrasound [16]. AFC may be evaluated using real time 2D US or 3D automated count, the latter require a shorter scanning time particularly when there is a large number of follicles (more convenient for the patient) [17].

Fertiliscan©: all-in-one exploration

Overall, a diagnostic strategy has to be safe, not invasive, well tolerated and at a lower cost. In the first line of the fertility workup, the US is an accurate choice and, moreover, it can combine all the tests in one, that make it also a faster screening test. 'One-stop shop' fertility testing has been recently introduced to provide infertile couples reliable results about their fertility potential, within only one visit [1]. 'One-stop' investigation described by Hrehorcak and Nargund was based on the realization of a high quality 3D ultrasound scan with Doppler and involves the assessment of tubal patency with Hycosy. They demonstrate that the fertility workup was reduced to 1 h compared to 13 weeks with standard investigation.

We propose a new concept with Fertiliscan© as opposed to the standard pelvic scan. The Fertiliscan© assesses both the anatomy and the function of the uterus, the ovaries as well as the tubes and detects endometriosis. It includes a dedicated 3D vaginal US with Hysono for the analysis of the uterine cavity and with respect to tubal patency, a Hyfosy.

When to perform

A key question is the timing of performance of the US. For the ovarian reserve assessment it is classical to perform the US in the early follicular phase, between days 3 and 5 of the menstrual cycle [18] but some authors [1] recommend performing the US in the proliferative phase (Day 10–14 of the menstrual cycle) to have a better evaluation of the endometrium and uterine cavity as well as for follicular maturation. There are intra-patient variations of the AFC during the menstrual cycle [19] however these variations are not significant in a clinical point of view [20]. We have recently shown (personal data, submitted), in a retrospective study including 131 patients, that AFC is strongly correlated to AMH and to the number of oocytes retrieved after ovarian stimulation, when performed in the early follicular phase (Day 1–6) or the late follicular phase (Day 7–12), respectively 0.81 and 0.80 for early and 0.92 and 0.93 for late, but to a less extent in the luteal phase, respectively 0.58 and 0.78. A recent practical guide on counting AFC [17] recommend that AFC may be performed at any point in the menstrual cycle with preference in the follicular phase. For the Hyfosy, the US have to be performed before the endometrium is too thick to avoid technical problems and endometrial effraction. Therefore, we recommend the performance of the Fertiliscan© between days 5 and 9 as it is more convenient for the women and the physician to avoid the bleeding period, and for a good evaluation of the endometrial and follicular maturation.

How to perform

Fertiliscan© is performed with empty bladder in gynecologic position between Day 5 and Day 9 of the menstrual cycle, to avoid the bleeding period and thick endometrium (risk of endometrial effraction with the catheter). It assesses both anatomy and function of ovaries, uterus and uterine cavity, tubes and peritoneal cavity (screening for endometriosis). The material needed to perform Fertiliscan© are (Fig. 1):

- Ultrasound machine with 3D capability and high frequency 3D vaginal probe ($\geq$ 7 MHz)
- One Colin speculum
- One intrauterine catheter, any one use for embryo transfers
- 20 ml physiological saline

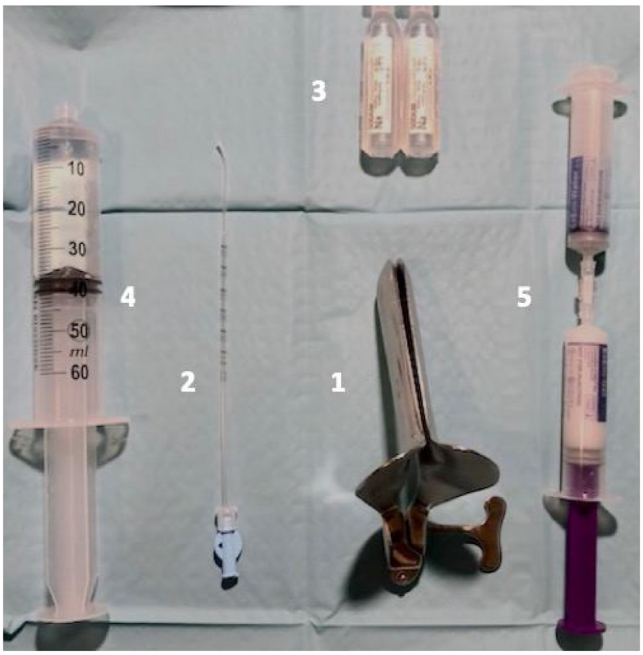

Fig. 1. The material needed to perform Fertiliscan©: Colin speculum (1), intrauterine catheter (2), 20 ml physiological saline (3), 20 ml (or more) syringe (4), Exem Foam kit® (one 10 ml syringe with 5 ml ExEm® Gel, one 10 ml syringe with 5 ml of purified water and a coupling device) (5).

- 20 ml (or more) syringe
- Exem Foam kit® that contains one 10 ml syringe with 5 ml ExEm® Gel (Hydroxyethylcellulose and glycerol), one 10 ml syringe with 5 ml of purified water and a coupling device. By diluting the ExEm® Gel with the water, a gel foam is created which enables a fast and simple distension of the walls of the fallopian tubes and high quality ultrasound images.

The Fertiliscan© is divided in 2 successive examination parts with a total duration about 25–30'. Firstly, a 3D vaginal US pelvic examination (with detection for hydrosalpinges which contra-indicated the second part) and secondly, warmed saline 5 ml infusion for Hysono examination, followed by aspiration of saline and then slow gel infusion for Hyfosy (5–10 ml). The first part of the US examination explores: ovaries, their accessibility and size, with description of any cysts, antral follicle count (AFC) for each ovary with 3D automated identification and quantification (Fig. 2); cervix with description of any abnormality; uterus, its position, size, structure, with 3D coronal view (Fig. 3a) to specify any myoma by FIGO classification [21] and uterine malformation by ESHRE classification [22], and interostial length; Fallopian tubes, normally unseen, with indication of presence of unilateral or bilateral hydrosalpinges; and finally, peritoneal cavity to detect direct or indirect signs of endometriosis (hypoechogenic nodules, fixed pelvis) [23] and adherences. Beside this anatomical examination, functional analysis is provided by description of follicular maturation, by the presence of a selected follicle within the whole cohort (Fig. 2), endometrial maturation, by the aspect (undifferentiated, proliferative, secretory) and thickness of the

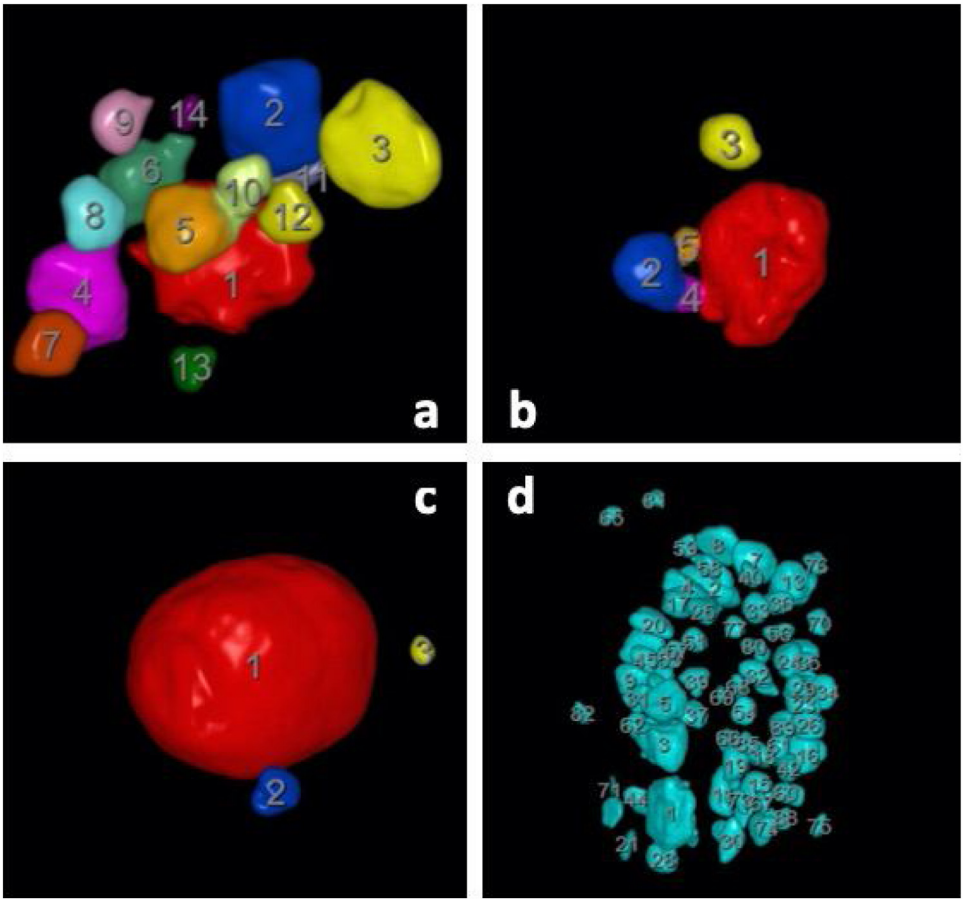

Fig. 2. 3D automated identification and quantification for AFC at D8: (a) normal situation with AFC 15 and a growing follicle at 10 mm; (b) diminished ovarian reserve with a growing follicle at 10 mm (normal cycle length); (c) severe diminished ovarian reserve with a preovulatory follicle (short cycle); (d) PCO-like ovary with a high AFC and no growing follicle (anovulatory cycle). (a,b,c) quantification with SonoAVC follicle mode; (d) quantification with SonoAVC antral mode. (Voluson E10 – BT18, General Electric).

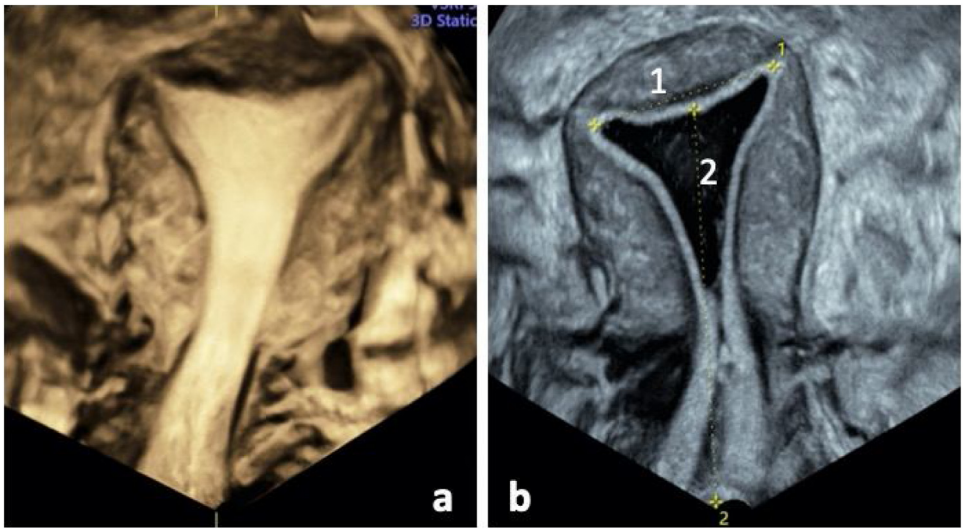

Fig. 3. Uterus and uterine cavity in 3D-coronal view at baseline (a) with omniview polyline mode and (b) with saline infusion in the cavity (hysono). (1) interostial length (2) hysterometry. (Voluson E10 – BT18, General Electric).

endometrium, and by presence of cervical mucus. For the second part, the vaginal probe is extracted and the material for Hysono and Hyfosy is prepared. The syringe is filled with 20 ml of warmed saline and mounted with the purged catheter. The syringe of Exem gel is prepared as instructed and kept within easy reach. The Colin speculum is placed to visualize the cervical orifice and the catheter is inserted in the uterine cavity through the orifice. The speculum is removed while the catheter is kept in place. The vaginal probe is

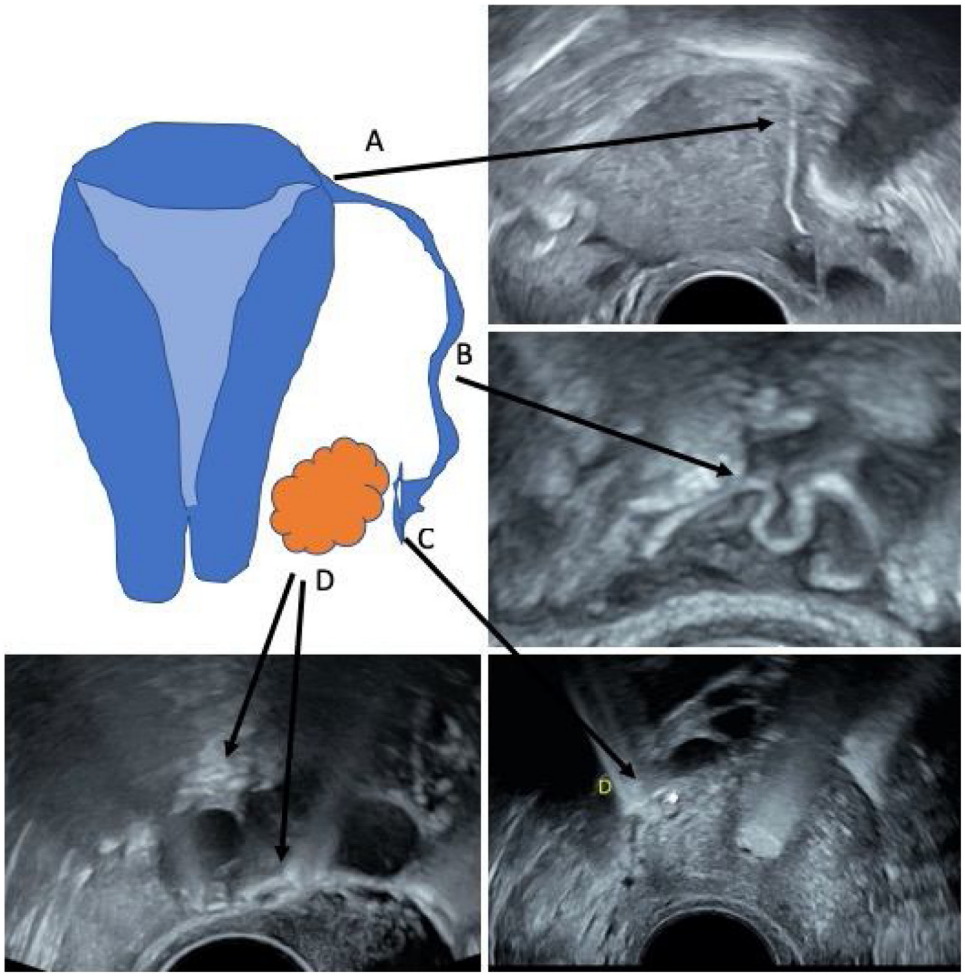

Fig. 4. Hyfosy : path of the hyperechogenic foam (Exem gel®) in the interstitial segment (A), route through the tube (B), flow in the ampulla (C) and periovarian diffusion (D). (Voluson E10 – BT18, General Electric).

inserted and 5 ml of warmed saline is gently infused in the uterine cavity. The Hysono reports uterine cavity distension capacity, uterine cavity shape with 3D coronal view, presence and description of any structure in or impacting the cavity (polyps, adhesions, myoma types 0–2 of FIGO classification, adenomyosis), presence and description of isthmocele if history of caesarian section, description of the path into the cervix and the ultrasound hysterometry (Fig. 3b). Then, the saline is totally aspirated from the uterine cavity with the same syringe. The syringe with the saline is separate from the catheter and replaced by the one with Exem gel. The gel is gently infused in the fundus to perform the Hyfosy. The examination reports for each side the tubal patency with the visualization of the gel flow in the 3 segments (interstitial, abdominal and ampulla, Fig. 4) and with the periovarian diffusion. Fig. 5: complementary material Hyfosy video file.

Risks and benefits

Some patients may experience painful uterine contractions, vasovagal reaction, abdominal pain, fluid loss or spotting. These symptoms are well known and related to all intrauterine and tubal patency testing procedures. Pain can be easily limited by avoiding touching the fundus with the catheter and by slow and gentle infusion, as well as by the limitation of the volume of the warmed saline and/or gel. A pain treatment should be proposed according to local protocol.

Expected patient benefits are: a faster and less painful tubal patency investigation, avoiding the menstrual bleeding period and X-ray/iodine allergy exposition; a shortened investigation process with an all-in-one ultrasound scan realized in less than one hour compared to several weeks; a better quality of life with no delay in the access to medically assisted reproduction (MAR) techniques; a less expensive investigation (estimation: 280€ vs 355€) and a limited number of needed visits (less impact on professional work) and an enhanced chance of pregnancy [13].

The Fertiliscan© is based on the consolidation of several validated techniques such as 3D endovaginal ultrasound and Doppler, Hysono and Hyfosy, in only one examination. The innovative aspect is the association with the new developed technique, Hyfosy, which accuracy has been demonstrated in comparison to laparoscopy [11]. However, another innovative aspect of this all-in-one test is its specific timing within the menstrual cycle.

The Fertiliscan© is a first-line examination. The fertiloscopy or laparoscopy may be discussed in a second step, depending on the medical history, as pelvic ultrasound as well as HSG are not able to detect subtle tubal abnormalities that may have on impact on fertility [24].

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