EDITORIAL

Home monitoring of ovarian stimulation: an important step towards more patient-centred IVF

Since the early 1980s there has been constant evolution in the clinical management of IVF treatments. From the patient's perspective, significant innovations have included: (i) the replacement of oocyte retrieval through laparoscopy under general anaesthesia by ultrasound-guided out-patient transvaginal puncture; (ii) the introduction of GnRH analogues to suppress a premature rise in LH (avoiding the need for frequent LH peak monitoring); (iii) calibrated pens allowing patients to inject gonadotrophins themselves and avoiding dependency on nurses or hospital facilities; (iv) the introduction of milder and less complex stimulation protocols (significantly reducing side effects and the need for intense ovarian response monitoring and frequent hospital visits) (*Nargund and Fauser, 2020*); and (v) the recognition of the distinct burden of treatment and psychological stress associated with IVF (resulting in significant treatment drop out and reduced cumulative pregnancy chances per started IVF treatment).

In addition, IVF treatments have been optimized by the successful introduction of intra-cytoplasmic sperm injection (ICSI), surgical testicular sperm extraction techniques, preimplantation genetic testing, blastocyst culture, judicious application of single embryo transfer (so avoiding complications due to multiple pregnancies), and finally by developing strategies to avoid ovarian hyperstimulation syndrome (OHSS). All of these improvements have been reported by patients themselves as very welcome developments indeed.

Assisted reproductive technology (ART) has become a mature, efficacious, widely applied and safe treatment modality for infertility. Yet for many it remains difficult to access IVF treatment due to financial, geographical or organizational reasons (*Macklon and Fauser, 2020*). Therefore, it seems pertinent to focus on novel approaches relevant from the point of view of the patient. Patients want modern ART treatment to be as simple as possible without significantly compromising the chance of success per IVF cycle. More patient-friendly IVF could well mean an increased cumulative chance of success per started treatment due to reduced drop-out rates. In addition, patients want IVF treatment to be affordable, compatible with existing responsibilities of work and family life, and accessible at a conveniently located IVF centre.

Before being able to achieve this ideal situation for patients, a number of practical challenges need to be overcome. The current editorial considers one of these challenges, with which the first author has gained direct experience over the past decade, involving several hundred IVF cycles where self-operated home-based ultrasound monitoring of ovarian response to stimulation has been used.

THE NEED FOR SIMPLIFIED AND TRULY PATIENT-CENTRED IVF

The need for serial transvaginal ultrasonographies to monitor ovarian response to stimulation for IVF remains a major logistical challenge for patients, as well as for healthcare providers. Frequent visits to the clinic may be time consuming, costly and certainly add to the psychological burden of treatment. All this hampers access to IVF for many couples or renders it strenuous and expensive. These complexities may result in early drop-out from IVF and may even prevent initiation of treatment for some potential patients. With this technique, however, hormonal monitoring of ovarian stimulation by repeated serum oestradiol assessment (and sometimes multiple additional hormone determinations) requiring repeated blood withdrawals, is no longer needed. A recent Cochrane review states clearly that following up the follicular phase of an IVF/ICSI cycle by ultrasound alone yields similar results to ultrasound combined with hormone determinations (*Kwan et al., 2014*; *Martins et al., 2014*). At present, ultrasound scans are performed by various care providers; gynaecologists, fertility nurses, midwives, radiologists, and sonographers. Traditionally, women must come repeatedly to the care provider working at or collaborating with the IVF centre. This may involve different personnel during a single cycle, resulting in significant inter-observer (in addition to intra-observer) measurement variability.

However, recording images using a vaginal probe is a simple and easy procedure. The evaluation of such images is simple and does not need to be performed by a healthcare professional or a highly specialized reproductive physician. The first author has explored in a step-wise manner the use of home ultrasonography by patients and/or their partners to carry out transvaginal sonographies at their convenience (*Gerris et al., 2009*, *2010*, *2014*), thereby significantly alleviating the cost and stress of monitoring (TABLE 1).

TECHNOLOGY OF ULTRASOUND DEVICES FOR SELF-USE AT HOME

In the current stage of development, patients are provide with a small, safe and easy-to-use customized device, essentially consisting of a tablet personal computer (TPC) to which a vaginal probe is connected using USB technology. Video-images are sent securely over the internet to the centre where they are analysed and stored. A structured response is sent with little or no delay informing the patient about the dose of gonadotrophins to be self-injected during the following day(s) (*Chen et al., 2014*), the timing of the next ultrasound scan and eventually the timing of the HCG injection and subsequent oocyte retrieval. This technology could

TABLE 1 PUBLISHED STUDIES OF A STEP-WISE EXPLORATION OF THE CLINICAL APPLICABILITY OF PATIENT-OPERATED HOME SONOGRAPHY IN ART

Study reference	Key finding
Gerris et al., 2009	Patients are willing to use home sonography provided results of the treatment remain unaffected. (n = 25)
Gerris et al., 2010	Proof of concept in a hospital setting: patients are able to perform vaginal sonograms themselves. (n = 20)
Gerris et al., 2014	Randomized controlled trial: patient-operated home sonography gives similar results (embryological and clinical) to traditional sonographic follow up. Both patient-reported outcomes and cost are in favour of home sonography. (n = 121)
Gerris et al., 2016	Observational study of ICSI attempts using home sonography showed just one method failure. (n = 100)

also be applied using oral compounds for IVF or even in other types of infertility treatment such as ovulation induction, although experience is currently limited. The device used at present is the result of a gradual optimization, but further improvements are likely to occur.

The technology features a patient unit and care-provider software. The patient unit consists of a dedicated TPC, connectable to an FDA-approved compatible vaginal probe (RInterson, Pleasanton, California, United States; for additional information see www.mysonaura.com), provided in a case with gel, condoms, and written instructions that repeat those previously discussed with the patient. In between cycles, the probe is sanitized using a sporicidal and disinfectant foam (*Casalegno et al., 2012*; *Ma et al., 2012*). Images from an ongoing stimulation remain on the TPC until it is returned at the time of oocyte retrieval. The images are deleted as soon as the IVF cycle is ended by the care provider, but they are stored permanently in the cloud. Patients perform sonograms at home, but actually they could do so wherever they happen to be as long as they have WiFi access. Similarly, recordings can be received, analysed, and responded to by the care provider at geographical locations all over the world. Recordings are sent as one uninterrupted recording in a fixed sequence setting: 30 seconds for the right ovary, 15 seconds for the uterus, 30 seconds for the left ovary. Recording is started after a search during which the patient sweeps the probe in several directions, creating a mental picture of the sequence she intends to record. This takes between 5 and 20 minutes. The care-provider software can be accessed from any personal computer through a user-specific password that can be customized per doctor or per centre, opening to a home page, a list of all patients, a list of patients presently in treatment, and a list of currently active cycles.

Recordings can be stopped and replayed (in slow-motion if needed) by the doctor or sonographer as often as needed. All follicles are measured in their two largest perpendicular diameters. After measuring all visible follicles, a reply is entered in the patient communication box and, if needed, suggestions to improve image quality. Patients are instructed to visualize the majority, if not all, of the largest follicles in such a way that the largest diameter and the diameter perpendicular to it come into view at the start of the recording. Recording starts with the probe pointed toward the largest follicle in its largest diameter(s). This allows the care provider to see immediately if the recording was successful.

Patient training is very important but is needed only for first-time users, not for repeat users. A slightly filled bladder may be helpful during initial training, but is not advisable for later recordings. The pelvis should ideally be normal with a normal location of the ovaries. Usually the endometrium is visible, although there is no triple-line image at this phase of the cycle. A short registration of the uterus is mainly intended to distinguish left and right ovarian recordings from each other. Probe movements (sideways, forward, backward, and rotating) are demonstrated when searching for the resting ovaries. First sonograms are not required before day 7 or 8 of gonadotrophin injection. The patient with the shortest follicular phase received HCG on day nine of stimulation.

PRELIMINARY STUDIES PERFORMED SO FAR

Table I provides a summary of the studies conducted so far. At the very start of the project we questioned 25 consecutive couples regarding their attitude toward home sonography. Their obvious willingness to use home sonography technology prompted further research (*Gerris et al., 2009*). Proof of concept was obtained via a pilot study including 20 stimulation attempts, in which patients were monitored traditionally by one physician. After each sonogram, they repeated the sonogram themselves using normal hospital equipment. Another physician, blinded to the treatment, later repeated all measurements in one single session. There was an excellent correlation between both sets of measurements and a perfect overlap between all clinical decisions taken by both observers (*Gerris et al., 2010*).

Next, a 2-year prospective randomized trial was conducted comparing clinical and laboratory outcomes between home sonography and traditional sonography, as well as patient-reported outcomes and a health-economic analysis (*Gerris et al., 2014*). A total of 121 randomized patients completed the study with either home sonography (n = 59) or with in-clinic sonography (n = 62). The number of follicles >15 mm, the number of oocytes retrieved, the number of metaphase II oocytes, the number of transferable embryos available, the number of morphologically excellent embryos, and the number of embryos frozen were all comparable. Similar conception rates were obtained. The home sonography group showed a significantly higher feeling of empowerment, partner participation, feeling of discretion, less stress, and a trend toward more contentedness. A detailed health-economic analysis showed home sonography attempts to have a distinct financial advantage over traditional monitoring.

Subsequently, we introduced home sonography as a routine possibility for telemonitoring follicular growth. The system has been used by a small percentage of selected patients only, namely in 100 consecutive ICSI cycles in 78 different patients over a 14-month period (*Gerris et al., 2016*). Patients were counselled regarding the possibility of poor ovarian response or ovarian hyperstimulation. No systematic serum oestradiol measurements were performed. Almost all patients succeed in making clear recordings (especially once follicles were >15 mm). There was only one true method failure; all other cases either

confirmed poor or absent follicular growth or were performed for circumstantial reasons. The total ongoing pregnancy rates per started cycle were comparable to the general figures of the centre. There was a calculated mean average saving of € 600 per attempt. There were no complications. The large majority of patients and their partners were very positive about the use of the system.

Experience with home sonography in the USA is currently limited to a group of researchers from Boston IVF who reported a limited but carefully conducted pilot study at the 2016 annual meeting of the American Society for Reproductive Medicine (*Resetkova et al., 2016*). Regarding image quality, a study has been conducted showing a very high correlation between measurements performed by the patient and subsequently by a professional (*Pereira et al., 2016*).

FUTURE PERSPECTIVE

Telemedicine – defined as healthcare provided by means of a variety of telecommunication tools – has gained increasing interest during recent years (*Dorsey and Topol, 2016*). Although much is published concerning telemedicine in cardiology, diabetes, dermatology and general practice, little has been reported with respect to reproductive medicine (*Agha et al., 2009*; *Davis et al., 2010*; *Khader et al., 2014*; *Ferreira et al., 2015*; *Rashid et al., 2015*). For obvious reasons, interest has accelerated tremendously due to the recent COVID-19 pandemic. An example of telemedicine in IVF is the monitoring of ovarian response to stimulation by the patient herself away from the clinic.

Home sonography has proved useful for two reasons: (i) clinical decisions taken on the basis of this simple device used at home by the patient do not differ from those taken on the basis of high-end machine sonographies, and (ii) a complete disjunction between place and time for both patient and care provider, rendering the process of follow-up during an IVF cycle very flexible.

Home ultrasound aims to make IVF more patient-friendly and therefore increase access to treatment both in large countries where huge distances may have to be covered to reach the nearest IVF centre and in smaller but traffic-jammed urban areas. The most suitable patient for home sonography is a woman who has already gone through at least one complete ART cycle; who knows what growing follicles look like; who has logistical difficulties attending clinic because of existing professional and/or domestic responsibilities or geographical location, who is at ease with a simple vaginal manipulation and who is open to innovation.

Patients will appreciate home sonography not only as a technological innovation but also as a method of improved patient–physician interaction (*Verdonckt et al., 2017*). Though conceived as a method to be used by the patient herself, in some circumstances local general practitioners, nurses, midwives, or gynaecologists could also be the operators of the system, sending images to the responsible clinician in a distant centre. In geographically remote or difficult (e.g. mountainous) areas or in busy urban centres where transport is difficult, this may prove highly efficient.

Patients are informed if OHSS is imminent (based on sonographic observations), and an easy switch can be made to a freeze-all procedure, in which no embryos are transferred during the stimulation cycle. Home sonography can be integrated structurally in how a centre works. Interpreting the sonograms is easy to learn and could be conducted by members of the nursing staff, under supervision of reproductive physicians, whose time will thus become available for new patients or for more demanding consultations. In some countries, these professionals are already engaged in the routine sonographic follow-up.

Undoubtedly, like all innovative reproductive technologies, home sonography will also have to withstand the test of ethical acceptability (*Dondorp et al., 2011*) and further technical improvements will surely be made. When legal and reimbursement impediments can be dealt with, and once employers and insurers realize that indirect financial gain is possible through individuals undertaking sonograms conveniently at home instead of disrupting the working day to do so, it may be a useful alternative for selected patients.

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