Intrauterine pregnancy following low-dose gonadotropin ovulation induction and direct intraperitoneal insemination for severe cervical stenosis

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Abstract
We present a case of primary infertility related to extreme cervical stenosis in a 37 year-old nulligravida, which was successfully treated with ovulation induction via recombinant FSH and direct intraperitoneal insemination (IPI). Anticipating controlled ovarian hyperstimulation with in vitro fertilization/embryo transfer (IVF), the patient underwent hysteroscopy and cervical recanalization, but safe intrauterine access was not possible due to severe proximal cervical stricture. Hysterosalpingogram established bilateral tubal patency and confirmed an irregular cervical contour. Since the cervical canal could not be traversed, neither standard intrauterine insemination nor transcervical embryo transfer could be offered. Prepared spermatozoa were therefore placed intraperitoneally at both tubal fimbria under real-time transvaginal sonographic guidance using a 17 gage single-lumen IVF needle. A singleton intrauterine pregnancy was achieved after the second ovulation induction attempt. In this report, we outline the relevance of cervical factor infertility to reproductive medicine practice. Additionally, our andrology evaluation, ovulation induction approach, spermatozoa preparation, and insemination technique in such cases are described.
Introduction

For couples diagnosed with cervical factor infertility, intrauterine insemination (IUI) usually is suggested early as an appropriate therapeutic consideration when semen parameters are normal and the suspicion for tubal pathology is low. However, should the cervical canal be tortuous or occluded, neither IUI nor transcervical embryo transfer (ET) after in vitro fertilization (IVF) may be technically feasible. While such anatomical challenges essentially render the intrauterine compartment inaccessible from below, for selected patients direct intraperitoneal insemination (IPI) can be an effective treatment option, as described in this report.
Case report

A 37 year-old Caucasian nulligravida and her husband presented for evaluation of primary infertility of approximately one year duration. Both were in good general health and neither were smokers. The provisional diagnosis of cervical stenosis had been made based on an abnormal hysterosalpingogram (HSG) performed approximately six months before referral. Although the radiograph was technically difficult because of the inability to pass the catheter fully through the cervical canal, the study was able to show a pronounced filling defect near the area of the internal cervical os (Figure 1). Fallopian tubes were patent bilaterally, and free intraperitoneal spill without peritubal loculation was documented.

Ovarian reserve was estimated as reported previously [1], with cycle day #2 serum FSH and E₂ measured at 7.0mIU/ml and <32pg/ml, respectively. All other laboratory tests were within normal limits. Andrology evaluation consisted of a semen analysis, which showed total spermatozoa concentration of 70.5M/ml, 60% forward progression motility, and 17% normal forms morphology (1999 WHO criteria). A previous urology consultation had identified a varicocele, which was repaired without complication approximately one month before the couple presented at our center. Four months post-varicocelectomy, repeat semen analysis found total spermatozoa concentration to be 46M/ml, 70% forward progression motility, and 3% normal forms morphology (Kruger strict criteria).

The couple elected to undergo ovulation induction followed by IUI, with the understanding that should such therapy fail, IVF with intracytoplasmic sperm injection
(ICSI) would be considered [2]. Prior to either therapy however, hysteroscopy was recommended to map cervical anatomy with greater precision. Therefore, about one month after presentation, assessment of cervical and endometrial contours was attempted under general anesthesia, via 3mm hysteroscope. However, due to extensive cervical fibrosis, instrumentation proximal to the internal cervical os was impossible and hysteroscopy was abandoned.

The defect identified at surgery was consistent with the stricture suggested on HSG, which appeared as a "D"-shaped protrusion into the cervical canal. When the patient was informed of the operative findings, she essentially decompensated and expressed suicidal ideation. The planned outpatient procedure was therefore modified to include a brief hospital stay to facilitate psychiatry consultation and formal mental status examination. She was discharged home in stable condition 14h after hysteroscopy following psychiatric clearance.

Follow-up consultation two weeks post-hysteroscopy included discussion of controlled ovarian hyperstimulation with gamete intrafallopian transfer [3]. IVF+ICSI, followed either by tubal embryo transfer [4] or transmyometrial embryo transfer [5] was also contemplated, as was ovulation induction with direct intraperitoneal insemination (IPI). After evaluating the risks and benefits of such therapies, the couple elected the latter option. An initial ovulation induction treatment with IPI occurred two months after the aborted hysteroscopy, but the patient did not conceive. The following month, the patient underwent a second gonadotropin ovulation induction sequence using 150 IU/d
recombinant FSH (Gonal-F®, Serono Laboratories; Norwell, Massachusetts USA) plus 150 IU/d human menopausal gonadotropin (Repronex®, Ferring Pharmaceuticals; Copenhagen, Denmark), both administered subcutaneously [6]. After a six day follicular recruitment phase, nonrecombinant hCG (10,000 IU; Novarel®, Ferring) was administered subcutaneously when serum estradiol and transvaginal sonography suggested follicular maturity [7].

The patient returned 24h after hCG injection, where informed consent was again obtained for direct IPI under real-time transvaginal sonographic guidance. On the day of insemination, the partner’s semen parameters were 70M/ml with 60% motile cells (morphology analysis not performed). The specimen was washed twice with human tubal fluid, and then layered upon a dual-density (90%/45%) gradient (PureSperm®, Nidacon International; Gothenburg, Sweden) and centrifuged at 300g [8]. Resuspended to a volume of 10ml, the sample was then divided into two components of 5ml each. These two equivalent samples were injected directly into the intraperitoneal cavity (5ml to each tubal fimbria). IPI was accomplished by 17 gage single-lumen oocyte retrieval needle (Cook IVF; Spencer, Indiana USA) passed under transvaginal sonographic guidance. No intravenous sedation was administered, but each vaginal fornix was pretreated with 1% lidocaine without epinephrine (AstraZenica Pharmaceuticals LP; Wilmington, Delaware USA) via 25 gage spinal needle. After transvaginal mucosal puncture, the proximal vagina was reexamined and good hemostasis was noted. She tolerated the procedure well and there were no complications.
The patient had no menses two weeks post-procedure; she returned for pregnancy test and a serum hCG of 223mIU/ml was registered. Two days later, the value had increased to 411mIU/ml. One month after insemination, transvaginal sonogram revealed a single intrauterine gestational sac with mean diameter of 15mm (5 6/7 weeks gestation). A 5mm fetal pole (6 0/7 weeks gestation) was also seen, with embryonic cardiac activity documented by B-mode Doppler pulse sonography (rate=124/min). The intrapartum course remains uncomplicated through the 20th gestational week.
Discussion

While cervical factor infertility accounts for only about 5% of reproductive endocrinology consultations [9], this subset of patients nevertheless represents a clinical group where satisfactory outcomes are attainable when therapy is properly targeted. In this report, we describe the management of severe cervical stenosis in a woman with bilateral tubal patency and a normal intrauterine cavity. Although prepared to undergo IVF-ET at our facility, the couple first wanted to attempt pregnancy by a less complicated and less costly method. Unfortunately, the tight cervical canal suggested by HSG (and corroborated at hysteroscopy) represented an unexpected technical challenge frustrating their plans both for IVF and IUI.

Intraperitoneal insemination (IPI) warrants consideration in such cases of cervical stenosis where tubal patency has been confirmed, no intrauteriune contour defects exist, and there is no profound male factor infertility diagnosis [10-12]. As with the more commonly performed IUI, the efficacy of IPI is directly related to the overall spermatozoa concentration, motility, and morphology [13,14]. Because tubal patency had been demonstrated radiographically in this case, we discussed laparoscopic gamete (or zygote) intrafallopian transfer as well as ovulation induction with IPI. The rationale for laparoscopy-based treatments would have been strengthened if multiple intraperitoneal inseminations had failed, yet controversy remains as to how many such unsuccessful inseminations should be performed prior to embarking on the advanced reproductive technologies [15].
How best to determine which couples would benefit most from IPI remains undecided, but our decision was influenced by semen parameters and the patient's willingness to undergo transvaginal needle punctures. Previous investigators have compared pregnancy rates after IPI and standard IUI, and found the outcomes to be roughly equivalent [16]. However, in this case the inability to attain safe instrumentation through an abnormal cervical canal sharply limited the options for fertility treatment, so IUI was not possible.

The relationship between de novo cervical stenosis and intrapartum events has received less study than the cervical injury attributable to ablative procedures and subsequent obstetric outcome [17]. Yet, whether or not the cervical stenosis observed in our case will be associated later with a complicated intrapartum course (perhaps mediated by impaired cervical dilation) remains to be seen and forms the basis of ongoing research.
Caption

Figure 1. Early fill view from hysterosalpingogram obtained from our patient with severe cervical stenosis (arrow). Extensive cervical stricture prohibited passage of insemination or embryo transfer catheters; safe transcervical instrumentation was also impossible. Bilateral tubal patency was confirmed in the subsequent images.
References


