Issue 8

Infertility and its management

The unusual & newer practices in reproductive medicine

Springer Healthcare Education

Abbott

FOR LUTEAL PHASE SUPPORT IN ART

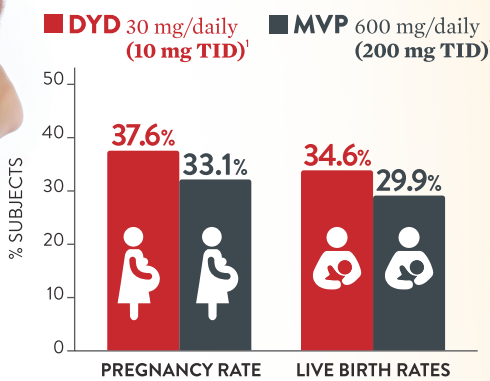
TRUST THAT'S PROVEN

IF IT'S ORALLY EFFECTIVE, IT'S†

duphaston®

Dydrogesterone Tablets IP 10mg

FINDINGS FROM LOTUS-1 2017



ORAL DYDROGESTERONE MAY REPLACE MVP

AS THE STANDARD OF CARE FOR LUTEAL PHASE SUPPORT IN IVF DUE TO:[1]

- Good efficacy and safety profile[1]
- Improved patient compliance[1]

ART: Assisted reproductive technology. **LPS:** Luteal phase support. **TID:** Ter in die (Three times a day). **IVF:** In vitro fertilisation. **MVP:** Micronized vaginal progesterone. **DYD:** Dydrogesterone. † Schindler AE. Progestational effects of dydrogesterone in vitro, in vivo and on the human incidence of miscarriage endometrium. Maturitas.2009; 65(1):S3–S11. ‡ Internal calculations based on Quintiles IMS database, IMS Health Analytics Link MAT03 2017. * Data on file.

Reference: 1. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. Aphase 3 randomised controlled trial comparing the ef2 cacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Human reproduction, Vol 32, no 5 pp.1019-1027,2017.

Abbreviated Prescribing Information: Dydrogesterone Tablets IP **Duphaston®. LABEL CLAIM:** Each film coated tablet contains: Dydrogesterone IP 10 mg, Excipients q.s. Colour: Titanium dioxide IP. **INDICATION:** Progesterone deficiencies: Treatment of dysmenorrhoea; Treatment of endometriosis; Treatment of secondary amenorrhoea; Treatment of irregular cycles; Treatment of dysfunctional uterine bleeding; Treatment of pre-menstrual syndrome; Treatment of threatened miscarriage; Treatment of habitual miscarriage; Treatment of infertility due to luteal insufficiency; Luteal support as part of an Assisted Reproductive Technology (ART) treatment and Hormone replacement therapy. **DOSAGE AND ADMINISTRATION** Dysmenorrhoea: 10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. Endometriosis: 10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously. Dysfunctional uterine bleeding: When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days. Secondary amenorrhoea: 10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen. Pre-menstrual syndrome: 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Irregular cycles: 10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Threatened miscarriage: An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30mg per day until symptoms remit. Habitual miscarriage: 10 mg dydrogesterone twice daily until the twentieth week of pregnancy. Infertility due to luteal insufficiency: 10 or 20 mg dydrogesterone daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles. Luteal support as part of an Assisted Reproductive Technology (ART) treatment: 10 mg Dydrogesterone three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed. Hormone replacement therapy: Continuous sequential therapy: An estrogen is dosed continuously and one tablet of 10mg dydrogesterone is added for the last 14 days of every 28-day cycle, in a sequential manner. Cyclic therapy: When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12 -14 days of estrogen therapy. **CONTRAINDICATIONS:** Known hypersensitivity to the active substance or to any of the excipients. Known or suspected progestogen dependent neoplasms (e.g. meningioma). Undiagnosed vaginal bleeding. Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion /miscarriage. Contraindications for the use of estrogens when used in combination with dydrogesterone. **WARNINGS & PRECAUTIONS:** Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with dydrogesterone and ceasing the treatment should be considered: Porphyria, Depression and Abnormal liver function values caused by acute or chronic liver disease. **PREGNANCY & LACTATION:** It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Dydrogesterone can be used during pregnancy if clearly indicated. Breastfeeding: No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicate that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period. Fertility: There is no evidence that dydrogesterone decreases fertility at therapeutic dose. **ADVERSE REACTIONS:** The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness. Undesirable effects in adolescent population: Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults. Undesirable effects that are associated with an estrogen-progestogen treatment (see also 'Warnings and Precautions' and the product information of the estrogen preparation): Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer; Venous thromboembolism; Myocardial infarction, coronary artery disease, ischemic stroke

Issued on: Date (27/06/2018)

Source: Prepared based on full prescribing information (version 6) dated 27/Jun/2018

® Registered Trademark of the Abbott Products Operations AG.

For full prescribing information, please contact: Abbott India Limited, 16th Floor, Godrej BKC, Plot C-68, 'G' Block, Bandra-Kurla Complex, Near MCA Club, Bandra East, Mumbai-400 051. www.abbott.co.in

Infertility and its management

The unusual & newer practices in reproductive medicine

Springer Healthcare Education

December 2018

Springer Healthcare

This edition is created in India for free distribution in India.

This edition is published by Springer Nature India Private Limited.
Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
91 (0) 11 4575 5888
www.springerhealthcare.com

Part of the Springer Nature group

Printed and Bound by: Hi-Tech Printing Services Pvt. Ltd., Mumbai, India.

Preface

Robotic tubal reanastomosis marked the beginning of the era of robotic surgery in gynecology. In 1998, Margossian *et al.* work on porcine animal models concluded that a robotic approach to tubal surgery is a safe and feasible technique, with 100% immediate and 67% 4-week patency rates. Two years later, Falcone et al. and Degueldre et al. described bilateral tubal reanastomosis in ten and eight cases, respectively, completed with the robotic surgical systems. Currently, robotics is being used in every area of infertility and gynecological surgery.

Advanced glycation end products are pro-inflammatory molecules that trigger a state of intracellular oxidative stress and inflammation after binding to their cell membrane receptors, such as RAGE. The activation of the AGE-RAGE axis has been well known to play a role in type 2 diabetes mellitus, obesity, metabolic syndrome, cardiovascular disease, aging, inflammation, and neurodegenerative disorders. AGEs might contribute to the etiology of polycystic ovary syndrome and infertility. There exists a complex relationship between the AGE-RAGE system and infertility as well as ovarian reserve in women of reproductive age.

Recently, increased attention has been placed on the male partner in infertility, and it is becoming clear that a diagnosis of male factor infertility may be associated with long-term health consequences that go beyond the immediate reproductive needs of patients, particularly in the current environment of increasing paternal age.

This book highlights some of the important insights into the newer and unusual practices in infertility and how to manage infertility effectively. We sincerely hope that this initiative goes a long way in managing patients with infertility and improve clinical outcomes in infertile couples.

Happy reading!

Contents

Role of Robotics in the Management of Infertility

Sami Gokhan Kilic, Bekir Serdar Unlu, Mertihan Kurdoglu

Robot-Assisted Tubal Reversal

Background

The permanent female family planning option of tubal ligation is a safe, highly effective, and permanent form of contraception. Tubal ligation includes a number of different procedures and techniques. The idea behind the technique is to prevent pregnancy by disrupting the patency of the fallopian tubes [1]. Depending on the timing of the procedure, tubal ligation may be performed in one of the several ways. It may be performed immediately after childbirth (postpartum sterilization) or at a time unrelated to a pregnancy (interval sterilization). Postpartum sterilization procedures are performed following Cesarean section or vaginal delivery via minilaparotomy. For interval sterilization, laparoscopy is the most preferred option. Pomeroy, Parkland, Irving, and Madlener procedures, as well as fimbriectomy, are common open surgical methods. Laparoscopic tubal sterilization is disruption of tubal continuity through the use of loops, clips, or electrocautery.

Although tubal sterilization procedures are considered to be permanent, requests for reversal of the procedure (recanalization) are not infrequent (1–5%) [2]. The reversal procedure can be done either by open

S.G. Kilic, M.D., F.A.C.O.G., F.A.C.S. (✉), B.S. Unlu, M.D. M. Kurdoglu, M.D.

Division of Minimally Invasive Gynecology and Research, Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, TX, USA
e-mail: gokilic@utmb.edu; drserdarunlu@yahoo.com; mkurdoglu@yahoo.com

laparotomy or by minimally invasive surgery (laparoscopic or robotic approaches). The damaged part of the tube is excised, and the remaining patent ends are brought together and sutured, thus reestablishing tubal patency. The use of a microscope or loupes for magnification has been shown to be beneficial during open surgery [3] but is not necessary with a robotic approach since robotic surgical equipment provides magnification in addition to three-dimensional (3D) viewing.

The method of sterilization, remaining tube length following reversal, the length of time from the original sterilization procedure to reversal, and the woman's age are important factors that affect the success of reversal procedures [4]. Women's age older than 36 years, remaining tube length less than 4 cm, and sterilization for more than 5 years were found to negatively influence the success rate of the reversal procedure [5]. In terms of pregnancy rates, reversal procedures using clip or Falope ring sterilization have better results compared to coagulation or Pomeroy's technique. The use of operating loupes or a microscope, fine sutures, operator experience, and surgical techniques plays an important part in the success of reversal procedures [5]. The most reversible procedure is the placement of the Falope ring (83% term delivery), and the least reversible is fimbriectomy (29% term delivery) [3].

Description of the Intervention

The traditional approach has been to perform a laparoscopy to determine operability followed by an open laparotomy procedure using microsurgical techniques. Pregnancy rates of 70–80% have been achieved in women with a good prognosis [3, 5].

Because technology has developed and equipment has improved, laparoscopic surgeons are now recommending laparoscopic tubal reanastomosis with more confidence. Quicker recovery time and return to the job, early hospital discharge, and smaller incisions are the main advantages of this approach for the patients [6]. However, laparoscopic tubal anastomosis requires a high level of surgical expertise and proficiency. The laparoscopic method has a long learning curve for attaining proficiency in successful tubal reanastomosis compared to traditional open methods and is therefore only available only in selected centers. Safety and success are

imperative in any surgery. According to some reports, laparoscopic tubal reanastomosis has more than 70% success for conception and ongoing pregnancy, a rate which is comparable to conventional open surgical techniques [6].

Robotic Surgery in Tubal Reversal

Robotic tubal reanastomosis marked the beginning of the era of robotic surgery in gynecology. In 1998, Margossian *et al.*'s work on porcine animal models concluded that a robotic approach to tubal surgery is a safe and feasible technique, with 100% immediate and 67% 4-week patency rates [7]. Two years later, Falcone *et al.* (ZEUS Robotic Surgical System, Computer Motion, now Intuitive Surgical, Sunnyvale, CA) and Degueldre *et al.* (da Vinci Surgical System, Intuitive Surgical) described bilateral tubal reanastomosis in ten and eight cases, respectively, completed with the robotic surgical systems [8, 9].

For the last decade, surgical sterilization has been the second most commonly used form of contraception overall in the United States and the most frequently used method among married women and women over 30 years old. Bilateral tubal ligation is the most effective and commonly used method of surgical sterilization [10]. While completion of childbearing and medical indications are the main reasons for undergoing tubal ligation, up to 30% of women will later regret their decisions. Change in a partner or marital status, young age, and nonwhite race are predictors for regret [2].

Microscopic tubal reanastomosis is generally recommended for women without a history of reproductive dysfunction [11]. Age is an important factor for prediction of pregnancy rates and pregnancy outcomes and should be considered along with other reproductive parameters as part of the preoperative workup.

Surgical Procedure

Several surgical techniques have been described for robotic tubal reanastomosis [11–13]. A commonly used protocol is to induce general anesthesia, place the patient in the dorsal lithotomy position, and apply intermittent pneumatic compression boots in both lower extremities.

A uterine positioning system is used to ensure consistent intrauterine manipulation and chromopertubation. Pneumoperitoneum is created with a Veress needle followed by port placement and placement of a Visiport (US Surgical, Norwalk, CT) 5-mm trocar along with an orogastric tube in the suction mode to deflate stomach air. The da Vinci Si robot (Intuitive Surgical, Sunnyvale, CA) is docked obliquely, and the patient is placed in a Trendelenburg position. The surgical team insufflates the abdomen up to 11–14 mmHg and inserts three robotic ports under direct visualization. The 12-mm camera trocar is generally placed at the umbilicus. Two 8-mm robotic trocars are placed 8–12 cm lateral and slightly caudal to the umbilicus. An additional 12-mm assistant port is placed in the left upper quadrant, replacing the 5-mm initial trocar. The standard protocol allows for positioning of the robot between the patient's legs, although side docking is our preferred approach due to ease of vaginal access for chromopertubation and uterine manipulation [14].

After the robot is docked, scissors and bipolar forceps are used to immobilize the mesosalpinx and distal and amputate proximal tubal segments. The third robotic arm is used to improve exposure with robotic forceps. In most cases, the preferred hemostasis routine is dilute vasopressin injection into the proximal and distal segments of the mesosalpinx. Preferably, the surgeon should minimize the use of electrosurgery to avoid damage to the fallopian tube tissues. After amputating both sides of the stumps, chromopertubation is performed to assure tubal patency.

A catheter is used as a tubal stent to identify the distal tubal lumen and secure the anatomic orientation of the tube during the reanastomosis. Two Black Diamond Micro Forceps (EndoWrist; Intuitive Surgical) are utilized for suturing. Most centers prefer using 6-0 polyglycolic acid (reapproximate the mesosalpinx) and 8-0 polypropylene sutures (reapproximate the tube). At the end of the procedure, chromopertubation is performed to assure tubal patency, and an adhesive barrier is placed.

After Surgery

For the postoperative follow-up, patients are taken to the recovery room and observed for several hours. Nonsteroidal anti-inflammatory drugs and narcotic pain medication are used for postoperative pain control. Patients can discharge the same day if there is no other contraindication

to discharge, but patient activity is limited for up to 14 days after surgery. Conception is not recommended until a hysterosalpingogram (HSG) at least 8 weeks after surgery confirms tubal patency.

After surgery, the risk of ectopic pregnancy is increased up to tenfold compared with the general population [15]. Therefore, patients should undergo a pregnancy test immediately following the first day of a missed menstrual period to exclude ectopic pregnancy.

In one study, the pregnancy rate was found to be 71% at 2-year follow-up after robotic tubal reanastomosis. The highest pregnancy rate, 91%, was observed in patients under 35 years old, and the lowest pregnancy rate, 33%, was in those over 43 years. Pregnancy rates among women aged 36–39 years were 75%; in those aged 40–42 years, the rate was 50% [16].

In two prospective studies evaluating surgical outcomes following robotic tubal reanastomosis (total of 95 patients), authors found prolonged surgical times and increased cost for the robotic versus a classic open microsurgical approach to tubal reanastomosis [13, 17]. Hospitalization times and pregnancy and ectopic pregnancy rates were comparable between the two groups. Dharia Patel *et al*. reported shorter hospitalization times and decreased time for recovery in the robotic surgery group. The cost per delivery was similar between the two approaches.

In conclusion, robotic tubal reanastomosis is a safe and feasible technique with pregnancy rates on par with those achieved following in vitro fertilization (IVF) [13].

Robot-Assisted Reconstruction of Uterine Anomalies

Introduction

Müllerian duct anomalies are congenital malformations caused by altered development of the genital tract with a prevalence of 5–7% in the female patient population [18–20]. They are often asymptomatic and therefore unrecognized until they present with a variety of gynecological and obstetrical problems [21, 22]. A variety of surgical treatment modalities are performed to restore a normal uterine and/or vaginal architecture and preserve fertility. Since vascularization of anomalous organs and myometrial and cervical functions may also be impaired, normal or near-normal architecture cannot always be achieved [23].

Surgical correction of these anomalies can be performed either by open abdominal/vaginal surgery or by endoscopic approaches including hysteroscopic, laparoscopic, or robot-assisted laparoscopic routes. The nature of the anomaly determines the most appropriate method.

In addition to a general outline of the classification, etiology, presentations, investigations, and available treatment options, this chapter will review robot-assisted laparoscopic surgery as a relatively new approach for correcting these congenital Müllerian anomalies.

Background/Etiology

A series of complex events including cellular differentiation, migration, fusion, and canalization are involved in the development of the female genital tract, and any failure of these processes at any step may lead to a congenital anomaly. Embryologically, Müllerian abnormalities arise mainly from four defective Müllerian duct steps with a sporadic occurrence and no evidence of familial inheritance [20, 24]:

- Unilateral maturation of one Müllerian duct with absent or incomplete development of the other side, either focal or whole-tube agenesis of both Müllerian ducts
- Absent or faulty midline fusion of the Müllerian ducts
- Defects of canalization

The most widely accepted classification of Müllerian duct anomalies is the American Fertility Society (AFS) classification which categorizes these anomalies into groups with similar clinical characteristics, pregnancy prognosis, and treatment. Reproductive tract abnormalities associated with the fetal exposure to diethylstilbestrol (DES) are also included in this classification as class VII [24].

The Class I defects caused by segmental Müllerian hypoplasia or agenesis may affect the vagina, cervix, uterine fundus, or fallopian tubes. These defects can occur in isolation or may be seen in association with other Müllerian defects. Class I vaginal abnormalities comprise vaginal agenesis and two types of congenital septa, arising from either a fusion, a resorption defect (longitudinal septum), or incomplete canalization/vertical fusion failure between the up-growing urogenital sinus and the down-growing Müllerian duct system (transverse septum). In Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, upper vaginal agenesis

is typically associated with hypoplasia or uterine agenesis and may be accompanied by renal, skeletal, and auditory system abnormalities. Class I cervical developmental abnormalities are constituted of duplication, partial or complete agenesis, and longitudinal septa [24, 25].

Although they may be observed in a variety of forms, the more common uterine abnormalities may be categorized in AFS classification as uterine fundal hypoplasia or agenesis (Class I), unicornuate uterus (Class II), uterine didelphys (Class III), bicornuate uterus (Class IV), septate uterus (Class V), and arcuate uterus (class VI) [24]. In a review by Nahum, the most common uterine anomalies were bicornuate (39%) and septate (34%), while didelphic, arcuate, unicornuate, and hypo or aplastic were observed as 11%, 7%, 5%, and 4%, respectively [26].

In unicornuate uterine anomaly, which develops in 1 in 4000 women [27], a rudimentary or underdeveloped horn may be present or absent. When it is present, there may or may not be communication with the other horn, and an endometrium-lined cavity may or may not exist [25].

A total lack of Müllerian duct fusion leads to uterine didelphys, which are characterized by two entirely separate cervices, hemi-uteri, and, usually, two vaginas or a longitudinal vaginal septum [28]. It can occur in isolation or may be part of a triad named shortly as obstructed hemivagina and ipsilateral renal agenesis (OHVIRA) which is also known as Herlyn-Werner-Wunderlich syndrome [29, 30].

The lack of fundal fusion may also result in two hemiuteri, with only one cervix and vagina, which is called bicornuate uterus. A longitudinal vaginal septum may also accompany this anomaly [25].

When a defect in resorption results in a persistent partial or complete longitudinal septum within the uterine cavity, a septate uterus is formed. A complete vaginocervicouterine septum may be detected in rare cases [25].

The arcuate uterus is a kind of malformation which is regarded as a mild deviation from normal uterine development [25].

Hybrid anomalies are not described in AFS classification. For example, the combination of a septate uterus and bicornuate uterus is called "hybrid septate variety" and is not included in the classification [24, 31]. Nonuterine anomalies are also not included in AFS classification, but it allows additional descriptors of associated vaginal, tubal, and urinary abnormalities.

Presentation, Investigation, and Treatment Options

The presentation of Müllerian anomalies varies greatly, depending on the defect involved. Either cyclic or noncyclic pelvic pain and dysmenorrhea with increasing intensity, abnormal vaginal bleeding, or pain may be observed in adolescent girls after the start of menstrual periods. As for menstrual abnormalities, while minimal endometrium may lead to hypomenorrhea in some cases, amenorrhea may signify a vertical fusion defect or Mayer-Rokitansky-Küster-Hauser syndrome. A longitudinal vaginal septum, which may occur alone or accompany a didelphic or other form of double uterine anomaly, may lead to dyspareunia, leukorrhea, bleeding complaints despite the use of a tampon, and dystocia at delivery. In some cases, a mass may be detected on bimanual examination due to a hydrocolpos, and hematocolpos may be caused by a one-sided obstruction in the vagina, which may be complicated with microperforations leading to infection. If a noncommunicating functioning horn leads to retro menstruation, a woman may present with endometriosis and its associated symptoms. Obstetrical complications, such as recurrent pregnancy loss, cervical incompetence, antepartum and postpartum bleeding, intrauterine growth restriction, malpresentation, preterm delivery, pregnancy-associated hypertension, uterine rupture, and cesarean delivery, are also more common in women with uterine anomalies [32]. Women with or without uterine anomalies have similar clinical pregnancy rates when they undergo IVF [33, 34] since uterine abnormalities typically don't interfere with conception and implantation.

During the evaluation of common gynecologic and obstetric problems mentioned above, most congenital anomalies of the uterus and vagina are diagnosed incidentally. During infertility or reproductive loss workup, anomalies are discovered after a two-dimensional ultrasonography or hysterosalpingogram, which are the acceptable first-line screening tools favoring assessment of the adnexa and fallopian tube patency, respectively. Ultrasonography is also helpful to detect associated renal anomalies. The uterine cavity may be well delineated by both hysterosalpingography and saline infusion sonohysterography. Magnetic resonance imaging and/or three-dimensional ultrasonography are also the best noninvasive means to diagnose uterine anomalies [32]. Although they are less frequently required because of the radiologic advances described above,

additional information may be obtained by examination with the patient under anesthesia, vaginoscopy, or laparoscopy alone or together with hysteroscopy in cases of complicated Müllerian anomalies [35, 36].

Among the various types of congenital uterine anomalies, uterine septa, bicornuate uteri, and obstructed hemiuteri, rather than unicornuate or arcuate uteri, are good candidates for surgical repair with the indications of pelvic pain and repetitive pregnancy loss after other causes are excluded [37].

The obstructed rudimentary noncommunicating uterine horn should be removed by laparoscopic or robot-assisted laparoscopic routes.

If medical therapy is ineffective, dysmenorrhea in women with septate uteri may be candidates for hysteroscopic metroplasty. In such cases, the possibility of coexistent endometriosis should also be evaluated by laparoscopy [23]. However, if the septum cannot be safely removed hysteroscopically or the uterine cervix cannot be dilated for introduction of the hysteroscope, then abdominal or laparoscopic approaches, such as the Jones metroplasty (a wedge resection of the portion of the uterine fundus containing the septum) or Tompkins metroplasty (a modified Jones metroplasty technique performed without removing any tissue) can be used [23]. As an acceptable alternative to abdominal metroplasty for uterine unification, robotic metroplasty with modified Jones metroplasty technique was reported for a patient with complete septated uterus with double cervix [38]. In a report by Gungor *et al*., a modified Tomkin's metroplasty procedure was performed with the use of robotic technology in a patient with hybrid septate variant anomaly [39].

For vaginal construction in patients with vaginal agenesis, androgen insensitivity syndrome, congenital adrenal hyperplasia, and gonadal dysgenesis, various nonsurgical and surgical techniques with different functional outcomes have been described [40]. As a first-choice treatment, nonsurgical vaginal dilation has been put forward. Although its functional results are good, keeping the neovagina patent requires mechanical dilatation with lubrication and periodically [41]. Among surgical techniques, the Abbe-McIndoe operation, the laparoscopic Davydov technique, the laparoscopic Vecchietti modified technique, and laparotomic and laparoscopic sigmoid vaginoplasty are the most widely used [42–46]. The first case of robot-assisted rectosigmoid vaginoplasty performed on an adolescent with congenital vaginal atresia was reported by a pediatric

surgeon group in 2008 [47]. Recently, Boztosun and Olgan presented a second case of a robotic approach to vaginal agenesis repair in an adolescent girl [48]. From India, Pushkar *et al*. reported a combined robotic and perineal approach for a 9-year-old girl with vaginal atresia in which the urogenital sinus (UGS) failed to contribute to the formation of the lower (distal) portion of the vagina [49].

For women with Müllerian agenesis and fusion defects, such as MRKH and congenital absence of the uterus, uterine transplant is a potential alternative to adoption or using a gestational carrier [23]. The robot-assisted approach has never been described for uterine transplantation, but it was recently proposed by Iavazzo and Gkegkes [50].

Surgical Technique

Initially, Kim *et al*. presented their technique for a completely robotic approach for the abdominal portion of a sigmoid vaginoplasty operation performed on a 17-year-old patient with 46,XY with androgen insensitivity syndrome [47]. Later, Boztosun and Olgan described their technique for robotic sigmoid vaginoplasty in an adolescent girl with MRKH. After the patient was positioned in a modified lithotomy position with PAS stockings with legs apart and secured to the bed with tape across the chest, four ports were used. The port placement was guided from prior reports of robotic sigmoid resection and the expected range needed to work in the patient's pelvis [51, 52]. Intraumbilically, a 12-mm trocar was placed, and two 8-mm robotic ports were placed in the left upper quadrant along the anterior axillary line and in the right lower quadrant lateral to the inferior epigastric vessels. As an accessory port, a fourth 5-mm laparoscopic port was placed just below the umbilicus and lateral to the inferior epigastric vessel port to provide additional retraction and expedite suture passage. After the table was rotated with the right side down approximately 30° for the small intestine to fall out of the surgical field, the robot was docked from the patient's left side [47]. After mobilization of the sigmoid colon, a 15-cm segment was measured with a piece of suture material and divided via a laparoscopic endovascular stapler introduced through the 12-mm umbilical port under temporary viewing with a 5-mm laparoscopic camera. With the robotic arms, the colon was reanastomosed, and the mesentery was reapproximated using a freehand technique. The

isolated sigmoid segment was brought to the true pelvis without tension on its blood supply. A metal dilator was introduced from the perineum, posterior to the bladder and anterior to the rectum, to identify a path to position the sigmoid segment. By using electrocautery from a robotic working arm, an access into the peritoneum was made, and the distal end of the sigmoid was brought out the perineum. Additional tacking sutures were placed from the abdomen to secure the serosa of the sigmoid to the peritoneum in the pelvis [47].

To alleviate dysmenorrhoea, prevent an intracornual pregnancy, and possibly prevent endometriosis in cases of a rudimentary horn, a robotic-assisted laparoscopic approach can be used to perform a hemi-hysterectomy. In such cases, it is better to insert a uterine manipulator via the cervix to enable lateralization and identification of the communicating hemiuterus. If the cystic mass is large, the trocars are placed higher, but equally distributed, with an aim to facilitate surgery in the upper abdomen, as used for standard robot-assisted surgery in the pelvis [53, 54].

Results

Robotic vaginoplasty provides an opportunity for healthy adolescent patients with vaginal agenesis to benefit from the satisfying functional and relatively cosmetic results [48]. Performing a vaginal reconstruction by using a sigmoid colon in a minimally invasive approach, a colon-colon anastomosis without using a stapling device in laparoscopy, or an extracorporeal reconstruction through an additional incision of 3–4 cm necessitates extra surgical skills and training. However, with the advent of robotic surgery, the articulating instruments of the robot may provide complete wrist dexterity, which combines fine control with precision when performing cutting and intracorporeal suturing [55]. Therefore, a robotic vaginoplasty performed with a robot-sewn anastomosis might avoid additional laparoscopic techniques and laparotomy, resulting in a reduced risk of anastomotic complications [56] and a hospitalization time approximately 3 days shorter than for laparotomy [48]. In a recent report of robotic sigmoid vaginoplasty technique [48], the docking, surgeon console (including both abdominal and vaginal procedures), and total operative times (from docking to undocking) were reported as 50, 180, and 240 min, respectively. In the first report by Kim *et al.*, the total time in

the operating room was 9 h and 45 min, more than 90 min of which was used for access issues [47].

Robotic metroplasty is reported to be a safe, feasible, and successful surgical option [38, 39]. In addition to the technologic advantages of ergonomics, magnified high-definition (HD) three-dimensional (3D) optics, the autonomy of camera control, and wristed instrumentation, robotics may simplify the operation by allowing a delicate dissection of the uterus with minimal injury to the uterine wall, which might be more difficult with a traditional laparoscopic approach.

The robotic system also facilitates minimally invasive surgery even in rare and complex conditions which may be encountered during the corrective surgeries of various anomalies. As demonstrated by Anderberg *et al.*, the meticulous retroperitoneal vessel dissection and subsequent step-by-step mapping and coagulation of the atypical blood vessels supplying the hemi-uterus and adnexa were successfully achieved with a robot-assisted laparoscopic approach during a hemi-hysterectomy procedure for a rare genitourinary malformation with associated duplication of the inferior vena cava [53]. The main disadvantages of a robot-assisted approach are the high cost for the health centers and the patients, the requirement for a larger operating room because of the bulky machinery, and the necessity of specific training for the surgical team. The need for more and larger ports may be a relative disadvantage for some patients who are highly worried about the cosmetic results.

Complications

The limited number of case reports related to corrective surgeries for female reproductive tract anomalies showed good results with no postoperative complications. The estimated blood loss was minimal, usually less than 100 mL [39, 47, 48, 57]. There is an increased risk of uterine rupture with procedures requiring fundal hysterotomy, and cesarean delivery is recommended for these women [23].

Conclusion/Personal Review

A steep learning curve is inevitable for reconstructive laparoscopic procedures. Robot-assisted laparoscopy may offer an avenue for overcoming

some of the technical limitations of traditional laparoscopic surgery. The feasibility of robotic sigmoid vaginoplasty and robotic metroplasty with various corrective surgery techniques for female genital tract anomalies has been well explored, and the robotic approach gives hope for a possible role in uterine transplantation, too. However, we should keep in mind the fact that with the refinement of the technology, the issues of cost and training need to be addressed for the full acceptance of these robotic-assisted laparoscopic techniques in the future.

Robotic Surgery in Cervical Insufficiency

Cervical insufficiency is also known as incompetent cervix, which is characterized classically by painless cervical dilatation in the second trimester. It can be followed by prolapse and ballooning of membranes into the vagina, which leads to loss of otherwise normal pregnancies or preterm birth, with an incidence of 0.1–1.0% of all pregnancies. If not effectively treated, this sequence may repeat in future pregnancies. The term has also been applied to women with one or two such losses/births or those at risk for second-trimester pregnancy loss or preterm birth [58].

Risk Factors

Risk of cervical insufficiency is increased with congenital and acquired cervical abnormalities; acquired risk factors are more common.

Acquired abnormalities include:

- Cervical trauma during labor or delivery (spontaneous, forcepsor vacuum-assisted, cesarean) [59]
- Rapid mechanical cervical dilation before a gynecologic procedure (e.g., uterine evacuation) [60] or treatment of cervical intraepithelial neoplasia

Congenital abnormalities include:

- Genetic disorders affecting collagen (e.g., Ehlers-Danlos syndrome) [61],
- Uterine anomalies [62, 63]
- In utero diethylstilbestrol (DES) exposure [64]
- Biologic variation

How Can We Make Diagnosis of Cervical Insufficiency?

In our clinical practice, two main diagnoses of cervical insufficiency are present:

- Based on historic factors, diagnosis is made in women with two or more consecutive prior second-trimester pregnancy losses associated with relatively painless early cervical dilation or three or more early (<34 weeks) preterm births in which other causes of pregnancy loss or preterm birth have been excluded.
- Diagnosis is also made on a combination of historic factors and transvaginal ultrasound measurement of cervical length. Having one or two prior second-trimester pregnancy losses or preterm births and cervical length ≤25 mm on transvaginal ultrasound examination or advanced cervical changes on physical examination before 24 weeks of gestation may be risk factors for cervical insufficiency that support the diagnosis.

Treatment

Nonsurgical and surgical modalities have been defined to treat cervical insufficiency.

Nonsurgical approaches. Unfortunately, nonsurgical approaches, such as activity restriction, bed rest, and pelvic rest, have not been proven effective for treating cervical insufficiency, and their use is discouraged [65, 66]. Vaginal pessary, which is another nonsurgical option, is considered in patients at risk for cervical insufficiency. Evidence is limited for potential benefit of pessary placement in select highrisk patients [67–69].

Surgical approaches. Transvaginal and transabdominal routes are identified procedures for cervical cerclage. More proximal placement of the stitch, decreased risk of suture migration, absence of a foreign body in the vagina that could promote infection, and the ability to leave the suture in place for future pregnancies are the main advantages of the transabdominal over transvaginal cerclage [70]. A disadvantage of this approach is the potential need for two laparotomies during pregnancy (one to place the cerclage and potentially another to remove it).

How Can We Treat the Patient Surgically?

Transvaginal cerclage. Modifications of the McDonald and Shirodkar techniques are the standard methods currently used. The superiority of one surgical technique or suture type over another has not been proven [71, 72]. In the McDonald procedure, a simple purse-string suture of nonresorbable material is inserted at the cervicovaginal junction [73]. The Shirodkar procedure involves dissection of the vesicocervical mucosa in an attempt to place the suture as close to the cervical internal os as might otherwise be possible. Dissection is necessary for the bladder and rectum from the cervix in a right plane through the cephalic line. Then the suture is placed and tied, and the mucosa is resutured over the knot [74, 75]. As in the McDonald procedure, nonresorbable sutures are preferred for cerclage placement in the Shirodkar procedure, too.

Transabdominal cerclage. Abdominal cerclage procedures are usually performed in the late first trimester or early second trimester (10–14 weeks of gestation) or in the nonpregnant state [76, 77]. The stitch can be left in place between pregnancies with subsequent cesarean delivery.

Transabdominal placement of a cerclage at the cervicoisthmic junction appears to be a safe and effective procedure for reducing the incidence of spontaneous pregnancy loss in selected patients with cervical insufficiency [78, 79]. Cervicoisthmic cerclage is generally reserved for when anatomical limitations (e.g., after a trachelectomy) prevent cerclage placement or when previous failed transvaginal cervical cerclage procedures have resulted in second-trimester pregnancy loss [80]. Two options available for transabdominal cerclage are open (laparotomy) or minimally invasive (laparoscopy/robotic).

The preferred route can depend on physician experience or patient preference. In a systematic literature review, no evidence exists to suggest that laparoscopically performed surgical approach for cervicoisthmic cerclage placement has an advantage over the laparotomic surgical approach [76].

Nevertheless, in a recent review of 14 studies of abdominal cerclage, high rates of third-trimester delivery and live birth after abdominal cerclage via laparoscopy were comparable to those via laparotomy [81]. Because cervical incompetence treated with transabdominal cerclage can

carry significant morbidity with the need for sequential laparotomies and prolonged postoperative recovery, preference for minimally invasive procedures is an increasing trend.

Laparoscopic transabdominal cerclage placement has been described but has significant limitations with only two-dimensional depth perception and limited dexterity. Robotic assisted cervical cerclage (RACC) is rapidly gaining acceptance in gynecologic surgery [82]. RACC has reportedly been used for placement of an interval transabdominal cerclage. RACC is less invasive and is effective not only as an interval procedure but also during pregnancy, offering the patient an alternative to the traditional laparotomy but with quicker recovery time [83].

Robot-Assisted Cervical Cerclage Procedure

Abdominal cerclage in pregnancy. In this section, we will describe the steps for uterine cerclage performed during pregnancy. In our clinic, the robot-assisted abdominal cervical cerclage procedure is usually performed between 12 and 14 gestational weeks after evaluating the first-trimester genetic screening data. According to the American College of Obstetricians and Gynecologist guidelines, there is insufficient evidence to recommend perioperative antibiotic prophylaxis; even so, we administer a single dose of cefazolin 2 g preoperatively [84].

In our clinic, after inducing general anesthesia, the patient is placed in the dorsal lithotomy position with intermittent pneumo-pressure boots on both lower extremities. The initial trocar entrance is from the Palmer point, which is left of the midclavicular line, 3 cm under the left coastal margin. The Visiport 5-mm trocar placement is synchronized with an orogastric tube in suction mode to deflate the stomach air. The SI robot is docked obliquely, and the patient is placed in a shallow Trendelenburg p (<25°) to be compliant with pregnancy-related hemodynamic changes. We insufflate the abdomen up to 11 mmHg and insert three robotic ports under direct visualization. The 12-mm camera trocar is generally placed 10 cm superior to the umbilicus. Two 8-mm robotic trocars are placed bilaterally 10 cm from the camera port (Fig. 1). An additional 12-mm assistant port is placed on the left upper quadrant, replacing the 5-mm initial trocar. A 0-degree camera allows visualization of the uterus (both anteriorly and posteriorly) while maintaining a wide view. The option

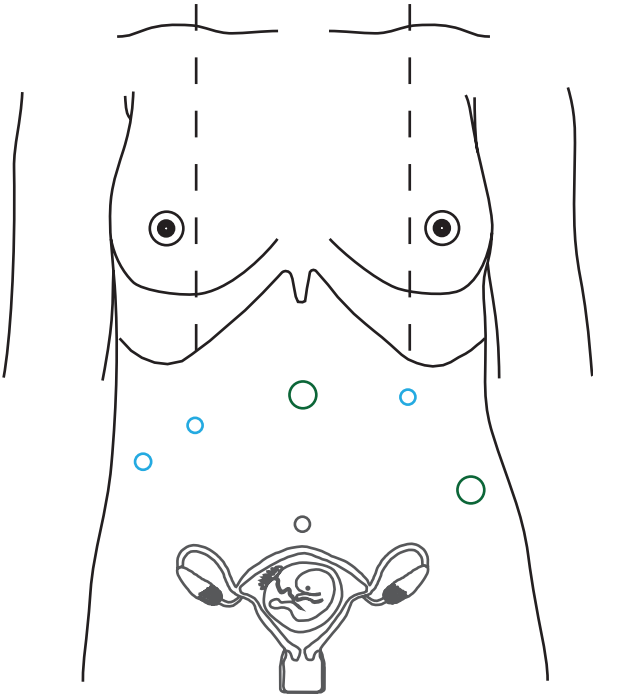


Fig. 1: Trocar distribution for pregnant uterine abdominal cerclage. The da Vinci Si robot is docked obliquely.

of using a 30-degree scope interchangeably during the procedure when needed is always a possibility. Intraabdominal pressure is maintained at about 11 mmHg throughout the case to give sufficient insufflation for visualization while not compromising uterine perfusion.

The peritoneum is incised at the vesicouterine reflection, and a bladder flap is created. The cervix is gently elevated by an assistant's fingers, which allows direct feedback to the surgeon for identifying the margins of the cervicoisthmic junction. After identifying landmarks, a sterile-covered transvaginal probe (M-Turbo; SonoSite, Bothell, WA) is inserted. Using the TilePro multi-input display feature, the ultrasound is connected to the da Vinci Si system (Intuitive Surgical, Sunnyvale, CA), allowing the surgeon to view both the operative field and the real-time ultrasound images capture by a transvaginal probe. An open fan retractor placed through the laparoscopic port allows the distribution of any pressure over a larger area, avoiding point pressure on the gravid uterus.

Dissection continues until the cervicoisthmic junction, uterine arteries, and parametrial vessels are exposed bilaterally.

The curved needles of a 30-cm long, double-swaged, 5-mm-wide Mersilene suture (RS20; Ethicon, Inc., Somerville, NJ) are straightened and introduced through the assistant port. A robotic needle driver is placed. Ultrasound is used to identify the endocervix and gestational sac in longitudinal views and the cervical edges and lateral structures in transverse images (Figs. 2 and 3). The tip of one needle is placed at the cervicouterine junction posteriorly medial to the uterine vessels. The split-screen ultrasound images allow constant visualization of the needle. Once visualized on the anterior aspect of the uterus, the needle is pulled through. Similarly, the second needle transfixes the cervicouterine junction on the opposite side (Fig. 4). Ultrasound verifies the proper Mersilene tape placement and fetal heart tones. Needles pass in a posterior-to-anterior fashion in the cervical isthmus area bilaterally to avoid the possibility of damaging presacral and pelvic vessels located posteriorly to the pelvis. Another technique for placing the Mersilene tape is to introduce the tape into the intraperitoneal cavity without the needles. Using a long, pointy

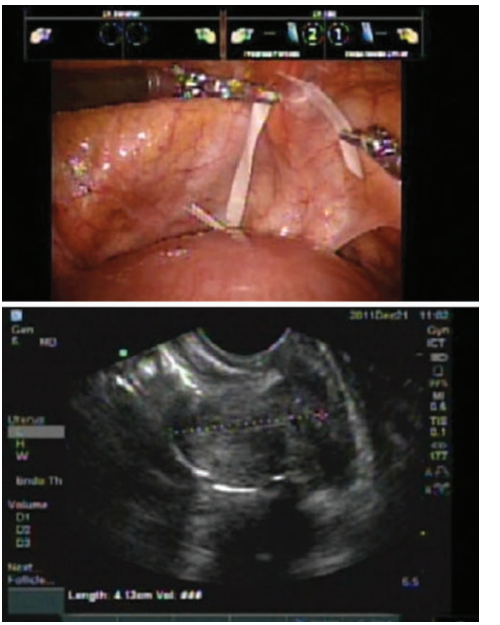


Fig. 2: Simultaneously showing a transvaginal ultrasound image of the cervical length and anteriorly placed cerclage stitch.

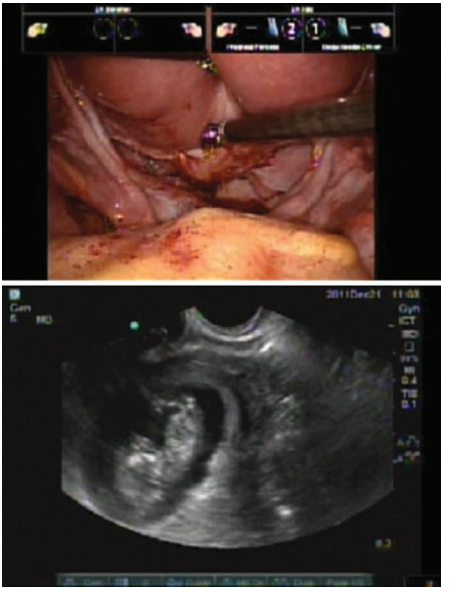


Fig. 3: Simultaneously showing transvaginal ultrasound image of the fetus at the completion of the case and intraoperative image of robotic cerclage placement.

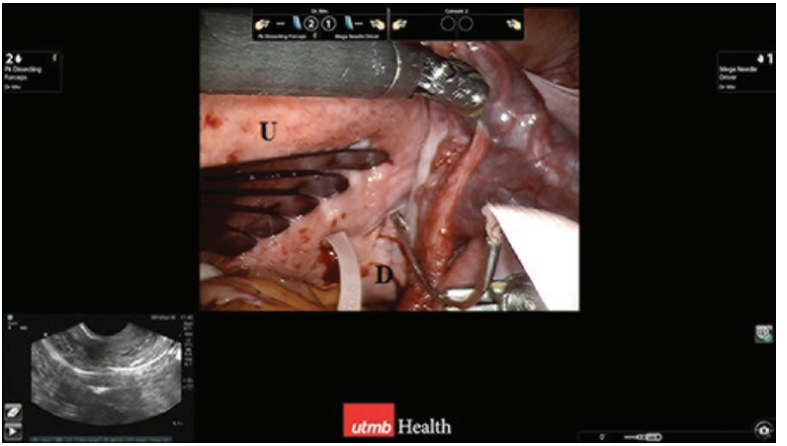


Fig. 4: Second needle passing from posterior to anterior in avascular area. *U* Uterus, *D* Douglas Pouch

tip grasper, the ligamentum latum is opened with a spreading, dissecting technique. After creating the passages bilaterally on both sides of the cervical isthmus, the mesh is introduced. An advantage of this technique is avoiding the use of needles, but precision in creating the surgical field is

not as good as the needle technique. At this point, the literature shows a similar success rate with both techniques [82].

Care is then taken to ensure that the cerclage is lying flat against the cervix and the knot is tied anteriorly (Fig. 5). Adjustment of the knot will be guided by the assistant's manual exam to leave the cervical os at 0.5 cm, allowing us to monitor for premature rupture of membranes during the pregnancy and menstrual bleeding (in case the patient chooses to keep the mesh after delivery). Cervical length is measured again after the procedure.

Robot-assisted cerclage performed during pregnancy— with the advantages of 3D visualization and endowrist instrumentation—has the potential to improve safety for the patient and the fetus. As we described earlier, the TilePro feature allows the ultrasound view to be projected with the surgical view on the same screen simultaneously [85]. Another feature is the option to utilize indocyanine green dye (Fig. 6) to identify the vascularity before you pass the needles [86].

Nonpregnant Uterine Cerclage. For nonpregnant cerclage, the steps will differ as follows compared to the technique for pregnant patients.

Preconceptual counseling is important, especially for discussing possible cerclage placement, and its potential impact on conception is critical to discuss. A few studies directly compare the insertion of a preconceptual transabdominal cerclage with insertion in early pregnancy [81, 87]. The most recent one concluded that preconceptual transabdominal cerclage is more successful in preventing pregnancy loss and preterm labor and is associated with less surgical and pregnancy-related morbidity compared to first-trimester transabdominal cerclage insertion [87]. Tulandi *et al*., however, found that the efficacy of the procedure performed either before or during pregnancy is similar [81]. Even so, preconceptual insertion should be considered when possible because of the technical advantage of operating on the uterus of a woman who is not pregnant. Furthermore, there is no evidence that preconceptual transabdominal cerclage has any detrimental impact on fertility or management of an early miscarriage [88]. Abdominal cerclage can be safely left in place if a further pregnancy is a possibility.

A pregnancy test is critical before beginning the procedure. Initial trocar entrance is the same as for pregnant patients. Enter from the Palmer point, which is left of the midclavicular line and 3 cm under the

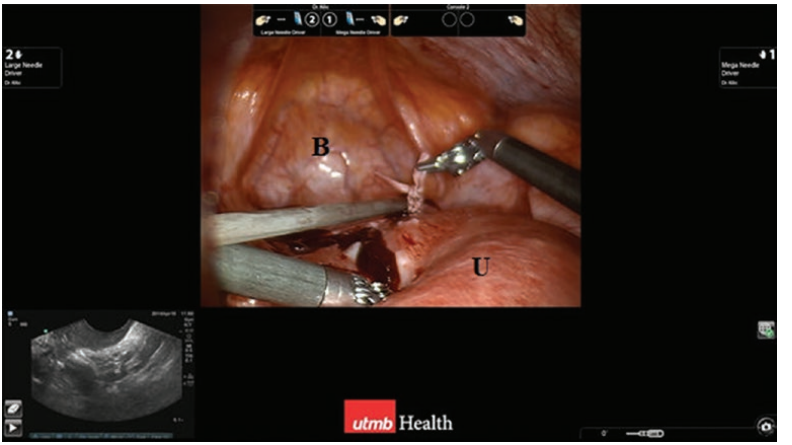


Fig. 5: The Mersilene tape is tied anteriorly. *B* Bladder, *U* Uterus

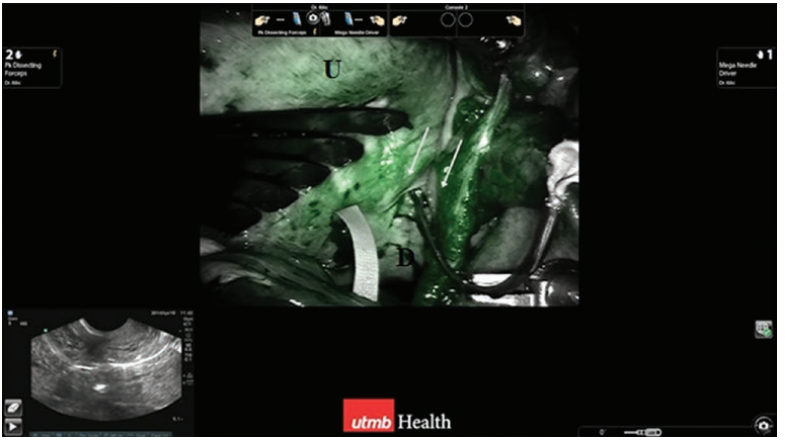


Fig. 6: Passing the suture in avascular space.

left coastal margin. Placement of a 5-mm Visiport (US Surgical, Norwalk, CT) is to be synchronized with an orogastric tube in the suction mode to deflate stomach air. We insufflate the abdomen up to 14 mmHg and insert three robotic ports under direct visualization. Trocar placement for nonpregnant women is more advantageous in terms of number of variations. Umbilical camera placement is an option. Generally, the 12-mm camera trocar is placed closer to the umbilicus than in pregnant patients (6–8 cm). Two 8-mm robotic trocars are placed bilaterally 10 cm from the

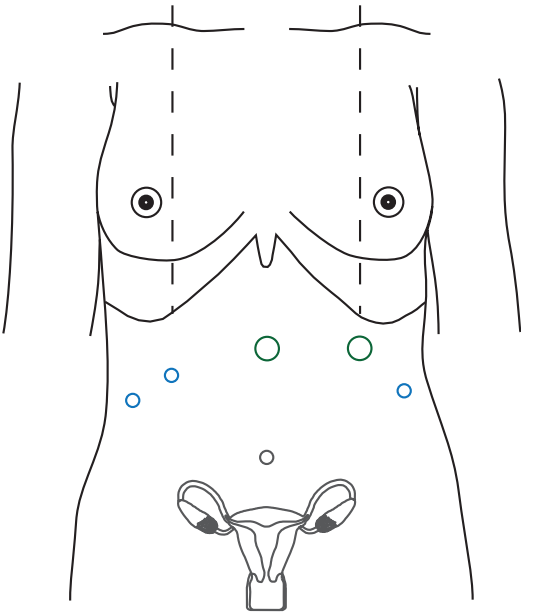


Fig. 7: Trocar distribution for nonpregnant uterine abdominal cerclage. The da Vinci Si robot is docked obliquely.

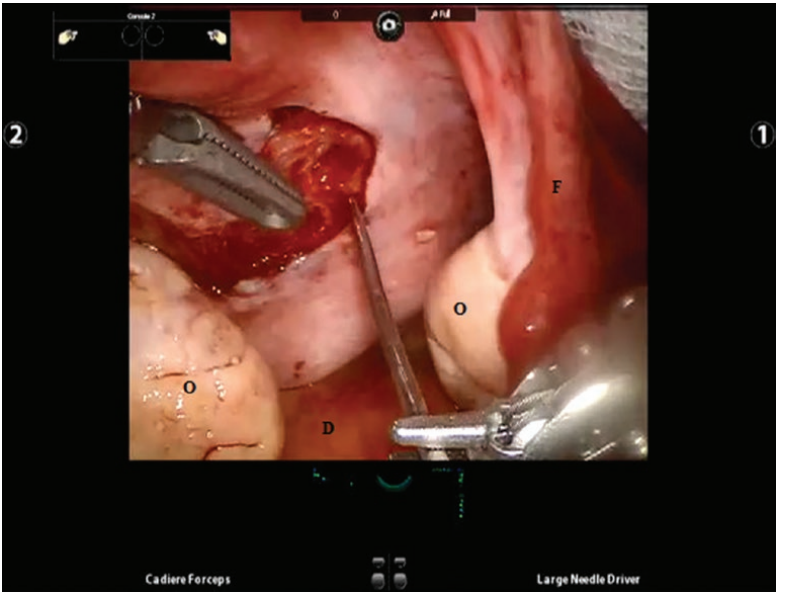


Fig. 8: Needle attached to Mersilene tape first passing from posterior to anterior. *D* Douglas Pouch, *O* Ovary, *F* Fallopian Tube

camera port (Fig. 7). An additional 12-mm assistant port is placed in the left upper quadrant, replacing the 5-mm initial trocar. If no assistant side trocar is placed, mesh can be introduced either from one robotic trocar side or through the camera port with the needle attached at the beginning of the procedure.

Place a uterine manipulator in the intrauterine cavity. We use VCare (ConMed) due to the fact that it helps to turn the manipulator 180° during the bladder flap to gain better counter tension, which will facilitate bladder dissection. In addition, the uterine manipulator will facilitate moving the uterus toward the bladder and rectum during the needle passage. Another difference for the nonpregnant cerclage procedure in our practice is that only one needle is attached to the Mersilene tape introduced into the intraperitoneal cavity instead of two. The first pass can be done from posterior to anterior (Fig. 8). After making the loop around the cervix anteriorly, it can be passed from anterior to posterior using the same needle (Fig. 9). This technique provides an option to place the knot on the posterior cervix to avoid the potential risk of having it irritate the bladder (Fig.

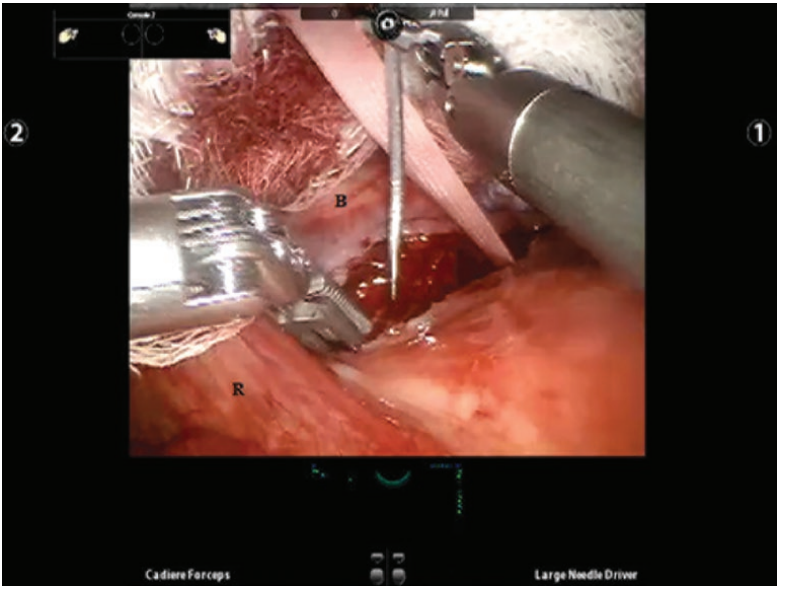


Fig. 9: The same needle attached to Mersilene tape then passing from anterior to posterior. *B* Bladder, *R* Round Ligament

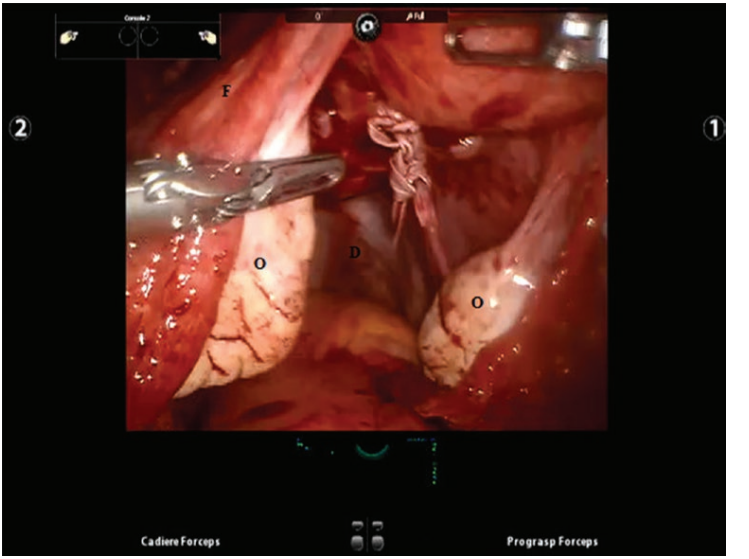


Fig. 10: The Mersilene tape is tied posteriorly. *D* Douglas Pouch, *O* Ovary, *F* Fallopian Tube

10). However, in our experience, an anteriorly placed knot did not cause bladder irritation, either. The biggest advantage of nonpregnant cerclage is easy exposure of the surgical field, especially with the help of a uterine manipulator. The manipulator is kept intrauterine during knot placement, thus providing a small opening on the cervical os for monitoring premature rupture of the membranes during pregnancy and menstrual flow after pregnancy.

In conclusion, robotic abdominal cerclage is found to have a success rate of 85% with lower incidence of preterm delivery and preterm premature rupture of membranes compared to the vaginal approach [82].

Robotic cerclage is currently a safe and effective technique, yet it is still open for new adaptations to make it even more safe and effective as technology evolves.

References

1. Moss C, Isley MM. Sterilization: a review and update. Obstet Gynecol Clin N Am. 2015;42(4):713–24.
2. Hillis SD, Marchbanks PA, Tylor LR, *et al*. Poststerilization regret: findings from the United States collaborative review of sterilization. Obstet Gynecol. 1999;93(6):889–95.
3. Henderson SR. The reversibility of female sterilization with the use of microsurgery: a report on 102 patients with more than one year of follow-up. Am J Obstet Gynecol. 1984;149(1):57–65.

4. Hanafi MM. Factors affecting the pregnancy rate after microsurgical reversal of tubal ligation. Fertil Steril. 2003;80(2):434–40.
5. Gordts S, Campo R, Puttemans P, *et al*. Clinical factors determining pregnancy outcome after microsurgical tubal reanastomosis. Fertil Steril. 2009;92(4):1198–202.
6. Yoon TK, Sung HR, Kang HG, *et al*. Laparoscopic tubal anastomosis: fertility outcome in 202 cases. Fertil Steril. 1999;72(6):1121–6.
7. Margossian H, Garcia-Ruiz A, Falcone T, *et al*. Robotically assisted laparoscopic tubal anastomosis in a porcine model: a pilot study. J Laparoendosc Adv Surg Tech A. 1998;8(2):69–73.
8. Degueldre M, Vandromme J, Huong PT, *et al*. Robotically assisted laparoscopic microsurgical tubal reanastomosis: a feasibility study. Fertil Steril. 2000;74(5):1020–3.
9. Falcone T, Goldberg JM, Margossian H, *et al*. Robotic-assisted laparoscopic microsurgical tubal anastomosis: a human pilot study. Fertil Steril. 2000;73(5):1040–2.
10. Zite N, Borrero S. Female sterilisation in the United States. Eur J Contracept Reprod Health Care. 2011;16(5):336–40.
11. Gargiulo AR. Fertility preservation and the role of robotics. Clin Obstet Gynecol. 2011;54(3):431–48.
12. Bedaiwy MA, Barakat EM, Falcone T. Robotic tubal anastomosis: technical aspects. JSLS. 2011;15(1):10–15. PMC3134681.
13. Dharia Patel SP, Steinkampf MP, Whitten SJ, *et al*. Robotic tubal anastomosis: surgical technique and cost effectiveness. Fertil Steril. 2008;90(4):1175–9.
14. Einarsson JI, Hibner M, Advincula AP. Side docking: an alternative docking method for gynecologic robotic surgery. Rev Obstet Gynecol. 2011;4(3–4):123–5. PMC3252883.
15. Schippert C, Soergel P, Staboulidou I, *et al*. The risk of ecto pic pregnancy following tubal reconstructive microsurgery and assisted reproductive technology procedures. Arch Gynecol Obstet. 2012;285(3):863–71.
16. Caillet M, Vandromme J, Rozenberg S, *et al*. Robotically assisted laparoscopic microsurgical tubal reanastomosis: a retrospective study. Fertil Steril. 2010;94(5):1844–7.
17. Rodgers AK, Goldberg JM, Hammel JP, *et al*. Tubal anastomosis by robotic compared with outpatient minilaparotomy. Obstet Gynecol. 2007;109(6):1375–80.
18. Lima M, Cantone N, Destro F, *et al*. Combined laparoscopic and hysteroscopic approach for the treatment of a hybrid Mullerian duct anomaly: a case report. J Laparoendosc Adv Surg Tech A. 2013;23(11):960–4.
19. Saygili-Yilmaz E, Yildiz S, Erman-Akar M, *et al*. Reproductive outcome of septate uterus after hysteroscopic metroplasty. Arch Gynecol Obstet. 2003;268(4):289–92.
20. Vallerie AM, Breech LL. Update in Mullerian anomalies: diagnosis, management, and outcomes. Curr Opin Obstet Gynecol. 2010;22(5):381–7.
21. Grimbizis GF, Gordts S, Di Spiezio Sardo A, *et al*. The ESHRE/ ESGE consensus on the classification of female genital tract congenital anomalies. Hum Reprod. 2013;28(8):2032–44. PMC3712660.
22. Arleo EK, Troiano RN. Complex Mullerian duct anomalies defying traditional classification: lessons learned. J Fertil. 2013;1:115.
23. Iverson R, Decherney A, Laufer M. Surgical management of congenital uterine anomalies. In: Barbieri R, editor. UpToDate. Waltham: Wolters Kluwer; 2016.
24. AFS. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. Fertil Steril. 1988;49(6):944–55.
25. Cunningham FG, Leveno KJ, Bloom SL, *et al*. Congenital genitourinary abnormalities. In: Williams obstetrics. New York: McGraw-Hill Education; 2014. p. 36–45.
26. Nahum GG. Uterine anomalies. How common are they, and what is their distribution among subtypes? J Reprod Med. 1998;43(10):877–87.
27. Reichman D, Laufer MR, Robinson BK. Pregnancy outcomes in unicornuate uteri: a review. Fertil Steril. 2009;91(5):1886–94.
28. Heinonen PK. Uterus didelphys: a report of 26 cases. Eur J Obstet Gynecol Reprod Biol. 1984;17(5):345–50.
29. Smith NA, Laufer MR. Obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome: management and follow-up. Fertil Steril. 2007;87(4):918–22.

30. Tong J, Zhu L, Lang J. Clinical characteristics of 70 patients with Herlyn-Werner-Wunderlich syndrome. Int J Gynaecol Obstet. 2013;121(2):173–5.
31. El Saman AM, Shahin AY, Nasr A, *et al*. Hybrid septate uterus, coexistence of bicornuate and septate varieties: a genuine report. J Obstet Gynaecol Res. 2012;38(11):1308–14.
32. Iverson R, Decherney A, Laufer M. Clinical manifestations and diagnosis of congenital anomalies of the uterus. In: Barbieri R, editor. UpToDate. Waltham: Wolters Kluwer; 2016.
33. Guirgis RR, Shrivastav P. Gamete intrafallopian transfer (GIFT) in women with bicornuate uteri. J In Vitro Fert Embryo Transf. 1990;7(5):283–4.
34. Marcus S, Al-Shawaf T, Brinsden P. The obstetric outcome of in vitro fertilization and embryo transfer in women with congenital uterine malformation. Am J Obstet Gynecol. 1996;175(1):85–9.
35. Markham SM, Waterhouse TB. Structural anomalies of the reproductive tract. Curr Opin Obstet Gynecol. 1992;4(6):867–73.
36. Pellerito JS, Mccarthy SM, Doyle MB, *et al*. Diagnosis of uterine anomalies: relative accuracy of MR imaging, endovaginal sonography, and hysterosalpingography. Radiology. 1992;183(3):795–800.
37. Acien P, Acien M, Sanchez-Ferrer M. Complex malformations of the female genital tract. New types and revision of classification. Hum Reprod. 2004;19(10):2377–84.
38. Chen YJ, Twu NF, Horng HC, *et al*. Robotic modified Jones metroplasty for uterine unification. J Minim Invasive Gynecol. 2010;17(6):S11–2.
39. Gungor M, Afsar S, Ozbasli E, *et al*. The robotic metroplasty in a patient with hybrid septate variant anomaly. J Robot Surg. 2016;10(3):271–4.
40. Wright C, Hanna MK. Thirty-six vaginal constructions: lessons learned. J Pediatr Urol. 2014;10(4):667–71.
41. Committee on Adolescent Health Care. Committee opinion: no. 562: Mullerian agenesis: diagnosis, management, and treatment. Obstet Gynecol. 2013;121(5):1134–7.
42. Dargent D, Marchiole P, Giannesi A, *et al*. Laparoscopic Davydov or laparoscopic transposition of the peritoneal colpopoeisis described by Davydov for the treatment of congenital vaginal agenesis: the technique and its evolution. Gynecol Obstet Fertil. 2004;32(12):1023–30.
43. Gauwerky JF, Wallwiener D, Bastert G. An endoscopically assisted technique for construction of a neovagina. Arch Gynecol Obstet. 1992;252(2):59–63.
44. Mcindoe A. The treatment of congenital absence and obliterative conditions of the vagina. Br J Plast Surg. 1950;2(4):254–67.
45. Popp LW, Ghirardini G. Creation of a neovagina by pelviscopy. J Laparoendosc Surg. 1992;2(3):165–73.
46. Urbanowicz W, Starzyk J, Sulislawski J. Laparoscopic vaginal reconstruction using a sigmoid colon segment: a preliminary report. J Urol. 2004;171(6 Pt 2):2632–5.
47. Kim C, Campbell B, Ferrer F. Robotic sigmoid vaginoplasty: a novel technique. Urology. 2008;72(4):847–9.
48. Boztosun A, Olgan S. Robotic sigmoid vaginoplasty in an adolescent girl with Mayer-Rokitansky-Kuster-Hauser syndrome. Female Pelvic Med Reconstr Surg. 2016;22(5):e32–5.
49. Pushkar P, Rawat SK, Chowdhary SK. Robotic approach to vaginal atresia repair in an adolescent girl. Urol Ann. 2015;7(3):396–8. PMC4518385.
50. Iavazzo C, Gkegkes ID. Possible role of DaVinci robot in uterine transplantation. J Turk Ger Gynecol Assoc. 2015;16(3):179–80. PMC4560477.
51. Braumann C, Jacobi CA, Menenakos C, *et al*. Computer-assisted laparoscopic colon resection with the Da Vinci system: our first experiences. Dis Colon Rectum. 2005;48(9):1820–7.
52. Denoto G, Rubach E, Ravikumar TS. A standardized technique for robotically performed sigmoid colectomy. J Laparoendosc Adv Surg Tech A. 2006;16(6):551–6.
53. Anderberg M, Bossmar T, Arnbjornsson E, *et al*. Robot-assisted laparoscopic hemihysterectomy for a rare genitourinary malformation with associated duplication of the inferior vena cava—a case report. Eur J Pediatr Surg. 2010;20(3):206–8.
54. Persson J, Reynisson P, Borgfeldt C, *et al*. Robot assisted laparoscopic radical hysterectomy and pelvic lymphadenectomy with short and long term morbidity data. Gynecol Oncol. 2009;113(2):185–90.

55. Liu XX, Jiang ZW, Chen P, *et al*. Full robot-assisted gastrectomy with intracorporeal robot-sewn anastomosis produces satisfying outcomes. World J Gastroenterol. 2013;19(38):6427–37. PMC3801313.
56. Uyama I, Sugioka A, Fujita J, *et al*. Completely laparoscopic extraperigastric lymph node dissection for gastric malignancies located in the middle or lower third of the stomach. Gastric Cancer. 1999;2(3):186–90.
57. Sheyn D, Abouassaly R, Paspulati R, *et al*. Multidisciplinary approach for management of obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome and rectal prolapse. Int Urogynecol J. 2015;26(7):1079–81.
58. Cunningham FG, Leveno KJ, Bloom SL, *et al*. Abortion, early pregnancy. In: Williams obstetrics. New York: McGraw-Hill Education; 2014. p. 350–76.
59. Vyas NA, Vink JS, Ghidini A, *et al*. Risk factors for cervi cal insufficiency after term delivery. Am J Obstet Gynecol. 2006;195(3):787–91.
60. Saccone G, Perriera L, Berghella V. Prior uterine evacua tion of pregnancy as independent risk factor for preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol. 2016;214(5):572–91.
61. Warren JE, Silver RM, Dalton J, *et al*. Collagen 1Alpha1 and transforming growth factor-beta polymorphisms in women with cervical insufficiency. Obstet Gynecol. 2007;110(3):619–24.
62. Chan YY, Jayaprakasan K, Tan A, *et al*. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. Ultrasound Obstet Gynecol. 2011;38(4):371–82.
63. Rackow BW, Arici A. Reproductive performance of women with Mullerian anomalies. Curr Opin Obstet Gynecol. 2007;19(3):229–37.
64. Kaufman RH, Adam E, Hatch EE, *et al*. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. Obstet Gynecol. 2000;96(4):483–9.
65. Grobman WA, Gilbert SA, Iams JD, *et al*. Activity restriction among women with a short cervix. Obstet Gynecol. 2013;121(6):1181–6. PMC4019312.
66. Sciscione AC. Maternal activity restriction and the prevention of preterm birth. Am J Obstet Gynecol. 2010;202(3):232.e1–5.
67. Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. Cochrane Database Syst Rev. 2013;5:Cd007873.
68. Dharan VB, Ludmir J. Alternative treatment for a short cervix: the cervical pessary. Semin Perinatol. 2009;33(5):338–42.
69. Goya M, Pratcorona L, Merced C, *et al*. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. Lancet (London, England). 2012;379(9828):1800–6.
70. Herron MA, Parer JT. Transabdominal cerclage for fetal wastage due to cervical incompetence. Obstet Gynecol. 1988;71(6 Pt 1):865–8.
71. Berghella V, Szychowski JM, Owen J, *et al*. Suture type and ultrasound-indicated cerclage efficacy. J Matern Fetal Neonatal Med. 2012;25(11):2287–90.
72. Harger JH. Comparison of success and morbidity in cervical cerclage procedures. Obstet Gynecol. 1980;56(5):543–8.
73. Mcdonald IA. Suture of the cervix for inevitable miscarriage. J Obstet Gynaecol Br Emp. 1957;64(3):346–50.
74. Shirodkar V. A new method of operative treatment for habitual abortions in the second trimester of pregnancy. Antiseptic. 1955;52:299–300.
75. Toaff R, Toaff ME, Ballas S, *et al*. Cervical incompetence: diagnostic and therapeutic aspects. Isr J Med Sci. 1977;13(1):39–49.
76. Burger NB, Brolmann HA, Einarsson JI, *et al*. Effectiveness of abdominal cerclage placed via laparotomy or laparoscopy: systematic review. J Minim Invasive Gynecol. 2011;18(6):696–704.
77. Wolfe L, Depasquale S, Adair CD, *et al*. Robotic-assisted laparoscopic placement of transabdominal cerclage during pregnancy. Am J Perinatol. 2008;25(10):653–5.
78. Fick AL, Caughey AB, Parer JT. Transabdominal cerclage: can we predict who fails? J Matern Fetal Neonatal Med. 2007;20(1):63–7.
79. Umstad MP, Quinn MA, Ades A. Transabdominal cervical cerclage. Aust N Z J Obstet Gynaecol. 2010;50(5):460–4.

80. Davis G, Berghella V, Talucci M, *et al*. Patients with a prior failed transvaginal cerclage: a comparison of obstetric outcomes with either transabdominal or transvaginal cerclage. Am J Obstet Gynecol. 2000;183(4):836–9.
81. Tulandi T, Alghanaim N, Hakeem G, *et al*. Pre and postconceptional abdominal cerclage by laparoscopy or laparotomy. J Minim Invasive Gynecol. 2014;21(6):987–93.
82. Zeybek B, Hill A, Menderes G, *et al*. Robot-assisted abdominal cerclage during pregnancy. JSLS. 2016;20(4):e2016.00072. PMC5118107.
83. Estape RE, Schroeder ED, Estape RA, *et al*. Robotic abdominal cerclage: a case series with pregnancy outcomes. J Minim Invasive Gynecol. 2015;22(6s):S235.
84. ACOG. ACOG Practice Bulletin No.142: cerclage for the management of cervical insufficiency. Obstet Gynecol. 2014;123(2 Pt 1):372–9.
85. Walsh TM, Borahay MA, Fox KA, *et al*. Robotic-assisted, ultrasound-guided abdominal cerclage during pregnancy: overcoming minimally invasive surgery limitations? J Minim Invasive Gynecol. 2013;20(3):398–400.
86. Zeybek B, Borahay M, Kilic GS. Overcoming the obstacles of visualization in robotically assisted abdominal cerclage using indocyanine green. J Robot Surg. 2016;10(4):361–4.
87. Dawood F, Farquharson RG. Transabdominal cerclage: preconceptual versus first trimester insertion. Eur J Obstet Gynecol Reprod Biol. 2016;199:27–31.
88. Pundir J, Coomarasamy A. Preterm labour (PTL). In: Obstetrics: evidence-based algorithms. London: Cambridge University Press; 2016.

Source: Sami Gokhan Kilic, Bekir Serdar Unlu, Mertihan Kurdoglu. Role of Robotics in the Management of Infertility. In: El-Ghobashy A., Ind T., Persson J., Magrina J.F. (eds). Textbook of Gynecologic Robotic Surgery. 1st ed. Switzerland: Springer International Publishing; 2017, pp 51-64. DOI 10.1007/978-3-319-63429-6_9.

Macroprolactinoma: Diagnosis and Management in a Patient with Infertility

Souad Enakuaa, Lisa B. Nachtigall

Case Presentation

A 31-year-old female presented with secondary amenorrhea and infertility. Prior medical history was unremarkable except for delayed puberty. Her growth curve reportedly showed a low but constant height percentile. She had the onset of menarche at the age of 16 years. Her menstrual cycles had been consistently irregular since their onset, with periods every 1–3 months. She received oral contraceptives for a few years before discontinuing their use 1 year ago. She reported taking no medications upon her initial consultation with neuroendocrine.

On physical examination, her weight was 110 lb, height was 5 ft, blood pressure was 90/60, and heart rate was 64. The exam was notable for galactorrhea. Visual fields were normal. She had no evidence of Cushing's or acromegaly.

Initial hormonal analysis showed serum prolactin (diluted) level of 1048 ng/dL (normal range 5–20). FSH was 2.7 U/L, LH was 4.7 U/L, and estradiol level was low. Insulin-like growth factor 1 (IGF-1), free T4, and TSH were normal. HCG Quant was <6 IU/L. Her Cortrosyn stimulation test was normal with a stimulated peak cortisol level of 21.5 μg/dL (normal > 18).

S. Enakuaa, L. B. Nachtigall (✉)
Neuroendocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: lnachtigall@partners.org

Pituitary magnetic resonance image (MRI) showed 1.4 cm macroadenoma without significant local invasion. Bone density was normal.

My Management

- Initiated dopamine agonist therapy with cabergoline 0.5 mg orally weekly. After 3 months of cabergoline treatment, prolactin level was 23.2 ng/dL (0–20).
- Cabergoline dose was increased to 0.75 mg weekly (the increase in dose was an effort to suppress tumor and also restore prolactin level to within the normal range, as to allow for return of menstrual cycle). Three months later, progesterone level confirmed spontaneous ovulatory cycle.
- At 6 months follow-up, she reported the return of regular menstrual cycles while on 0.75 mg weekly of cabergoline with a prolactin level of 13 ng/dL, and MRI showed decrease in tumor size from 1.5 to 1 cm, with a question of an area of hemorrhage within the tumor.
- She was then referred to a neurosurgeon who suggested observation with close follow-up by MRI.
- After 10 months of cabergoline therapy (4 months after the prior MRI), her MRI was stable.
- After 18 months on cabergoline, she spontaneously conceived, and cabergoline was discontinued.
- She continued to follow up during pregnancy with observation of symptoms and exam including a neuro-ophthalmology exam with visual field testing every trimester.

Three months postpartum prolactin level was 563 ng/dL. She opted to bottle-feed, but the amenorrhea persisted. Cabergoline was restarted and titrated to achieve a normal prolactin level and return of regular menstrual cycles.

Assessment and Diagnosis

This patient presented with secondary amenorrhea and infertility, which are typical features of a prolactinoma. Primary amenorrhea and delayed puberty can be the initial presentation of this disease. Interestingly, she had delayed menarche and oligomenorrhea but had not undergone a

pituitary evaluation until many years later when she presented with infertility. She is representative of cases in which the diagnosis of hyperprolactinemia is delayed and only discovered many years after a late puberty or late menarche [1]. Her late puberty may well have been due to hyperprolactinemia.

Detailed history of medications is important, as many commonly used drugs can cause hyperprolactinemia [2]. Metoclopramide, antipsychotics, antidepressants, antihypertensives, and opiates among many other pharmacological agents all may increase prolactin levels. Metoclopramide, haloperidol, risperidone, and phenothiazines may be associated with particularly elevated prolactin levels. Illicit drug use is another important history element because of the association of cocaine and heroin with hyperprolactinemia [3, 4].

Galactorrhea is present in less than half of patients with prolactinomas [5]. While in this case, her visual field exam was normal, it is important to evaluate visual field exams in any patient who has a lesion that extends to the suprasellar area and contacts or invades the optic chiasm.

There are many physiological causes of hyperprolactinemia including pregnancy, lactation, nipple stimulation, post-coitus state, and exercise. Pathological factors such as hypothyroidism, liver disease, renal failure, and seizure can also increase the prolactin level. Prolactinoma may co-secrete growth hormone. Therefore, IGF-1 should be evaluated to screen for acromegaly, particularly if there is clinical evidence of the disease. Typically prolactin levels greater than 250 ng/dL are associated with the presence of a prolactinoma [6]. A prolactin level above 500 ng/dL confirms prolactinoma as the diagnosis [7].

Our patient's initial level was above 1000 ng/dL, confirming the diagnosis of prolactinoma definitively. Pregnancy test and other hormonal assays of FSH, LH, TSH, and IGF-1 were normal. It is notable that rare cases of extremely high levels of prolactin can cause a false-negative assay result due to the "hook effect." In immunoassays, hook effect may occur when the amount of prolactin is so high that it impairs binding to antibody, causing falsely low results. To avoid the hook effect, the sample should be diluted with the patient's serum [8].

After confirming hyperprolactinemia and excluding other causes, imaging of the pituitary gland with an MRI is the next step. Prolactinomas are classified as either microprolactinoma (less than 1 cm) or a

macroprolactinoma (greater than or equal to 1 cm). MRI is important for assessment of tumor size and to evaluate for mass effect on surrounding tissues. Ongoing imaging of the tumor is required in addition to biochemical testing to assess response to therapy. The presence of a macroadenoma on the MRI was expected in our patient given the severity of hyperprolactinemia, since an association between the degree of hyperprolactinemia and tumor size has been reported [9]. However, there are cases in which there can be discrepancy between the hormone levels and tumor size.

Management

Once the diagnosis is established, goals of therapy should be set. In women, the goals are usually to restore menstrual cycle in reproductive age women and fertility in those who desire it. For women who are not trying to conceive, therapy should aim to avoid complications on bone health (which results from low estrogen levels, due to the suppression of gonadotropin-releasing hormone caused by hyperprolactinemia) [10] and to suppress tumor growth in order to prevent mass effects. Dopamine agonists (DAs) are the first line of therapy for prolactinomas [11]. DAs bind to dopamine receptors on lactotroph cells leading to decrease prolactin synthesis and reduction of tumor size [12, 13]. The currently available FDA-approved dopamine agonists in the USA that are used to treat hyperprolactinemia include bromocriptine and cabergoline. Both are effective in treating prolactinomas with a slight efficacy advantage of cabergoline [14, 15], which also has been associated with fewer side effects [15]. We typically suggest that the patients use or switch to bromocriptine prepregnancy since more data is available on its safety during pregnancy [5]. This patient preferred to stay on cabergoline since she tolerated it well and was concerned about having side effects if she switched drugs. Surgery is another modality of treatment for macroprolactinoma.

Surgical removal is not usually the first line of therapy but could be considered if there is optic chiasm compression affecting the visual field, bleeding within the tumor, or if the patient has a contraindication to use DAs, such as psychosis [16]. Surgery may also be appropriate if medical therapy fails and is not tolerable, if the tumor grows on medical therapy, or if a woman wants to conceive soon and has a large tumor [17]. Radiotherapy is reserved for prolactinomas that continue to grow after

surgery, inoperable tumors, or patients who have failed to respond or tolerate medical therapy. Single-dose radiosurgery can be used in select cases of prolactinoma but is contraindicated if tumors are very large or approach the chiasm. In these cases, the risk of visual field loss is high with single-dose radiotherapy, and fractionated radiotherapy would be required [18].

Outcome

The patient had a normal prolactin within 3 months of starting a low dose of cabergoline. This illustrated her dramatic response to this dopamine agonist with normalization of her prolactin level within a short period of time.

The return of spontaneous menstrual cycles occurred within weeks after she obtained a normal prolactin level, which is not uncommon [19], and was ultimately associated with spontaneous conception at 18 months after the initiation of dopamine agonist therapy. The time to obtaining fertility after correction of hyperprolactinemia is variable. Studies have shown that fertility can be restored within the first cycle after correction of high prolactin in some women but may take as long as 2 years [19] especially if there are other factors contributing to infertility. In this case, the patient's low weight when she first presented (BMI < 20) may have had a role in her infertility. It was after she had gained some weight that she ultimately conceived.

The patient developed the finding on MRI of a pre-contrast T1 bright spot, consistent with a possible area of hemorrhage, after the initiation of the dopamine agonist. While in this case, this was self-limited and follow-up imaging confirmed stability, a neurosurgical referral was obtained to entertain the possibility of surgical intervention if necessary.

Bleeding of the tumor is not an infrequent occurrence, especially in macroprolactinomas [20]. The bleeding can present as an emergency, as in the case of pituitary apoplexy. However, some degree of bleeding may be asymptomatic and resolves spontaneously [21]. Dopamine agonists are recognized as one of the precipitating factors of tumor hemorrhage and pituitary apoplexy [22]. Although this does not usually occur, most prolactinomas remain stable during pregnancy [23], but macroprolactinomas are more likely than microprolactinomas to grow during gestation

[23]. Safety of DAs during pregnancy is not completely known, and thus both cabergoline and bromocriptine are class B medications, as designated by the FDA. However, observational data of fetal exposure either in the first trimester or throughout pregnancy to both bromocriptine and cabergoline did not show any significant harm [5]. Recommended management is stopping the dopamine agonist as soon as the pregnancy is known. Follow-up of the tumor size should be performed by relevant symptom review and visual field examination in every trimester. Prolactin level is not meaningful during pregnancy because hyperprolactinemia is physiological and expected during pregnancy. If there is any change in the symptoms suggestive of tumor enlargement, official visual field evaluation and non-contrast MRI should be obtained. Our patient had normal visual fields throughout her pregnancy. Postpartum her prolactin levels remained elevated despite the fact that she was not nursing and her menstrual periods did not resume. For that reason, the cabergoline was restarted postpartum and again associated with return of regular cycles and normalization of prolactin, and she had ongoing improvement with decrease in pituitary tumor size.

Clinical Pearls and Pitfalls

- Delayed puberty may be a sign of hyperprolactinemia.
- Prolactin level should be evaluated in women with absent or irregular menses prior to initiating birth control pills.
- When prolactin level is very high, diluted prolactin should be obtained to avoid the hook effect if an immunoassay is used.
- Even though her prolactin level normalized within 3 months of therapy with a dopamine agonist, her persistence of a macroadenoma remained. This illustrates the importance of following both the biochemical parameters and the imaging in patients with macroprolactinomas who were treated medically.
- While the prolactin trend will typically mirror the tumor size response, they are not always completely linked [24].
- One of the consequences of a dopamine agonist in patients with a prolactinoma can include hemorrhage into the tumor. This requires close follow-up with imaging and neurosurgical consultation as well

as evaluation of anterior pituitary function, particularly if symptoms of apoplexy are present.

- Lactotroph hyperplasia can occur during normal pregnancy, and in patients with macroprolactinoma, enlargement during pregnancy is a concern, as the risk of growth is much greater than that of microprolactinoma [23]. Therefore, visual field tests were done each trimester and are important in the management of patients with macroprolactinomas during pregnancy.

References

1. Landolt AM. [Prolactin-producing pituitary adenomas as a cause of primary amenorrhea and their neurosurgical treatment]. Dtsch Med Wochenschr. 1983;108(8):298–301.
2. Ajmal A, Joffe H, Nachtigall LB. Psychotropic-induced hyperprolactinemia: a clinical review. Psychosomatics. 2014;55(1):29–36.
3. Shin SH, *et al*. Morphine can stimulate prolactin release independent of a dopaminergic mechanism. Can J Physiol Pharmacol. 1988;66(11):1381–5.
4. Gold MS, *et al*. Increase in serum prolactin by exogenous and endogenous opiates: evidence for antidopamine and antipsychotic effects. Am J Psychiatry. 1978;135(11):1415–6.
5. Glezer A, Bronstein MD. Prolactinomas, cabergoline, and pregnancy. Endocrine. 2014;47(1):64–9.
6. Melmed S, *et al*. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88.
7. Vilar L, Fleseriu M, Bronstein MD. Challenges and pitfalls in the diagnosis of hyperprolactinemia. Arq Bras Endocrinol Metabol. 2014;58(1):9–22.
8. St-Jean E, Blain F, Comtois R. High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. Clin Endocrinol (Oxf). 1996;44(3):305–9.
9. Moraes AB, *et al*. Giant prolactinomas: the therapeutic approach. Clin Endocrinol (Oxf). 2013;79(4):447–56.
10. Brue T, Castinetti F. The risks of overlooking the diagnosis of secreting pituitary adenomas. Orphanet J Rare Dis. 2016;11(1):135.
11. Faje A, Nachtigall L. Current treatment options for hyperprolactinemia. Expert Opin Pharmacother. 2013;14(12):1611–25.
12. Biller BM, *et al*. Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J Clin Endocrinol Metab. 1996;81(6):2338–43.
13. Molitch ME, *et al*. Bromocriptine as primary therapy for prolactinsecreting macroadenomas: results of a prospective multicenter study. J Clin Endocrinol Metab. 1985;60(4):698–705.
14. Colao A, *et al*. Long-term and low-dose treatment with cabergo line induces macroprolactinoma shrinkage. J Clin Endocrinol Metab. 1997;82(11):3574–9.
15. Webster J, *et al*. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med. 1994;331(14):904–9.
16. Donegan D, *et al*. Surgical outcomes of prolactinomas in recent era: results of a heterogenous group. Endocr Pract. 2017;23(1):37–45.
17. Wilson CB. Surgical management of pituitary tumors. J Clin Endocrinol Metab. 1997;82(8):2381–5.
18. Pashtan I, Oh KS, Loeffler JS. Radiation therapy in the management of pituitary adenomas. Handb Clin Neurol. 2014;124:317–24.
19. Ono M, *et al*. Individualized high-dose cabergoline therapy for hyperprolactinemic infertility in women with microand macroprolactinomas. J Clin Endocrinol Metab. 2010;95(6):2672–9.
20. Sarwar KN, *et al*. The prevalence and natural history of pituitary hemorrhage in prolactinoma. J Clin Endocrinol Metab. 2013;98(6):2362–7.

21. Watt A, Pobereskin L, Vaidya B. Pituitary apoplexy within a macroprolactinoma. Nat Clin Pract Endocrinol Metab. 2008;4(11):635–41.
22. Briet C, *et al*. Pituitary apoplexy. Endocr Rev. 2015;36(6):622–45.
23. Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. Eur J Endocrinol. 2015;172(5):R205–13.
24. Maiter D, Delgrange E. Therapy of endocrine disease: the challenges in managing giant prolactinomas. Eur J Endocrinol. 2014;170(6):R213–27.

Source: Souad Enakuaa, Lisa B. Nachtigall. Macroprolactinoma: Diagnosis and Management in a Patient with Infertility. In: Nachtigall L.B. (ed). Pituitary Tumors: A Clinical Casebook. 1st ed. Switzerland: Springer International Publishing; 2018, pp 1-8. DOI 10.1007/978-3-319-90909-7_1.

Diabetes and Female Sterility/ Infertility

Kuniaki Ota, Hiroaki Ohta, Sho-ichi Yamagishi

Abstract

Advanced glycation end products (AGEs) are pro-inflammatory molecules that trigger a state of intracellular oxidative stress and inflammation after binding to their cell membrane receptors, such as RAGE. The activation of the AGE-RAGE axis has been well known to play a role in type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome (MetS), cardiovascular disease (CVD), aging, inflammation, and neurodegenerative disorders. AGEs might contribute to the etiology of polycystic ovary syndrome and infertility. This article explains for the relationship between the AGE-RAGE system and infertility as well as ovarian reserve in women of reproductive age.

Keywords: Advanced glycation end products, Receptor for AGE, Polycystic ovarian syndrome, In vitro fertilization, Anti-Müllerian hormone

AGE-RAGE and Insulin Resistance

Polycystic ovarian syndrome (PCOS), while clinically heterogeneous, commonly exhibits hyperandrogenism and ovulatory dysfunction and is

K. Ota, M.D., Ph.D. (✉), H. Ohta
Department of Obstetrics and Gynecology, Nasu Red Cross Hospital, 1081-4 Nakadawara, Otawara, Tochigi 324-8686, Japan
e-mail: kuniakiota@gmail.com

S.-i. Yamagishi
Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume 830-0011, Japan

associated with obesity, insulin resistance, and subfertility [1, 2]. Overall, insulin resistance and the compensatory hyperinsulinemia affects some 65–70% of women with PCOS [3, 4], with 70–80% of obese (BMI >30) and 20–25% of lean (BMI <25) women exhibiting these characteristics. Part of the insulin resistance appears to be independent of obesity and related specifically to PCOS, with abnormalities of cellular mechanisms of insulin action and insulin receptor function having been documented [5, 6].

Other criteria that can be used include those from the National Institutes of Health (NIH) and the Androgen Excess Society (AES) [7]. PCOS has estimated prevalence of over 10% in women of childbearing age. Besides being associated with infertility, PCOS is also associated with a higher incidence of type 2 diabetes mellitus (T2DM) such as the status of insulin resistance.

On the other hand, AGEs have been proposed to be among the main intermediaries of several diseases such as type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome (MetS), cardiovascular disease (CVD), aging, inflammation, and neurodegenerative disorders [8–10]. Along with the appreciation of these problems, there has been recognition that AGEs have a wider range of actions, including in reproduction.

Insulin resistant women with PCOS without hyperglycemia have elevated serum AGE levels and increased RAGE expression in their circulating monocytes [11]. Additionally, serum AGE levels are positively correlated with testosterone level, free androgen index, insulin, HOMA, and waist-to-hip ratio in women with PCOS without hyperglycemia [12]. Another study has shown that increased serum AGE level is a distinct finding in non-insulin resistant lean women with PCOS suggesting that serum AGEs are elevated in PCOS independently of the presence of insulin resistance [11].

Recent studies have demonstrated that RAGE- and AGE-modified proteins are expressed in human ovarian tissue [10, 13]. In ovarian tissue samples, women with PCOS have increased AGEs and RAGE expression in theca and granulosa cell layers compared with normal women [9]. Additionally, a differential qualitative distribution of AGE and RAGE subunit was observed in women with PCOS compared with healthy controls, where a more pronounced staining density of both AGE and RAGE was observed in the granulosa cell layer of PCOS ovaries [9].

The ovaries of women with PCOS have alterations in enzymes responsible for collagen synthesis [14]. Lysyl oxidase enzyme is one of the key enzymes in the ovary responsible for collagen and elastin cross-linking in the organization of ECM during follicular development [15]. A study has shown that the deposition of excess collagen in PCO tissue may, in part, be due to AGE-mediated stimulation of lysyl oxidase activity [16]. These results indicate that AGE signaling could regulate ovarian follicular ECM organization in PCOS. Other data demonstrated that AGEs could reduce the activity of some "good" detoxifying enzymes (such as glyoxalase-I) in the ovary of PCOS rats [17].

The AGE system has been shown to play a role in ovarian aging and reproduction [10, 13]. The accumulation of AGEs in the human ovary may account for a number of age-related features of ovarian dysfunction reflected by oxidative stress, such as impaired vascularization with its subsequent hypoxia and reduced intake of nutrients by granulosa cells [10, 18]. Prolonged exposure to AGEs, which are characterized by a long half-life, during reproductive life may cause subtle oxidative damage to follicles inside the ovary [19]. These alterations in the ovarian microenvironment may adversely impact granulosa cell metabolism, the assembly of antioxidant defense, and the development of adequate perifollicular vascularization, thus endangering follicular health and maturation. Markers of ovarian reserve, such as AMH, reflect ovarian aging. Studies pertaining to the effect of AGEs on ovarian aging have been reported [13, 16]; however, no studies to date have examined the relationship between the follicular AGE system and ovarian reserve measures, specifically granulosa cell AMH synthesis and release.

Because AGEs are elevated in the serum of women with PCOS, Christakou *et al.* [20] investigated whether oral contraceptives (OCPs) or metformin affect serum AGEs levels in women with PCOS. They randomized women with PCOS ($n = 109$) to receive either OCP or metformin (850 mg twice daily) for 6 months and determined serum AGE levels at baseline and after 3 and 6 months of treatment. Their results indicated that serum AGE levels were significantly reduced in all groups at 6 months of treatment compared with baseline, but the percentage reduction was significantly greater in the metformin group compared with the OCP group. Although they showed that metformin may be superior to OCP in reducing serum AGE levels, this does not necessarily mean that metformin is

better than OCP in alleviating the cardiovascular risk associated with PCOS. Whether metformin lowers cardiovascular risks in PCOS women via the AGE-RAGE system remains to be determined.

AGE-RAGE and In Vitro Fertilization

Some researchers have already reported a relationship between the AGE-RAGE system and infertility included in in vitro fertilization (IVF) [13, 21, 22]. One of researchers measured the levels of toxic AGE (TAGE), pentosidine, and CML in blood and follicular fluid of 157 patients undergoing IVF [22]. They analyzed the association between these levels and assisted reproduction technology (ART) outcomes and pre-ART clinical factors. Their results elucidated that the accumulation of TAGE, pentosidine, and CML in the follicular fluid and TAGE in serum negatively correlated ($P < 0.05$) with follicular growth, fertilization, and embryonic development. Lower concentrations of pentosidine in the follicular fluid and TAGE in the serum were the most significant predictors for achievement of ongoing pregnancy, acting independently of conventional determinants, such as age and Day 3 FSH level. Additionally, elevation of serum TAGE >7.24 U/ml appeared to indicate ovarian dysfunction causing diminished fertility, even at a young age (<40 years old) or with normal FSH during menses (below 10 IU/l). These data explain that there is a clinical evidence for an important role of AGE accumulation in ovarian dysfunction and poorer outcome in women with elevated AGEs and undergoing IVF [22].

Another study evaluated sRAGE, as decoy receptor, levels in serum, and follicular fluid of 33 women under IVF program [21]. The control group of serum samples was collected from 35 healthy females. Their results indicated that sRAGE levels of follicular fluid were several times higher than serum levels ($P < 0.001$). Additionally, it was found that serum levels of sRAGE in women after controlled ovarian hyperstimulation (COH) were significantly lower than in controls ($P = 0.045$). They also found a significant negative correlation between serum sRAGE levels and the number of stimulated follicles ($r = 20.71$, $P = 0.01$) and retrieved oocytes ($r = 20.54$, $P = 0.048$). Women in that study who conceived following IVF showed significantly higher sRAGE levels in the follicular fluid compared with women who did not conceive ($P = 0.031$). A similar study

evaluated follicular fluid and plasma sRAGE levels in 28 participants who underwent IVF and found a positive correlation between follicular fluid and plasma sRAGE levels and a borderline positive correlation between follicular fluid sRAGE and the number of collected oocytes ($r = 0.25$; $P = 0.05$). These data speculate that the decoy sRAGE, via binding circulating and follicular fluid AGEs, might be able to serve as a useful biological marker of the follicular environment [13].

AGE-RAGE and Anti-Müllerian Hormone

Anti-Müllerian hormone (AMH) is a very sensitive indicator of the ovarian follicular content. AMH is produced by granulosa cells of preantral and small antral follicles, and its main physiological role seems to be the inhibition of the initial follicular recruitment from the primordial to the antral pool [23]. It has been extensively studied in assisted reproductive therapy processes. It is now well established that AMH is the more accurate marker of the ovarian reserve [24].

One researcher showed that there was a positive correlation between follicular fluid sRAGE and follicular fluid AMH protein levels ($r = 0.5$, $P = 0.008$) while, in contrast, RT-PCR results showed no correlation between follicular fluid sRAGE and AMH or AMHR-II mRNA levels, suggesting that sRAGE has an effect on AMH release rather than AMH synthesis in granulosa cells. The potential accumulation of AGEs in the ovary may account for compromised efficiency of vascularization and for activation of oxidative stress response through interaction with cellular RAGE [18]. Similar to sRAGE, follicular fluid AMH reflects ovarian health and constitutes a useful biological marker of the follicular environment [25]. Within follicles, AMH is expressed exclusively by granulosa cells with mitotic activity [25, 26] presumably because it interacts with mitogenic growth factors during follicle development. Therefore, a positive relationship between intrafollicular AMH and sRAGE concentrations suggests that AGEs play a role in the inhibition of cellular proliferation or a role in enhancing granulosa cell apoptosis. It is unclear whether the AMH system has a role in the mechanistic effect of sRAGE on the number of oocytes retrieved. It is well known that AMH release inhibits, in paracrine fashion, the depletion of the oocyte pool by slowing down growth

followed by atresia of follicles containing the oocytes [27]. Thus, clearly a favorable interrelationship exists between sRAGE and AMH in the follicular environment. Altogether, the AGE-RAGE system could represent a potential therapeutic target in women with a diagnosis of diminished ovarian reserve undergoing ART.

AGE-RAGE and Recurrent Pregnancy Miscarriage

It is estimated that 20–30% of pregnant women may experience one or more spontaneous pregnancy losses [28]. Recurrent pregnancy losses (RPL) are often defined as three or more consecutive pregnancy losses prior to 20 weeks' gestation [28], and more than 500,000 women per year have experienced recurrent pregnancy losses in the United States [29].

The outcomes for approximately half the patients remain unexplained with current medical practice patterns, and they are classified as idiopathic or unexplained RPL [30]. Therefore, identifying new biomarkers for RPL is urgently needed for the proper diagnosis and management of RPL.

We investigated whether sRAGE is increased in women with PRL and which anthropometric, metabolic, and inflammatory variables are independently correlated with sRAGE in women with idiopathic RPL [31]. We measured the levels of AGERAGE, anthropometric, metabolic, and inflammatory immune markers as AGERAGE related factor in blood of 63 women with RPL. Levels of sRAGE were statistically significantly higher in RPL patients than in control patients (1528.9 ± 704.5 vs. 1149.9 ± 447.4 pg/mL). In the multivariate analysis, the levels of insulin, plasminogen activator inhibitor-1, the resistance index of the uterine radial artery, and the ratio of tumor necrosis factor-a/interleukin-10 producing T helper cells were statistically significantly associated with the serum sRAGE level. We concluded that elevated levels of serum sRAGE are associated with RPL. The soluble receptor for advanced glycation end products might contribute to RPL by reducing uterine blood flow and subsequently causing ischemia in the fetus via inflammatory and thrombotic reactions. Furthermore, our data suggest that sRAGE may be a novel biomarker of RPL and that RAGE might be a therapeutic target for this devastating disorder.

References

1. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997;18:774–800.
2. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod Update. 2009;15:477–88.
3. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38:1165–74.
4. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979;237:E214–23.
5. Ovesen P, Moller J, Ingerslev HJ, *et al*. Normal basal and insulin-stimulated fuel metabolism in lean women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1993;77:1636–40.
6. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. J Clin Endocrinol Metab. 1987;65:499–507.
7. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25:544–51.
8. Yamagishi S, Nakamura K, Imaizumi T. Advanced glycation end products (AGEs) and diabetic vascular complications. Curr Diabetes Rev. 2005;1:93–106.
9. Diamanti-Kandarakis E, Piperi C, Patsouris E, *et al*. Immunohistochemical localization of advanced glycation end-products (AGEs) and their receptor (RAGE) in polycystic and normal ovaries. Histochem Cell Biol. 2007;127:581–9.
10. Tatone C, Amicarelli F. The aging ovary—the poor granulosa cells. Fertil Steril. 2013;99:12–7.
11. Diamanti-Kandarakis E, Katsikis I, Piperi C, *et al*. Increased serum advanced glycation endproducts is a distinct finding in lean women with polycystic ovary syndrome (PCOS). Clin Endocrinol (Oxf). 2008;69:634–41.
12. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab. 1980;50:113–6.
13. Fujii EY, Nakayama M. The measurements of RAGE, VEGF, and AGEs in the plasma and follicular fluid of reproductive women: the influence of aging. Fertil Steril. 2010;94:694–700.
14. Henmi H, Endo T, Nagasawa K, *et al*. Lysyl oxidase and MMP-2 expression in dehydroepiandrosterone-induced polycystic ovary in rats. Biol Reprod. 2001;64:157–62.
15. Harlow CR, Rae M, Davidson L, Trackman PC, Hillier SG. Lysyl oxidase gene expression and enzyme activity in the rat ovary: regulation by follicle-stimulating hormone, andro gen, and transforming growth factor-beta superfamily members in vitro. Endocrinology. 2003;144:154–62.
16. Papachroni KK, Piperi C, Levidou G, *et al*. Lysyl oxidase interacts with AGE signalling to modulate collagen synthesis in polycystic ovarian tissue. J Cell Mol Med. 2010;14:2460–9.
17. Kandaraki E, Chatzigeorgiou A, Piperi C, *et al*. Reduced ovarian glyoxalase-I activity by dietary glycotoxins and androgen excess: a causative link to polycystic ovarian syndrome. Mol Med. 2012;18:1183–9.
18. Tatone C, Amicarelli F, Carbone MC, *et al*. Cellular and molecular aspects of ovarian follicle ageing. Hum Reprod Update. 2008;14:131–42.
19. de Bruin JP, Dorland M, Spek ER, *et al*. Age-related changes in the ultrastructure of the resting follicle pool in human ovaries. Biol Reprod. 2004;70:419–24.
20. Christakou C, Diamanti-Kandarakis E. Structural, biochemical and non-traditional cardiovascular risk markers in PCOS. Curr Pharm Des. 2013;19:5764–74.
21. Malickova K, Jarosova R, Rezabek K, *et al*. Concentrations of sRAGE in serum and follicular fluid in assisted reproductive cycles—a preliminary study. Clin Lab. 2010;56:377–84.
22. Jinno M, Takeuchi M, Watanabe A, *et al*. Advanced glycation end-products accumulation compromises embryonic development and achievement of pregnancy by assisted reproductive technology. Hum Reprod. 2011;26:604–10.
23. Weenen C, Laven JS, Von Bergh AR, *et al*. Anti-Mullerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod. 2004;10:77–83.

24. La Marca A, Broekmans FJ, Volpe A, Fauser BC, Macklon NS. ESHRE Special Interest Group for Reproductive Endocrinology—AMH Round Table. Anti-Mullerian hormone (AMH): what do we still need to know? Hum Reprod. 2009;24:2264–75.
25. Hirobe S, He WW, Lee MM, Donahoe PK. Mullerian inhibiting substance messenger ribonucleic acid expression in granulosa and Sertoli cells coincides with their mitotic activity. Endocrinology. 1992;131:854–62.
26. Hirobe S, He WW, Gustafson ML, MacLaughlin DT, Donahoe PK. Mullerian inhibiting substance gene expression in the cycling rat ovary correlates with recruited or graafian follicle selection. Biol Reprod. 1994;50:1238–43.
27. Durlinger AL, Gruijters MJ, Kramer P, *et al*. Anti-Mullerian Hormone Inhibits Initiation of Primordial Follicle Growth in the Mouse Ovary. Endocrinology. 2002;143:1076–84.
28. Li TC, Makris M, Tomsu M, Tuckerman E, Laird S. Recurrent miscarriage: aetiology, management and prognosis. Hum Reprod Update. 2002;8:463–81.
29. Bick RL. Recurrent miscarriage syndrome due to blood coagulation protein/platelet defects: prevalence, treatment and outcome results. DRW Metroplex Recurrent Miscarriage Syndrome Cooperative Group. Clin Appl Thromb Hemost. 2000;6:115–25.
30. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril. 2010;93:1234–43.
31. Ota K, Yamagishi S, Kim M, *et al*. Elevation of soluble form of receptor for advanced glycation end products (sRAGE) in recurrent pregnancy losses (RPL): possible participation of RAGE in RPL. Fertil Steril. 2014;102:782–9.

Source: Kuniaki Ota, Hiroaki Ohta, Sho-ichi Yamagishi. Diabetes and Female Sterility/Infertility. In: Yamagishi Sho-ichi (ed). Diabetes and Aging-Related Complications. 1st ed. Singapore: Springer; 2017, pp 177-183. DOI 10.1007/978-981-10-4376-5_14.

Male Infertility as a Marker of Future Health

Brent M. Hanson, James M. Hotaling

Introduction

Infertility is a common problem in the United States, affecting approximately 8–15% of couples. The male partner is identified as the sole cause of infertility in approximately 20% of infertile couples, but male factor infertility is believed to contribute to greater than 50% of infertility cases [1]. Traditionally, a primary focus has been placed on female infertility and the female partner's overall health status in order to achieve a healthy pregnancy. Publications within the medical literature have long neglected the male component of reproduction [2]. Recently, increased attention has been placed on the male partner, and it is becoming clear that a diagnosis of male factor infertility may be associated with long-term health consequences that go beyond the immediate reproductive needs of patients, particularly in the current environment of increasing paternal age [3]. Since approximately 15% of the male genome is involved in reproduction, it is entirely possible that problems related to fertility may also be linked to overall somatic health issues in men [3]. While the exact mechanism of these changes remains largely unknown, ongoing work has postulated that genetic, epigenetic, environmental, or hormonal changes may account for some of the associations between male infertility and

B. M. Hanson, MD
Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT, USA
e-mail: brent.hanson@hsc.utah.com

J. M. Hotaling, MD, MS, FECSM (✉)
Department of Surgery—Urology, Center for Reconstructive Urology and Men's Health, University of Utah, Salt Lake City, UT, USA
e-mail: Jim.hotaling@hsc.utah.edu

somatic health problems. Further, another work has demonstrated that male infertility may not only be a biomarker of a man's health but also of the health of his family [4, 5].

Genetics, Epigenetics, and Environmental Factors

Associations between male infertility and somatic health issues may be related to underlying genetic abnormalities. As stated above, nearly 15% of the male genome is involved with reproduction [3]. Spermatogenesis is a complex process that involves approximately 2300 genes which regulate the development and maturation of germ cells [6]. Underlying genetic abnormalities are common in infertile men. Nearly 8% of men with severe oligospermia and approximately 20% of men with nonobstructive azoospermia will have chromosomal abnormalities detected during an infertility workup [7, 8]. Variations in published prevalence of genetic abnormalities in the infertile male population appear to be related to differences in patient selection or the composition of the specific study population, but it is clear that men with infertility have a significantly elevated risk of genetic abnormalities.

In a large Chinese study from 2017, it was found that 27.3% of men with nonobstructive azoospermia and 15.9% of men with severe oligospermia had underlying genetic abnormalities. As a comparison, only 1.3% of normozoospermic controls possessed an underlying genetic abnormality. Of the men with nonobstructive azoospermia, the most common genetic abnormalities were sex chromosomal abnormalities such as Klinefelter syndrome and Y chromosome deletions. Autosomal translocations and inversions were less common. Men with severe oligospermia demonstrated similarly low rates of autosomal translocations and inversions. Klinefelter syndrome or mosaic was also less common in men with severe oligospermia, with the majority of chromosomal abnormalities being Y chromosome deletions [9].

Although infertile men with underlying genetic abnormalities may be able to father offspring with the use of assisted reproductive technologies such as microdissection testicular sperm extraction (microTESE) and intracytoplasmic sperm injection (ICSI), the risk of passing genetic aberrations to future generations is increased [9, 10].

Men with infertility related to known genetic syndromes such as Klinefelter syndrome, Kallmann syndrome, sickle cell anemia, Kartagener's syndrome, myotonic dystrophy, Fanconi anemia, and beta thalassemia face many somatic health risks related to their specific disease processes [11]. Historically, infertility limited the natural transmission of genetic abnormalities to future generations. While the use of assisted reproductive technologies has made it possible for these men to have families, it has also necessitated the development of genetic screening protocols for partners as well as embryos. Recently, genomic microarray tools have been increasingly used and have been applied to the entire male genome to assist in identifying novel genetic causes of infertility [12]. This recent data has proposed possible genetic links between male infertility and common health problems such as diabetes and obesity [13, 14]. Patients with genetic problems such as Klinefelter, Prader-Willi, and Laurence-Moon-Bardet-Biedl syndrome generally display both obesity and infertility. The specific genes involved with these syndromes are well documented, but it is possible that other, less conspicuous genetic abnormalities may explain the common correlations between infertility, obesity, and diabetes [15]. Emerging data continue to show a likely genetic link between infertility and numerous disease processes which may develop years later. Early evidence suggests that specific genetic pathways may link infertility to testicular cancer, prostate cancer, nonfatal stroke, nonfatal coronary heart disease, psychosexual dysfunction, and mood disorders [16]. For infertile men with a normal chromosomal analysis, the use of microarray may identify subtle genetic abnormalities causing both infertility and possible long-term health consequences.

The study of epigenetics has also attracted increasing attention in recent years. Spermatogenesis involves several genes which are regulated through epigenetic mechanisms, and epigenetic aberrations such as hypermethylation, histone remodeling, and chromatin modification in many of these genes have been associated with poor sperm quality and male infertility [17]. Epigenetic changes can be transmitted to future generations, often with negative health consequences. See Figure 1 regarding the impact of lifestyle and epigenetic changes on somatic health and fertility. Paternal epigenetic changes may result in abnormal gene expression in children which could predispose offspring to metabolic abnormalities, obesity, type 2 diabetes, hypertension, and disruptions in body fat

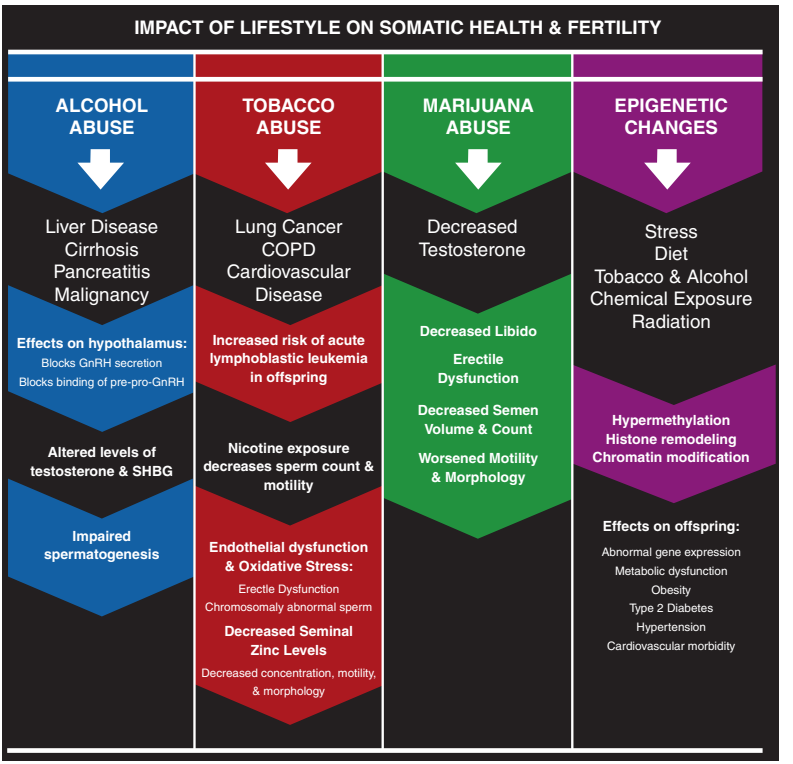


Fig. 1: The detrimental effects and proposed mechanistic roles of alcohol, tobacco, marijuana, and lifestyle on male fertility.

composition [18, 19]. Unlike genetic causes of infertility, many epigenetic causes of infertility are induced by lifestyle factors. Stress, physical activity, diet, alcohol intake, smoking, and sleep disturbances such as shift work have been associated with infertility in men and have been implicated with epigenetic changes [20, 21].

Specific environmental or occupational exposures may also result in epigenetic changes that impact future generations. Paternal exposure to pesticides may result in nervous system tumors in children, cigarette smoking may result in increased rates of childhood leukemia, and chemicals related to woodwork and wood processing may increase rates of leukemia in children [22–24]. Exposure to ionizing radiation may result in increased DNA methylation and impaired DNA repair processes which can lead to persistent instability of the male germ line [25].

Table 1: Key studies evaluating male infertility and nonmalignant health risks.

Study author	Title	Year	*Journal*	Sample size	Main findings
Alvarez *et al.*	Do some addictions interfere with fertility?	2015	*Fertil Steril*	N/A (review article)	Tobacco abuse results in erectile dysfunction and chromosomal aberrations of sperm Sperm quality improves after 3 months of cessation 33% of chronic marijuana users have oligospermia Marijuana results in low libido, gynecomastia, erectile dysfunction Alcohol consumption >5 drinks per week has adverse effects on sperm with profound effects at >25 drinks per week Alcohol negatively impacts testosterone and SHBG
Babore *et al.*	Male factor infertility and lack of openness about infertility as risk factors for depressive symptoms in males undergoing assisted reproductive technology treatment in Italy	2017	*Fertil Steril*	340 participants (170 men and their female partners)	51.8% of males do not discuss ART treatments with people outside of their partners Male factor infertility increases depressive symptoms (Likert scale score 30.7 vs. 28.6) The decision to not share infertility experience was associated with higher levels of depressive symptoms ($F1,162 = 5.115$)
Calogero *et al.*	Klinefelter syndrome: cardiovascular abnormalities and metabolic disorders	2017	*J Endocrinol Invest*	Review of 56 publications	KS patients have increased risk of cerebrovascular disease (SMR 2.2), cardiovascular congenital anomalies (SMR 7.3), development of thrombosis and leg ulcers (SMR 7.9)[a] KS increases risk of obesity, metabolic syndrome, type 2 diabetes
Eisenberg *et al.*	Semen quality, infertility, and mortality in the USA	2014	*Hum Reprod*	11,935 men evaluated for infertility	Men with 2 or more abnormal semen parameters have a 2.3-fold higher risk of death compared to men with normal semen (95% CI 1.12–4.65)[b]

(continued)...

...(continued)

Eisenberg *et al.*	The relationship between male BMI and waist circumference on semen quality: data from the LIFE study	2014	*Hum Reprod*	501 couples attempting to conceive	Men in the highest category of waist circumference had a 22% lower total sperm count Linear association between higher BMI and low semen volume (<1.5 ml), low sperm concentration (<15 M/mL), and low total sperm count (<39 M) Waist circumference was correlated with low sperm concentration ($P = 0.025$) and low count ($P = 0.008$)
Eisenberg *et al.*	Increased risk of incident medical conditions in infertile men: analysis of the United States claims data	2016	*Fertil Steril*	13,027 men with male factor infertility	Men with infertility had a higher risk of developing diabetes (HR 1.30, 95% CI 1.10–1.53), ischemic heart disease (HR 1.48, 95% CI 1.19–1.84), alcohol abuse (HR 1.48, 95% CI 1.07–2.05), and drug abuse (1.67, 95% CI 1.06–2.63) compared with men who only received infertility testing[c]
Eisenberg *et al.*	Diabetes, medical comorbidities, and couple fecundity	2016	*Hum Reprod*	501 couples desiring pregnancy	Longer time to pregnancy for male partners with diabetes (0.35, 95% CI 0.14–0.86) Couples' medical comorbidity was associated with pregnancy status
Emanuele *et al.*	Alcohol and the male reproductive system	2001	*Alcohol Res Health*	Review of 30 publications	Alcohol is associated with low levels of hypothalamic LHRH and pituitary LH Alcohol use is associated with low testosterone and altered levels of additional reproductive hormones
Haring *et al.*	Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania	2009	*Diabetes*	1004 men without baseline metabolic syndrome	Low testosterone predicted metabolic syndrome (RR 1.38 [95% CI 1.13–1.69]), particularly among men aged 20–39 years (2.06 [1.29–3.29]), even after adjustment for age, smoking, alcohol consumption, physical activity, waist circumference, self-related health, and time of blood sampling. DHEA-S levels were not related to incident MetS (0.99 [0.83–1.19])[d]

(continued)...

...(continued)

Jensen *et al.*	Habitual alcohol consumption associated with reduced semen quality and changes in reproductive hormones; a cross-sectional study among 1221 young Danish men	2014	*BMJ Open*	1221 young Danish men	Men with alcohol use >40 drinks per week had a 33% (95% CI 11–59%) reduction in sperm concentration compared to men with an intake of 1–5 drinks/week. A significant increase in serum-free testosterone was noted with increasing alcohol consumption
Katib *et al.*	Mechanisms linking obesity to male infertility	2015	*Cent Eur J Urol*	N/A (review article)	The prime hormonal defect in obese men is hypotestosteronemia, which results in impaired spermatogenesis leading to poor fecundability
Kovac *et al.*	The effects of cigarette smoking on male fertility	2015	*Postgrad Med*	Review of 31 publications	Men who smoked >20 cigarettes per day had a 19% reduction in sperm concentration compared with nonsmokers, even after controlling for other factors Smoking was associated with decreases in sperm density (15.3%), total sperm counts (17.5%), and total motile sperm (16.6%) compared with nonsmokers Morphology and volume were slightly affected by smoking
Krajewska-Kulak *et al.*	Thyroid function in male infertility	2013	*Front Endocrinol*	N/A (review article)	Hypothyroidism decreases SHBG, total serum testosterone, LH, and FSH Hyperthyroidism can lead to infertility through elevated levels of testosterone, LH, and FSH

(continued)...

...(continued)

Kulej-Lyko *et al.*	Could gonadal and adrenal androgen deficiencies contribute to the depressive symptoms in men with systolic heart failure	2016	*Aging Male*	226 men	Testosterone deficiency was related to higher prevalence of mild depression (OR = 3.6, 95% CI 1.2–10.63)
Kupelian *et al.*	Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men	2006	*J Clin Endocrinol Metab*	1709 men	Lower levels of total testosterone and SHBG were predictive of metabolic syndrome, particularly in men with a BMI below 25 kg/m^2 with adjusted RRs for a decrease in 1 sd of 1.41 (95% CI, 1.06–1.87) and 1.65 (95% CI, 1.12–2.42)
Liu *et al.*	Lower SHBG level is associated with higher leptin and lower adiponectin levels as well as metabolic syndrome, independent of testosterone	2017	*Sci Rep*	614 Taiwanese men	Subjects in the lowest quartile of testosterone and SHBG are exposed to a 1.58 and 3.22 times risk of developing metabolic syndrome compared to men in the highest quartile of testosterone and SHBG levels SHBG served as a major predictor for the risk of metabolic syndrome and was correlated with serum adiponectin and leptin levels

(continued)...

...(continued)

Liu *et al.*	Seminal plasma zinc level may be associated with the effect of cigarette smoking on sperm parameters	2010	*J Int Med Res*	79 nonsmokers, 68 smokers	Seminal plasma zinc concentrations were found to be significantly lower in smokers than in nonsmokers (1.84 vs. 2.38 mmol/L, $P < 0.05$) Concentration, motility, and morphology were found to be significantly lower among smokers than nonsmokers (58.6 vs. 75.7 × 10^6/mL, 10.4% vs. 16.6%, 8.2% vs. 12.5%)
Nguyen *et al.*	Men's body mass index and infertility	2007	*Hum Reprod*	26,303 couples	Increased infertility with increased BMI. OR for infertility was 1.20 for overweight men [BMI 25–29.9; 95% CI 1.04–1.38] and 1.36 for obese men (BMI 30–34.9; 95% CI 1.13–1.63) relative to men with low-normal BMI (20.0–22.4)[e]
Omani-Samani *et al.*	Evaluation on hope and psychological symptoms in infertile couples undergoing assisted reproduction treatment	2017	*Int J Fertil Steril*	180 infertile couples	Infertility is associated with increased anxiety, depression, and stress
Park *et al.*	Cannabis, cannabinoids, and reproduction	2004	*Prostaglandins Leukot Essent Fatty Acids*	N/A (review article)	Marijuana smoking decreases serum LH when compared to hormone levels in nonsmoking controls. Chronic marijuana use is associated with decreased plasma testosterone
Patel *et al.*	Thyroid dysfunction and male reproductive physiology	2016	*Semin Reprod Med*	N/A (review article)	Hyperthyroidism leads to decreased free testosterone (1.7 ng/mL vs. 3.1 ng/mL) After treatment for 12 months, 85% of males with seminal alterations had normalization of semen quality

(continued)...

...(continued)

Ramlau-Hansen *et al.*	Subfecundity in overweight and obese couples	2007	*Hum Reprod*	47,835 couples	In men with a BMI of 18.5 kg/m^2 or more, there is a dose-response relationship between increasing BMI and subfecundity (time to pregnancy of 12+ months): OR 1.19 (95% CI 1.14–1.24)
Rojdmark *et al.*	Hypothalamic-pituitary testicular axis in patients with hyperthyroidism	1988	*Horm Res*	8 hyperthyroid men	Chronic hyperthyroidism makes the pituitary hypersensitive to exogenous GnRH LH and FSH responsiveness to GnRH was significantly larger in the thyrotoxic state compared with the euthyroid state (LH incremental areas, 3999 +/– 665 vs. 2640 +/– 430, $p < 0.02$; FSH incremental areas, 825 +/– 193 vs. 542 +/– 98, $p < 0.05$)
Sahin *et al.*	Psychologic and sexual dysfunction in primary and secondary infertile male patients	2017	*Arch Ital Urol Androl*	70 infertile men	Depression and erectile dysfunction seen in the patients with secondary infertility were significantly higher than the patients with primary infertility A statistically significant difference was detected between groups for Beck depression inventory scores ($p = 0.015$; $p < 0.05$)
Sallmen *et al.*	Reduced fertility among overweight and obese men	2006	*Epidemiology*	1329 men	A 3-unit increase in BMI was associated with infertility OR 1.12; 95% CI 1.01–1.25

(continued)...

...(continued)

Verze *et al*.	The link between cigarette smoking and erectile dysfunction: a systematic review	2015	*Eur Urol Focus*	Review of 13 publications	Smoking-related erectile dysfunction is mainly associated with endothelial impairment, reduction in nitric oxide availability, and imbalance between oxidative and antioxidative reactions increasing oxidative stress. Passive second-hand cigarette smoking negatively impacts erectile function
Wdowiak *et al*.	Impact of emotional disorders on semen quality in men treated for infertility	2017	*Neuro Endocrinol Lett*	112 subfertile males	Higher Beck depression inventory scores were correlated with significantly decreased testosterone ($p = 0.001$) and increased prolactin and cortisol ($p < 0.001$). Sperm count and volume were correlated with BDI scores

[a]*SMR* standardized mortality ratio
[b]*CI* confidence interval
[c]*HR* hazard ratio
[d]*RR* risk ratio
[e]*OR* odds ratio

Paternal diet may also play a role in gametogenesis. Human studies evaluating paternal obesity have demonstrated altered methylation in offspring, suggesting that developing sperm is susceptible to environmental insults related to diet. There is also some evidence that cardiovascular mortality in offspring may be related to epigenetic changes in the spermatozoa, although this effect may take multiple generations to manifest itself [26]. A recent comprehensive meta-regression analysis published in 2017 demonstrated a dramatic 50–60% decline in sperm counts in men in North America, Europe, Australia, and New Zealand between 1973 and 2011. While this downward trend in sperm counts has not been fully explained, lifestyle factors and epigenetic changes may play a large role in the overall reduction in male fertility in recent decades. Based on the epigenetic data discussed above, these factors may not only have negative consequences for male fertility and paternal health but may also negatively impact the health of future generations [27].

Mental Health and Substance Abuse

Certain associations have been documented between infertile men and mental health disorders. See Table 1 for details regarding key studies evaluating associations between male infertility and nonmalignant health risks. Male factor infertility appears to be associated with both depression and anxiety, although at relatively lower rates than in females who are diagnosed with infertility [28]. When evaluating the impact of male infertility on mental health, it is difficult to determine whether a cause and effect relationship exists since some men present at the time of the infertility diagnosis with known mental health issues and others will be diagnosed with mental health issues years later. Men with infertility undoubtedly experience a certain level of distress related to their diagnosis, and a portion of the mental health issues seen in infertile men may be explained by an emotional response to the infertility diagnosis. In a recent study, 51.8% of men reported a lack of willingness to discuss their reproductive problems with people other than their partner. A man's decision to not discuss his infertility with other individuals was associated with increased depressive symptoms based on self-reported questionnaires [29]. However, there may be underlying differences in infertile men that predispose them to mental health diagnoses independent of the emotional

stress of an infertility diagnosis, the process of achieving a pregnancy, and the emotionally taxing nature of infertility treatments. See Fig. 2 for details regarding male infertility and disease processes.

Infertile men have been shown to have lower secretion of sex hormone-binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEA-S), significantly decreased testosterone levels, as well as elevated secretion of cortisol and prolactin [30]. These hormonal abnormalities appear to result in decreased semen volume and sperm density, but they have also been associated with increased rates of anxiety and depression.

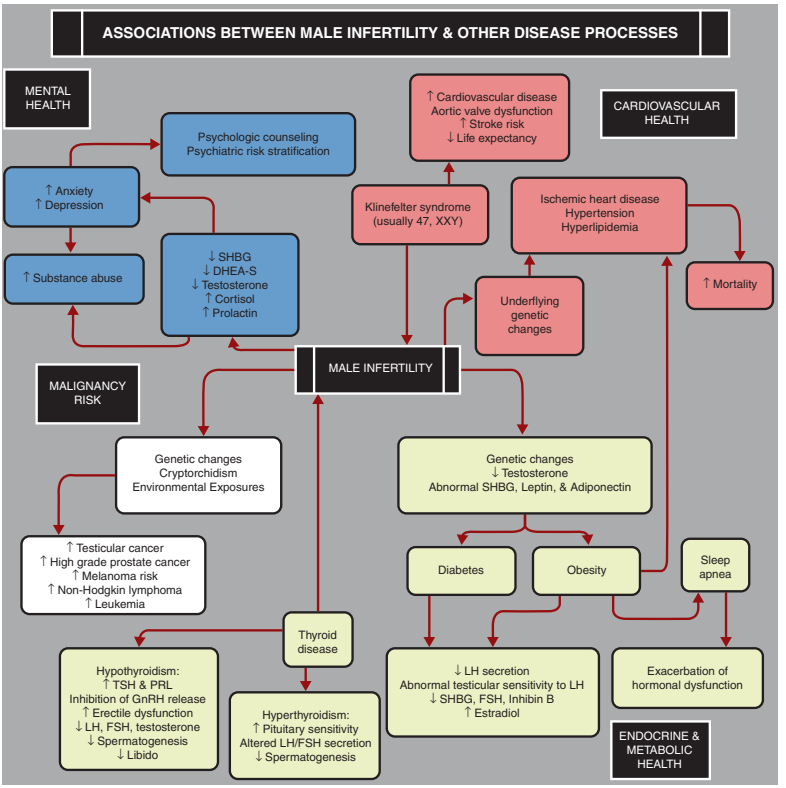


Fig. 2: The associations between male infertility and various aspects of somatic health, including cardiovascular disease, endocrine and metabolic derangement, malignancy risk, and mental illness. *SHBG* sex hormone-binding globulin, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *TSH* thyroid stimulating hormone, *PRL* prolactin, *GnRH* gonadotropin-releasing hormone, *DHEA-S* dehydroepiandrosterone sulfate

Overall, a higher incidence of depression appears to exist in infertile men when compared to the general population, and men who are diagnosed with secondary infertility have been found to have significantly higher rates of depression than men with primary infertility [31]. Depression and anxiety in otherwise healthy individuals who are diagnosed with male factor infertility may be the result of hormonal deficiencies in testosterone and DHEA-S rather than simply a response to the distress of the diagnosis [32]. Psychological counseling sessions may be beneficial in addressing the mental health needs of male patients who are diagnosed with infertility, although there has traditionally been a reluctance among men to seek out mental health resources [2, 29, 33].

It has been demonstrated that older men with infertility may be more likely to have children diagnosed with autism, schizophrenia, and bipolar disorder, particularly in the setting of conception achieved through intracytoplasmic sperm injection (ICSI) [34, 35]. The use of genetic sequencing technologies has highlighted associations between male factor infertility, particularly in men of advanced age, and mental health consequences in offspring [36]. However, there has been virtually nothing published regarding rates of these psychiatric disorders in the infertile men themselves. To date, it remains unknown whether rates of autism, schizophrenia, and bipolar disorder are different in the infertile population than the general male population. Studies evaluating the likelihood of developing these psychiatric illnesses among infertile men would be beneficial in determining future risk to patients since an association has been demonstrated in future generations.

In addition to depression and anxiety, substance abuse disorders appear to be more common in men who are diagnosed with infertility. Based on the U.S. claims data, both alcohol abuse and drug abuse appear to be elevated (HR 1.48 and 1.67, respectively) in men with infertility compared to men who underwent infertility testing but had normal semen analyses [37]. See Fig. 1 for the impact of lifestyle on somatic health and fertility. A clear explanation for the increased risk of drug and alcohol abuse among infertile men is lacking in the literature. The association between alcohol abuse and male infertility has been evaluated, with studies demonstrating that alcohol acts on the hypothalamus and blocks the secretion of gonadotropin-releasing hormone (GnRH) as well as the binding of the GnRH precursor pre-pro-GnRH to the functionally active

GnRH hormone, resulting in impaired spermatogenesis [38]. Even modest alcohol consumption of more than five drinks per week has been shown to negatively impact sperm quality, although the most significant impact on semen analysis parameters is seen with heavy drinking of greater than 25 drinks per week [39]. Alcohol consumption in men has also been linked to changes in testosterone and SHBG levels, so identification of infertile men who use alcohol is an important aspect of a comprehensive male infertility workup [40]. Lifestyle modifications among infertile men who consume alcohol may be warranted to improve sperm quality, but interventions or recommendations to prevent the future development of alcohol abuse in patients with male factor infertility are an area which remains uninvestigated. Since infertile men have a higher likelihood to develop alcohol abuse in the future, further studies that provide insight into the mechanistic link between male infertility and predisposition to these risks are vital.

Men who use tobacco are known to have higher rates of erectile dysfunction and increased levels of chromosomally abnormal sperm, and smoking rates have been shown to be higher in infertile men than the general population [37]. Additionally, the offspring of men who smoke near the time of conception has an elevated risk of developing acute lymphoblastic leukemia in the future (OR 1.1) [24]. A mechanistic explanation for the association between smoking and male infertility may be related to lower seminal zinc levels observed in smokers when compared to nonsmokers. Lower seminal zinc levels appear to be associated with decreased sperm concentration, motility, and morphology [41]. There is also some evidence that nicotine itself, rather than the additional toxins associated with cigarettes, may lead to adverse effects on fertility. In animal models, exposure to oral nicotine has been associated with decreased sperm motility and sperm count [42]. Cigarette smoking is a well-established risk factor for erectile dysfunction, with endothelial dysfunction and increased oxidative stress representing the primary pathophysiologic mechanisms for this association [43]. 21.6% of American men smoke cigarettes, and it is clear that smoking has a detrimental effect on male fertility [44]. Smoking cessation in men can lead to improvements in semen parameters in as little as 3 months, so tobacco habits should be addressed in all men who are diagnosed with infertility [40]. The increased use of tobacco among infertile men predisposes this population to the known health consequences of smoking such as emphysema, lung cancer, COPD,

and cardiovascular disease. Tobacco cessation in the infertile population may lead to both improvements in reproductive health as well as overall somatic health.

Additionally, men who abuse marijuana have been found to have decreased libido, increased rates of erectile dysfunction, decreased semen volume, decreased sperm count, and higher rates of abnormal sperm morphology and motility. Marijuana also decreases the production of testosterone, and more than 33% of men who abuse marijuana on a regular basis will present with oligospermia [45]. While associations between male factor infertility and other drugs of abuse have been published, large studies often lack details about specific substances being abused and the frequency of use. The fertility impact of many recreational drugs is not known, but thorough patient counseling about possible risks and avoidance of addictive substances is prudent.

Cardiovascular Health

Both congenital and acquired causes of male infertility have been associated with an increased risk of cardiovascular disease. One of the most common congenital causes of male factor infertility is Klinefelter syndrome, affecting approximately 1 in 1000 males. This disease process results in an overall lower life expectancy and is associated with an increased risk of cerebrovascular disease or stroke (standardized mortality ratio [SMR], 2.2) and cardiovascular congenital anomalies such as aortic valve disease (SMR 7.3) [46]. Cardiovascular health for this specific patient population appears to be improved with long-term testosterone replacement therapy, which may also be beneficial for psychosocial morbidity and behavioral problems seen in patients with Klinefelter syndrome [46, 47].

Acquired or unexplained male factor infertility is more commonly encountered than congenital infertility in the clinical setting, with approximately 40–50% of male infertility cases being classified as idiopathic or unexplained [48]. Despite the frequent lack of an identifiable cause for infertility, infertile men as a whole still appear to be at an elevated risk for the development of cardiovascular disease later in life. When compared to previously fertile men who had undergone vasectomy, men diagnosed with infertility were at a higher risk to develop ischemic heart disease (HR 1.41), hypertension (HR 1.09), and hyperlipidemia (HR 1.14) [37].

Associations between infertility and obesity as well as higher smoking rates in infertile men appear to provide the most plausible explanations for the association between male factor infertility and relatively poorer cardiovascular health.

Increasing rates of obesity in the United States and other developed nations have coincided with rising rates of poor sperm quality and male infertility [49]. In the United States, rates of obesity among men of reproductive age have tripled since the 1970s, with recent data estimating an obesity rate of 33.9% for individuals over age 20 [19]. There appears to be a direct relationship between increasing body mass index (BMI) and higher rates of male factor infertility. This relationship has been reproduced in multiple studies [50–52]. See Table 1 for key studies evaluating associations between male infertility and nonmalignant health risks. Increases in BMI and waist circumference have been shown to have a linear, negative impact on semen volume, concentration, and sperm count [53]. The mechanisms by which obesity results in infertility are complex and incompletely understood, but it is known that obesity can negatively impact the secretion of luteinizing hormone (LH) from the pituitary gland as well as testicular sensitivity to LH. Reductions in SHBG, follicle-stimulating hormone (FSH), and inhibin B and elevations in estradiol (E2) can all result in decreased sperm quality. Hormonal changes seen in obese men may be exacerbated by comorbidities such as sleep apnea and diabetes, which are frequently observed together [19].

While the hormonal changes seen in obesity may result in infertility for many men, there is emerging evidence that infertility itself may actually cause or worsen obesity. Low testosterone levels may induce changes that result in the metabolic syndrome, leading to increased risk of obesity in the future [14]. A German study from 2009 demonstrated that in men who did not meet criteria for the metabolic syndrome, low levels of testosterone were predictive of a subsequent diagnosis of the metabolic syndrome during a 5-year follow-up period [54]. In a 2017 study from Taiwan, men with low serum testosterone and low SHBG levels were found to have a 1.58–3.22 times increased risk of developing the metabolic syndrome in the future when compared to men with higher levels of testosterone and SHBG [55]. This study also demonstrated that lower SHBG levels were associated with higher leptin levels and lower adiponectin levels, which can both exacerbate weight gain [55–57]. Similarly, a 2006 study from

Massachusetts demonstrated that low serum SHBG, low total testosterone, and androgen deficiency are associated with an increased risk for the development of metabolic syndrome in the future. This increased risk was seen in men of normal BMI (less than 25) at the time of initial presentation. Low testosterone, low SHBG, and male infertility in general may be early warning signs for future risk of obesity in men who are not obese at the time of their infertility diagnosis [58].

Overall, men with infertility appear to have higher mortality than the general population, with a 2.3-fold increased risk of death compared to men with normal semen analyses [59]. While increased mortality cannot be entirely attributed to cardiovascular health consequences, the effects of obesity, ischemic heart disease, and cardiovascular disease should not be overlooked since they play a significant role in the general health status of infertile men. It is vital to recognize that infertility may be the primary marker in a man's life for these future health complications and the hormonal changes related to infertility may be the underlying cause for subsequent health issues.

Endocrine Dysfunction

Male infertility can also result in significant endocrine abnormalities [3]. Men with impaired semen parameters as well as ejaculatory and erectile dysfunction are frequently diagnosed with concomitant diabetes [60, 61]. As discussed previously, infertility can result in abnormalities in serum testosterone, SHBG, leptin, and adiponectin which predispose patients to insulin resistance and metabolic syndrome [55–57]. See Table 1 for a list of key studies evaluating associations between infertility and nonmalignant health risks. The insulin resistance that is a component of the metabolic syndrome greatly increases a man's risk of developing diabetes. Patients frequently present with both diabetes and obesity, which often makes it difficult to fully characterize the reproductive impact of these two disease processes independently. In the United States, 3.4% of the general population is diagnosed with both diabetes and obesity [62]. Infertility can lead to a positive feedback loop in which endocrine abnormalities related to infertility worsen diabetes and obesity, which subsequently worsen semen parameters. This cycle appears to result in reduced synthesis of SHBG in

the liver, resulting in elevations in free testosterone and subsequent down-regulation of the androgenic axis. While data are somewhat conflicting, this appears to result in further decreased fecundity and semen quality [19, 63].

Because of the endocrine abnormalities described above, men with infertility and no prior diagnosis of diabetes are at an elevated risk to develop diabetes later in life. A large prospective cohort study published in 2017 evaluated 39,516 men without diabetes who were undergoing IVF for male factor infertility and found that with a median follow-up time of 5.6 years, 1.6% of subjects were ultimately diagnosed with diabetes during the study period (HR 1.45) [13]. These findings indicated that compared to men with normal semen analyses or sterilized men, men with male factor infertility were at a statistically significant increased risk to subsequently develop diabetes. Implementation of diabetes screening in men who are diagnosed with infertility and long-term follow-up appear to be important methods to provide appropriate care for this group of patients.

In addition to diabetes, proper thyroid function appears to be important for the maintenance of male reproductive health. Infertility in men may be a marker of underlying thyroid pathology. In initial studies, there was felt to be little association between male fertility and the thyroid [64]. More recently, multiple studies have shown that abnormal semen analysis parameters and poor male sexual function may be a sign of improper thyroid function [65]. Both hyperthyroidism and hypothyroidism have been associated with problems related to male fertility. Chronic hyperthyroidism may result in a state of pituitary hypersensitivity which can impact LH and FSH secretion as well as testicular function [66]. In an opposite manner, hypothyroidism may result in increased secretion of TSH and prolactin. Increased prolactin can inhibit the release of GnRH which results in a decrease in LH and FSH. Decreases in LH and FSH can negatively impact testosterone levels and spermatogenesis, resulting in loss of libido, erectile dysfunction, and infertility [65]. In order to appropriately screen men with infertility for thyroid disease, the American Society for Reproductive Medicine recommends measurement of the thyroid-stimulating hormone (TSH) in men undergoing a thorough endocrine evaluation [1].

Malignancy

Many early studies evaluating the risk of male factor infertility on long-term health focused on a man's risk of developing cancer. The most well-documented association between infertility and cancer is that of testicular germ cell tumors, but men with infertility may also be at an increased risk to develop prostate cancer, melanoma, non-Hodgkin's lymphoma, and other types of malignancy [67]. See Table 2 for details regarding key studies evaluating a link between male infertility and malignancy. Multiple studies have uniformly shown that men with abnormal semen analysis parameters are at increased risk to develop testicular cancer. A retrospective study from Cornell evaluating 3800 men with abnormal semen analyses demonstrated that the study population had a significantly elevated risk for a subsequent diagnosis of testicular cancer following their infertility diagnosis (standardized incidence ratio [SIR] 18.3) [68]. Similarly, a large Danish cohort study of 32,442 men undergoing semen analysis documented statistically significant elevations in risk of testicular germ cell tumors in men with abnormal semen analyses compared to the general population (SIR 1.6) [69]. A large cohort study linking 15 fertility centers in California to the California Cancer Registry also reported that men with male factor infertility were 2.8 times more likely to develop testicular cancer than the general male population [70]. A population-based study in Utah showed increased rates of testicular cancer in men with oligospermia (HR 11.9), reduced sperm motility (HR 1.3), and lowest quartile morphology (HR 4.2) compared to fertile controls [71]. This strong association is important in the counseling and screening of patients with male factor infertility The risk of prostate cancer may also be elevated in men with infertility, although publications related to this topic are somewhat conflicting. A large population-based study of 20,433 men in Utah did not demonstrate an association between male factor infertility and prostate cancer [71]. Some European studies have shown decreased rates of prostate cancer in childless men, but these studies are limited by the fact that childless men are not necessarily infertile [72, 73]. On the other hand, a California study of 22,562 men with infertility found that male factor infertility was associated with an increased risk of developing high-grade prostate cancer (SIR 2.0) [74]. Additionally, a study evaluating 76,083 infertile men based on claims data also found an increased risk of

Table 2: Key studies evaluating male infertility and malignancy.

Study author	Title	Year	Journal	Sample size	Main findings
Eisenberg *et al.*	Increased risk of cancer in infertile men: analysis of US claims data	2015	*J Urol*	76,083 infertile men	Infertile men had a 49% higher risk of all cancers compared to controls and a twofold higher risk of testicular cancer The risks of melanoma, prostate cancer, bladder cancer, thyroid cancer, HL, NHL, and leukemia were all higher in infertile men
Hanson *et al.*	Subfertility increases risk of testicular cancer	2016	*Fertil Steril*	20,433 men undergoing semen analysis	Men undergoing semen analysis have increased risk of testicular cancer (HR 3.3). Increased risk of testicular cancer in men with oligozoospermia based on concentration (HR = 11.9) and sperm count (HR = 10.3). Men in the lowest quartile of motility (HR = 4.1), viability (HR = 6.6), morphology (HR = 4.2), or total motile count (HR = 6.9) have higher risk of testicular cancer
Jacobsen *et al.*	Risk of testicular cancer in men with abnormal semen characteristics: cohort study	2000	*BMJ*	32,442 men undergoing semen analysis	Elevated risk of testicular cancer with low semen concentration (SIR 2.3), poor motility (SIR 2.5), and high proportion of abnormal morphology (SIR 3.0)[a]
Jorgensen *et al.*	Fatherhood status and prostate cancer risk	2008	*Cancer*	All men born in Denmark 1935–1988	Childless men were found to be at a 16% reduced risk of prostate cancer compared with fathers (rate ratio [RR] 0.84; 95% CI 0.73–0.95)
Raman *et al.*	Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis	2005	*J Urol*	3800 men with infertility	SIR of testicular cancer was 22.9 (95% CI 22.4–23.5) when comparing the infertile group to the control population

(continued)...

...(continued)

Rogers *et al.*	Male infertility and risk of cancer	2017	*Semin Reprod Med*	N/A (review article)	Elevated risk of testicular germ cell tumors, prostate cancer, melanoma, non-Hodgkin's lymphoma in infertile men
Venn *et al.*	Cancer risks associated with the diagnosis of infertility	2003	*Best Pract Res Clin Obstet Gynaecol*	Review of six publications	The strongest and most widely recognized risk of testicular cancer is cryptorchidism, associated with RRs of 4–9 Increased risk of testicular cancer in men with reduced fertility
Walsh *et al.*	Increased risk of testicular germ cell cancer among infertile men	2009	*Arch Intern Med*	22,562 male partners	Men seeking infertility treatment had an increased risk of testicular cancer (SIR 1.3; 95% CI 0.9–1.9). Markedly higher risk among men with known male factor infertility (2.8; 1.5–4.8). In multivariable analysis, men with male factor infertility were 3 times more likely to develop testicular cancer compared with those without (HR, 2.8; 95% CI 1.3–6.0)[b]
Walsh *et al.*	Increased risk of high-grade prostate cancer among infertile men	2010	*Cancer*	22,562 men evaluated for infertility	Male factor infertility patients were found to be 2.6 times more likely to be diagnosed with high-grade prostate cancer (hazard ratio, 2.6; 95% CI, 1.4–4.8)
Walsh *et al.*	Male reproductive health and prostate cancer risk	2011	*Curr Opin Urol*	N/A (review article)	Studies evaluating male infertility and prostate cancer are inconsistent. Despite this, there is an association between reproductive health in a man's fourth decade (30s) and his development of aggressive prostate cancer in his sixth decade (50s)
Wiren *et al.*	Fatherhood status and risk of prostate cancer: nationwide, populationbased case-control study	2013	*Int J Cancer*	117,328 prostate cancer patients	Childless men had a decreased risk of prostate cancer compared to fathers, OR 0.83 (95% CI 0.82–0.84), and risk was lower for low-risk prostate cancer, OR = 0.74 (95% CI = 0.72–0.77), than for metastatic prostate cancer, OR = 0.93 (95% CI = 0.90–0.97)

[a]*SIR* standardized incidence ratio
[b]*HR* hazard ratio

prostate cancer associated with male factor infertility [75]. A clear explanation for the possible association between male infertility and prostate cancer is lacking, although reproductive disorders such as cryptorchidism, environmental factors, abnormal hormonal function, and genetics may be involved with the development of both infertility and prostate cancer [76].

The literature is relatively lacking regarding associations between male infertility and other types of malignancy, although there appears to be a positive correlation between abnormal semen analysis parameters and melanoma (1.37), leukemia (HR 1.82), and non-Hodgkin's lymphoma (HR 1.76) [67, 75]. When evaluated as a whole, infertile men appear to be at an elevated lifetime risk of malignancy.

Conclusions

The relationship between male reproductive health and overall somatic health remains complex and largely poorly understood. Numerous environmental, genetic, and lifestyle factors likely influence a man's overall health as well as his ability to reproduce. However, it is clear that men with infertility may be predisposed to develop other health conditions which may not be present at the time of their infertility diagnosis. Using infertility as a marker of future health can allow for appropriate health screening, detailed counseling of risks, and long-term follow-up for men with infertility. As men delay fatherhood and as problems such as obesity, diabetes, and infertility become more common, healthcare providers should be aware of the specific risks that patients face to provide the most up-to-date information and provide the most appropriate interventions for patients.

References

1. ASRM. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2015;103(3):18–25.
2. Petok W. Infertility counseling (or the lack thereof) of the forgotten male partner. Fertil Steril. 2015;104(2):260–6.
3. Eisenberg M. Relationship between semen production and medical comorbidity. Fertil Steril. 2015;103(1):66–71.
4. Anderson R. Childhood cancer risk in the siblings and cousins of men with poor semen quality. J Urol. 2017;197(3 pt 2):898–905.
5. Anderson R. Cancer risk in firstand second-degree relatives of men with poor semen quality. Fertil Steril. 2016;106(3):731–8.
6. Schultz N. A multitude of genes expressed solely in meiotic or postmeiotic spermatogenic cells

offers a myriad of contraceptive targets. Proc Natl Acad Sci U S A. 2003;100:12201–6.
7. Pylyp L. Chromosomal abnormalities in patients with oligospermia and non-obstructive azoospermia. J Assist Reprod Genet. 2013;30:729–32.
8. Kosar P. Cytogenetic abnormalities detected in patients with non-obstructive azoospermia and severe oligozoospermia. J Assist Reprod Genet. 2010;27:17–21.
9. Xie C. Multicenter study of genetic abnormalities associated with severe oligospermia and non-obstructive azoospermia. J Int Med Res. 2018;46(1):107–14.
10. Balkan M. Cytogenetic and Y chromosome microdeletion screening studies in infertile males with oligozoospermia and azoospermia in Southeast Turkey. J Assist Reprod Genet. 2008;25(11–12):559–65.
11. Zorrilla M. The genetics of infertility: current status of the field. Curr Genet Med Rep. 2013;1(4):247–260.
12. Aston K. Genetic susceptibility to male infertility: news from genome-wide association studies. Andrology. 2014;2(3):1–7.
13. Glazer C. Risk of diabetes according to male factor infertility: a register-based cohort study. Hum Reprod. 2017;32(7):1474–81.
14. Palmer N. Impact of obesity on male fertility, sperm function, and molecular composition. Spermatogenesis. 2012;2(4):253–63.
15. DuPlessis S. The effect of obesity on sperm disorders and male infertility. Nat Rev Urol. 2010;7:153–62.
16. Tarin J. Infertility etiologies are genetically and clinically linked with other diseases in single meta-diseases. Reprod Biol Endocrinol. 2015;13:31.
17. Rajender S. Epigenetics, spermatogenesis and male infertility. Mutat Res. 2011;727(3):62–71.
18. Stuppia L. Epigenetics and male reproduction: the consequences of paternal lifestyle on fertility, embryo development, and children lifetime health. Clin Epigenetics. 2015;7(120):1–15.
19. Craig J. Obesity, male infertility, and the sperm epigenome. Fertil Steril. 2017;107(4):848–59.
20. Alegria-Torres J. Epigenetics and lifestyle. Epigenomics. 2011;3:267–77.
21. Sharma R. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol. 2013;11:66.
22. Feychting M. Paternal occupational exposures and childhood cancer. Environ Health Perspect. 2001;109:193–6.
23. Reid A. Parental occupational exposure to exhausts, solvents, glues and paints, and risk of childhood leukemia. Cancer Causes Control. 2011;22:1575–85.
24. Liu R. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. J Oncol. 2011;2011:1–16.
25. Dubrova Y. Transgenerational mutation by radiation. Nature. 2000;405:37.
26. Bygren L. Change in paternal grandmothers early food supply influenced cardiovascular mortality of the female grandchildren. BMC Genet. 2014;15:12.
27. Levine H. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update. 2017;23(6):646–59.
28. Karimzadeh M. Psychological disorders among Iranian infertile couples undergoing assisted reproductive technology (ART). Iran J Public Health. 2017;46(3):333–41.
29. Babore A. Male factor infertility and lack of openness about infertility as risk factors for depressive symptoms in males undergoing assisted reproductive technology treatment in Italy. Fertil Steril. 2017;107(4):1041–7.
30. Wdowiak A. Impact of emotional disorders on semen quality in men treated for infertility. Neuro Endocrinol Lett. 2017;38(1):50–8.
31. Sahin A. Psychologic and sexual dysfunction in primary and secondary infertile male patients. Arch Ital Urol Androl. 2017;89(2):120–4.
32. Kulej-Lyko K. Could gonadal and adrenal androgen deficiencies contribute to the depressive symptoms in men with systolic heart failure? Aging Male. 2016;19(4):221–30.
33. Omani-Samani R. Evaluation on hope and psychological symptoms in infertile couples undergoing assisted reproduction treatment. Int J Fertil Steril. 2017;11(2):123–9.
34. Sharma R. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. Reprod Biol Endocrinol. 2015;13:35.

35. Catford S. Long-term follow-up of intra-cytoplasmic sperm injection-conceived offspring compared with in vitro fertilization-conceived offspring: a systematic review of health outcomes beyond the neonatal period. Andrology. 2017;5(4):610–21.
36. Kovac J. Relationship between advanced paternal age and male fertility highlights an impending paradigm shift in reproductive biology. Fertil Steril. 2013;100(1):58–9.
37. Eisenberg M. Increased risk of incident medical conditions in infertile men: analysis of United States claims data. Fertil Steril. 2016;105(3):629–36.
38. Emanuele M. Alcohol and the male reproductive system. Alcohol Res Health. 2001;25:282–7.
39. Jensen T. Habitual alcohol consumption associated with reduced semen quality and changes in reproductive hormones; a cross-sectional study among 1221 young Danish men. BMJ Open. 2014;4(9):e005462.
40. Alvarez S. Do some addictions interfere with fertility? Fertil Steril. 2015;103:22–6.
41. Liu R. Seminal plasma zinc level may be associated with the effect of cigarette smoking on sperm parameters. J Int Med Res. 2010;38(3):923.
42. Oyeyipo I. Effects of nicotine on sperm characteristics and fertility profile in adult male rates: a possible role of cessation. J Reprod Infertil. 2011;12(3):201.
43. Verze P. The link between cigarette smoking and erectile dysfunction: a systematic review. Eur Urol Focus. 2015;1(1):39–46.
44. Kovac J. The effects of cigarette smoking on male fertility. Postgrad Med. 2015;127(3):338–41.
45. Park B. Cannabis, cannabinoids and reproduction. Prostaglandins Leukot Essent Fatty Acids. 2004;70:189–97.
46. Calogero A. Klinefelter syndrome: cardiovascular abnormalities and metabolic disorders. J Endocrinol Investig. 2017;40(7):705–12.
47. Simm P. The psychosocial impact of Klinefelter syndrome—a 10 year review. J Ped Endocrinol Metab. 2006;19(4):499–505.
48. Fritz M. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
49. Katib A. Mechanisms linking obesity to male infertility. Cent Eur J Urol. 2015;68:79–85.
50. Sallmen M. Reduced fertility among overweight and obese men. Epidemiology. 2006;17:520–3.
51. Nguyen R. Men's body mass index and infertility. Hum Reprod. 2007;22:2488–93.
52. Ramlau-Hansen C. Subfecundity in overweight and obese couples. Hum Reprod. 2007;22:1634–7.
53. Eisenberg M. The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. Hum Reprod. 2015;30(2):493–4.
54. Haring R. Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania. Diabetes. 2009;58(9):2027–31.
55. Liu C. Lower SHBG level is associated with higher leptin and lower adiponectin levels as well as metabolic syndrome, independent of testosterone. Sci Rep. 2017;7(1):2727.
56. Kawano J. The role of adiponectin in obesity, diabetes, and cardiovascular disease. J Cardiometab Syndr. 2009;4(1):44–9.
57. Scarpace P. Elevated leptin: consequence or cause of obesity. Front Biosci. 2007;1(12):3531–44.
58. Kupelian V. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. J Clin Endocrinol Metab. 2006;91(3):843–50.
59. Eisenberg M. Semen quality, infertility, and mortality in the USA. Hum Reprod. 2014;29(7):1567–74.
60. Dinulovic D. Diabetes mellitus/male infertility. Arch Androl. 1990;25:277–93.
61. Gaunay G. Reproductive sequelae of diabetes in male patients. Endocrinol Metab Clin N Am. 2013;42:899–914.
62. Mokdad A. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003;289:76–9.
63. Eisenberg M. Diabetes, medical comorbidities and couple fecundity. Hum Reprod. 2016;31:2369–76.
64. Krajewska-Kulak E. Thyroid function in male infertility. Front Endocrinol. 2013;4:174.
65. Patel N. Thyroid dysfunction and male reproductive physiology. Semin Reprod Med. 2016;34(6):356–60.

66. Rojdmark S. Hypothalamic-pituitary-testicular axis in patients with hyperthyroidism. Horm Res. 1988;29(5–6):185–90.
67. Rogers M. Male infertility and risk of cancer. Semin Reprod Med. 2017;35(3):298–303.
68. Raman J. Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol. 2005;174(5):1819–22.
69. Jacobsen R. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ. 2000;321(7264):789–92.
70. Walsh T. Increased risk of testicular germ cell cancer among infertile men. Arch Intern Med. 2009;169(4):351–6.
71. Hanson H. Subfertility increases risk of testicular cancer: evidence from population-based semen samples. Fertil Steril. 2016;105(2):322–8.
72. Jorgensen K. Fatherhood status and prostate cancer risk. Cancer. 2008;112(4):919–23.
73. Wiren S. Fatherhood status and risk of prostate cancer: nationwide, population-based casecontrol study. Int J Cancer. 2013;133(4):937–43.
74. Walsh T. Increased risk of high-grade prostate cancer among infertile men. Cancer. 2010;116(9):2140–7.
75. Eisenberg M. Increased risk of cancer in infertile men: analysis of U.S. claims data. J Urol. 2015;193(5):1596–601.
76. Walsh T. Male reproductive health and prostate cancer risk. Curr Opin Urol. 2011;21(6):506–13.

Source: Brent M. Hanson, James M. Hotaling. Male Infertility as a Marker of Future Health. In: Carrell D.T., Racowsky C., Schlegel P.N., DeCherney A.H. (eds). Emerging Topics in Reproduction: Volume 5. 1st ed. Switzerland: Springer International Publishing; 2018, pp 47-67. DOI 10.1007/978-3-319-90823-6_4.

Abbott

In Anovulatory Infertility*

Let Life Bloom

Letrolife™

Letrozole Tablets I.P. 2.5 mg

High Quality Ovulation Inducer#

Globally Recommended as 1st line therapy by guidelines of American College of Obstetricians and Gynaecologists [1]

High Quality Standards ensures improved dissolution, better disintegration & free from traces of solvents#

DOSAGE *

2.5 mg from day
2 or 3 of the cycle for 5 days

Images are for representational purpose only.

* Prescribing Information of Letrolife | # Data on file

Ref: 1. American College of Obstetricians and Gynaecologists. Aromatase Inhibitor in Gynecologic Practice. Committee Opinion. Number 663. June 2016.

Prescribing Information: Letrozole™

COMPOSITION: Each film coated tablet contains:Letrozole I.P. 2.5 mg; Excipients q.s.; Colour: Tartrazine Lake & Titanium Dioxide IP. **INDICATION:** Letrozole is indicated for induction of ovulation in anovulatory infertility. **DRUG DESCRIPTION:** Letrozole belongs to a class of medications known as Aromatase inhibitors. Aromatase is an enzyme that is responsible for the production of estrogen in the body. **DOSAGE AND ADMINISTRATION:** Letrozole is given in the dose of 2.5 mg tablets from day 2 or 3 of the cycle for 5 days or as directed by the Gynecologist/ Registered Medical Practitioner. **ADVERSE REACTIONS:** Stop using the Letrozole and get emergency medical help if you have any of these signs of allergic reactions: difficulty in breathing, swelling of face, lips, tongue, or throat. Less serious side- effect may include hot flashes, warmth or redness in the face or chest, headache, muscle or joint pain,night sweats, weight gain, fatigue, weakness, nausea or swelling in hands, ankles or feet. **WARNINGS & PRECAUTIONS:** The medication is to be avoided if one is allergic to Letrozole or any of its ingredient or similar drugs. The medicine is likely to cause dizziness and hence driving is to be avoided. The medicines should not be taken with alcohol. Intake of Letrozole with tablets of Tamoxifen should be avoided because it can decrease the drug's effectiveness. Keep the drug out of the reach of children. **DRUG INTERACTION:** Some drugs that may interact with this drug include estrogens (such as ethinylestradiol, conjugated estrogens) and estrogen blockers (such as anastrozole,Tamoxifen). **MISSED DOSE:** Take the missed dose as soon as it is remembered. Skip the missed dose if it is almost time for the next scheduled dose. Do not take extra medicine or double dose to make up for the missed dose. **PHARMACOLOGICAL ACTION:** Letrozole works by inhibiting Aromatase thereby suppressing estrogen production, so the pituitary gland produces more of the hormones needed to stimulate the ovaries. These hormones, FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone), can cause the development of ovulation in women who are anovulatory or increase the number of eggs developing in the ovaries of women who already ovulate. **STORAGE:** Store protected from moisture, at a temperature not exceeding 30°C. Keep all medications away from children. **Presentation:** One Blister of 5 Tablets.

Manufactured by: Acme Life Tech – LLP, Plot No. 103, 104, 105 - EPIP, PHASE-I, Jharmajri, Baddi, Dist. Solan, (H.P.) - 173 205.

Marketed by: Abbott India Limited: Angel Space, Lifestyle Bldg. No. D-4,Gala No. 7 to 10, 17 to 20, Ground Floor, 107 to 110 & 117 to 120, First Floor, Pimplas Village, Dist. Thane, Bhiwandi - 421 302, India.

TM Trade Mark of Abbott India Ltd.