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CLINICAL AND EXPERIMENTAL OBSTETRICS AND GYNECOLOGY (ISSN 0390-6663) publishes original work, preferably brief reports, in the fields of Gynecology, Obstetrics, Fetal Medicine, Gynecological Endocrinology and related subjects. (Fertility and Sterility, Menopause, Uro-gynecology, Ultrasound in Obstetrics and Gynecology, Sexually Transmitted Diseases, Reproductive Biological Section). The Journal is covered by INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica.

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A 59-year-old woman gives birth to twins - when should a fertility specialist refuse treatment?  
J.H. Check - Camden, NJ (USA)  
Several successful cases are described where couples with low odds of successful outcomes were willing to subject themselves to personal risk or risks to the fetus to achieve their dream of having a baby.

Placenta percreta presenting in the first trimester: Review of the literature  
J.C. Papadakis, N. Christodoulou - Crete, GREECE  
A review of all reported cases of placenta percreta presenting in the first trimester with emphasis on diagnosis and management is presented.

Intrauterine devices and extrauterine pregnancy. A literature review  
A literature review organized to clarify the relationship between the use of intrauterine devices and ectopic pregnancy is presented.

Analysis of perioperative morbidity according to whether the uterine cavity is opened or remains closed during abdominal myomectomy - results of 423 abdominal myomectomy cases  
An analysis of perioperative morbidity according to whether the uterine cavity is opened or remains closed during abdominal myomectomy is presented.

Autofluorescence reveals menstrual phase in the endometrium  
The capability and reliability of autofluorescence phase determination in samples of human endometrium are explored.

Study of pubertal development in Abruzzo (Italy) and analysis of factors implicated in puberty variability  
G. Mascaretti, C. Di Berardino - L'Aquila, ITALY  
Changes in pubertal development and the relationship with age at menarche are analyzed.

An objective measurement to diagnose micrognathia on prenatal ultrasound  
G. Palit, Y. Jacquemyn, M. Kerremans - Edegem, BELGIUM  
The frontal naso-mental angle is described as a practical and objective tool to diagnose retrognathia in the foetus.

Laparoscopic treatment of ovarian dermoid cysts  
Laparoscopic dermoid cyst enucleation is the most commonly applied procedure and is a safe, effective method in the management of dermoid cysts.

Misoprostol use as a method of medical abortion  
N. Salakos, C. Iavazzo, K. Bakalianou, O. Gregoriou, G. Paltoglou, K. Kalmantis, D. Botsis - Athens, GREECE  
The effectiveness of misoprostol in medical abortions with the use of ultrasound screening is reported.

“Chromohysteroscopy” for evaluation of endometrium in recurrent miscarriage  
T. Kucuk, S. Deveci - Ankara, TURKEY  
The efficacy of hysteroscopy in recurrent miscarriages is improved by chromohysteroscopy.

CA 19-9 can be a useful tumor marker in ovarian dermoid cysts  
A. Coskun, G. Kiran, O. Ozdemir - Kahramanmaras, TURKEY  
The importance of CA 19-9 as an aiding tool in the diagnosis of mature cystic teratomas is evaluated.
Neurofibroma of the vaginal wall
S. Baulies, M.T. Cusidó, P.J. Grases, B. Úbeda, M.A. Pascual, R. Fábregas - Barcelona, SPAIN
Periodical check-ups are recommended in asymptomatic vaginal neurofibroma whereas radical excision of a vaginal neurofibroma should be avoided as such surgery is highly aggressive.

Mucinous cystadenoma in a female patient with 45,X/46,XY karyotype
A case of mucinous cystadenoma with a mosaic karyotype of 45,X/46,XY is presented.

Secondary amenorrhea with normal ovulatory cycles in a young virgin with normal follicle stimulating hormone levels - a case report
B. Katsoff, J.H. Check - Camden, N.J. (USA)
A 17-year-old virgin with normal sexual development and secondary amenorrhea failed to menstruate despite proven ovulation, progesterone withdrawal and even exposure to pharmacologic levels of estrogen (oral contraceptives).

Tuberculosis of the cervix and infertility: report of a rare case
P. Guié, P. Iovenitti, K. N’guessan, J. Tegnan, K. Koffi, G. Carta, S. Anongba - L’Aquila, ITALY
A rare case of cervical tuberculosis in a young woman diagnosed in the Ivory Coast is presented.

Irregular dental structures in a benign ovarian cystic teratoma (dermoid cyst): case report
V. Liberis, P. Tsikouras, E. Sivridis, M. Dadidou, N. Koutlaki, G. Galazios - Thrace, GREECE
The simultaneous appearance of two teeth and dermoid cysts is a rare event.

Prenatal diagnosis of type I sacrococcygeal teratoma and its management
E.S. Saygili-Yilmaz, K.K. Incki, M. Turgut, S. Kelekci - Adana, TURKEY
A case of type I sacrococcygeal teratoma diagnosed prenatally and successfully managed surgically in the neonatal period is presented.

Uterus didelphys with blind hemivagina and ipsilateral renal agenesis complicated by pyocolpos and presenting as acute abdomen 11 years after menarche: presentation of a rare case with review of the literature
M. Varras, Ch. Akrivis, St. Karadaglis, G. Tsoukalos, Ch. Plis, I. Ladopoulos - Ioannina, GREECE
A unique clinical syndrome in a patient with uterine didelphys, blind hemivagina and ipsilateral renal agenesis presenting with acute abdomen secondary to pyocolpos 11 years after menarche is reported.
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A 59-year-old woman gives birth to twins - when should a fertility specialist refuse treatment?

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Summary

Objective: To review cases of infertility where despite extremely low odds of success and potential risks to the woman if she became pregnant or to the fetus, the couples elected to take a chance to fulfill their dreams of having a baby. Materials and Methods: Six cases are described: case 1, a 59-year-old woman with hyperstimulation and intramuscular fibroids compressing the uterine cavity who wanted to be a donor egg recipient; case 2, a 59-year-old woman desiring a second transfer of sibling frozen embryos who had previously conceived with donor eggs at age 57; case 3, a 33-year-old woman with a subseptated uterus and cervical abnormality from intrauterine diethilstilbestrol exposure plus hemoaphilia trait, and only 25% of her liver remaining from a previous partial liver resection; case 4, a woman with an unicornuate uterus refusing reduction of her twins to a singleton; case 5, a 39-year-old woman willing to try again to have her first live born child with a history of a large macroprolactinoma that was resected but markedly enlarged in her previous pregnancy despite bromocryptine therapy; and, case 6, a woman willing to try a unique experimental therapy with extremely high thyroid stimulating immunoglobulins to inhibit severe intrauterine growth retardation and potential premature synostosis for her condition of Hashimoto’s disease. Results: Cases 2-5 all had successful outcomes. Case 1 was never given the chance for donor oocytes since she was rejected by a majority vote of our physicians because of the fear of a malpractice suit. Discussion: If a couple understands the potential risks and the low odds of success, they should be given the opportunity to fulfill their dreams of having a baby. However, treating physicians are under no obligation to take malpractice risks. Key words: Advanced maternal age; Premature ovarian failure; Uterine anomalies; Intrauterine growth retardation.

Introduction

Patients have certain health issues that may make them seek help from physicians. The role of a physician is to make an assessment of the condition and offer advice on treatment options; the chance of successfully fulfilling the patient’s goal, what the risks and costs would be for various therapies and their likelihood of success. Then given these options and after the physician ascertains that the patient truly understands the risks and benefits of these treatment options the right thing to do in my opinion is to allow the patients to make the choice that suits them the most, even if that choice would not be the one that the given physician would make for him/herself or his or her own family. Unfortunately in our litigious society, sometimes the patient’s choice may make the physician quiver for fear of a lawsuit but if the decision made by the patients is best suited for them and is a legitimate option, the proper physician should not dissuade any patient from making that choice. When it comes to achieving pregnancy in an infertile woman some physicians may consider that the need for a baby is not a true “medical reason” and thus should not be deemed an entity worthy of therapy that could put the patient at risk for harm or the physician at risk for a malpractice suit. However, there are many women who suffer so much from their infertility problems that given a choice would gladly give up their right arm to accomplish that goal. A lot of time and money is invested in becoming a physician and one large law suit can end that physician’s career. Thus a physician should not be censured if he/she chooses not to render a particular therapy that could work but could also lead to complications to the patient which the patient is willing to risk – but the physician is still not willing to risk – the patient may still turn around and sue the physician. However, we should not censure any physician willing to take the risk of a malpractice suit if the treatment could work but has risks – if the pros and cons of therapy have been properly explained to the patient.
Case Reviews

Case 1

A 59-year-old woman with a history of hypertension and intramuscular fibroids partially compressing the uterine cavity requested to be an egg recipient. She was advised of both general risks for her age and specific risks that she had based on her medical history.

She was advised that 1) because of her chronic essential hypertension she had at least a 20% risk of superimposed preeclampsia with no current strategy to reduce this risk. In addition, she was at risk for placental insufficiency, fetal growth restriction, stillbirth and placental abruption that could result in a state of disseminated intravascular coagulation, heart failure, stroke, seizures, or possibly death. Furthermore, there may have been a need for iatrogenic prematurity that could have led to permanent neurologic disability in the child. 2) Because of her prior myomectomy she had an increased risk of a potential rupture of the uterus. These fibroids could also cause intense pain from degeneration, fetal growth delay with oligohydramnios, stillbirth, and the fibroids could also obstruct the birth canal or cause a deformation in the baby. 3) Her advanced maternal age, although she would obtain a donor egg and in vitro fertilization with her husband’s sperm, would still increase her risk of miscarriage, growth restriction from placental insufficiency, oligohydramnios, stillbirth, cesarean section, wound infection, postpartum endometritis, gestational diabetes and potentially maternal death.

Despite hearing all the risks the woman still wanted to proceed with the transfer of embryos derived from donor eggs and her husband’s sperm. She stated that as a nurse in South Africa she had taken many chances with her life by treating victims during South African riots. She had been a midwife in South Africa and she stated that young women there have a greater risk of complications than she had at age 59 when she would deliver. She took chances of possibly dying from infectious diseases by treating patients with highly deadly diseases. Her question was why it is considered appropriate for a nurse to take chances with her life when it comes to helping other people but that when it comes to taking a risk to her own life to bring a child into this world that would fulfill her needs, it is frowned upon? She had no living children but had delivered one child who died at birth.

I decided to treat her and it made me reminisce about other infertility cases that presented with significant risks but the women were steadfast in being willing to take a risk to fulfill their dream. Unfortunately, I could not convince my other three associates that she had the right to take a risk as long as she was fully aware. Nonetheless, they were concerned about malpractice risks and since our practice worked on a democratic basis I regretfully had to inform the woman that we could not include her in the recipient program.

Case 2

A 57-year-old woman who had had a baby with her former husband at age 33 was interested in having another child with her new husband who was 20 years younger. She was advised of the risks which were similar to the 59-year-old nurse/mid-wife from South Africa (case 1) except she did not have fibroids or hypertension. She did, however, have Graves’ disease and was being treated with propylthiouracil. She came to our practice from another state because she had seen our case report in the literature of the first woman to conceive in the United States over the age of 50 with donor eggs [1]. In that instance the woman also had a much younger husband.

There was an opportunity to fertilize donor eggs that were appropriate for the couple but they had to be frozen because the woman had not as yet completed all the testing and consults required. These were all necessary to have obtained before a vote from the ethics committee.

Probably the most swaying argument that convinced the ethics committee for the Cooper Center for Reproductive Hormonal Disorders, was the fact that her husband was only 37, had no children from any other relationships, and no one would have had a problem with the reverse situation, i.e., a 57-year-old male trying to achieve a pregnancy with a 37-year-old female. Though one thought was to suggest a gestational carrier (and we did) we could not insist on it when the woman stated she did not have an extra 50-70 thousand dollars (she had checked into this option and this was her conclusion).

She conceived on her first frozen embryo transfer cycle (3 embryos) at 57.6 years of age. She delivered at 36.3 weeks a healthy baby girl weighing 5 pounds, 2 ounces.

We had advised her that the embryo transfer leading to her delivery would be the last time that we would do a frozen ET. However, she still had three left and she pleaded to have them transferred to give her child the chance of a sibling. Half of our doctors refused to do the transfer, but two agreed, and the remaining three embryos were transferred (a 9 cell, 6 cell, and an 8 cell embryo with ≤25% fragmentation). Another pregnancy was achieved though this time a dichorionic diamniotic pregnancy was obtained. We strongly recommended reducing it to a singleton. We explained that she would be just one month shy of 60 and her chances of a successful outcome would be improved if she only had one child to carry.

She was advised that we had had a woman aged 54 who had conceived twins but terminated the pregnancy at the end of the first trimester because she was exhausted. However, without any religious or ethical concerns she decided to carry the twins.

Her pregnancy was complicated by placenta previa and placenta percreta. She delivered at 30.5 weeks a male weighing three pounds, six ounces and a female weighing three pounds, six ounces. Both children were doing well seven months after delivery.

The rest of this editorial will consist of cases where despite what seemed to be either impossible odds of either achieving a pregnancy or carrying one full-term, couples persisted in their dreams.

Case 3

A 33-year-old female lawyer who was married to a 38-year-old lawyer was advised from a major university infertility center that due to of her intrauterine exposure to diethylstilbestrol she would never conceive because of hostile cervical mucus of very poor quality. This was before the days of intrauterine insemination. Moreover her uterus had complex septae so that it seemed to be in five compartments. The case presented before the days of hysteroscopic surgery. She was told that even if she did conceive she could never successfully progress to term.
Furthermore she was advised that because she had only 25% of her liver due to a previous partial resection for a benign hepatoma that she did not have enough liver to sustain a pregnancy. I advised her that I disagreed that 25% of a liver was insufficient and that it was possible to correct the cervical factor. However, I did agree that because of the septae there was a great likelihood of marked prematurity with adverse health consequences for the fetus.

The couple wanted to proceed despite the precautions. In fact the female partner advised me that she had a hemophilia trait and that her hematologist had told her that she could bleed excessively with delivery or cesarean section and advised her not to become pregnant. She still wanted to take her chances. The couple decided that they wanted to end the genetic passage of hemophilia. Thus they planned to do chorionic villus sampling and genetic testing for hemophilia. Since a heterozygote could not be detected, their plan was to terminate the pregnancy if she was having a female baby or if she was having a male with hemophilia.

She was treated with guaifenesin and ethinyl estradiol and human menopausal gonadotropins to treat the cervical factor and she used progesterone vaginal suppositories in the luteal phase [2, 3]. This therapy enabled the woman to attain an adequate postcoital test. She conceived on her second treatment cycle. The results of chorionic villus sampling showed a male without hemophilia. She decided not to perform the reduction procedure in honor of their godson’s prediction.

Case 4

A 34-year-old woman presented with infertility related to having a unicorneate uterus. She had only one fallopian tube and it was congenitally obstructed. She had presented in the early days of in vitro fertilization and we had just developed a technique for embryo freezing [4, 5].

We only transferred two fresh embryos which failed to result in a pregnancy. Though we cautioned her that multiple births would not be a good idea based on her small uterine cavity, she elected to have three frozen embryos transferred because of the uncertainty that they would result in a pregnancy. We did not know if embryos could be successfully refrozen at that time [6].

The day after her frozen embryo transfer her godson, who was dying from hypernephroma stuffed a pillow under his shirt and predicted that she was going to become pregnant that cycle. He then stuffed a second pillow under his shirt and predicted twin boys.

She had a positive pregnancy test. Shortly after she had received the good news her godson died. Previous to the embryo transfer we had discussed multifetal reduction if there was more than one fetus and the couple agreed to have this procedure performed in the event of twins or triplets. However, they decided not to perform the reduction procedure in honor of their godson’s prediction.

She delivered healthy twin boys at 35 weeks.

Case 5

A 35-year-old woman with amenorrhea since age 18 and primary infertility sought help to become pregnant [7]. She was told that based on elevated gonadotropins at age 18 and 27 with estrogen deficiency that she had premature menopause. However, she had heard we had some success in inducing ovulation with normal pregnancy in some cases of hypergonadotropin amenorrhea, so she sought help in trying to conceive with her own eggs [7]. At this time donor oocyte programs did not exist.

Her follicle stimulating hormone (FSH) at age 27 was 78 mIU/ml. She was advised that because of the number of years that she had been in ovarian failure that it would not be likely to reverse the ovarian failure since the principle in inducing ovulation in these cases is based on the fact that in the early stages of apparent menopause there are some preantral or antral follicles still present. However, they are resistant to gonadotropins unless the elevated serum FSH is lowered and the down-regulated receptors are restored [8-10].

Just to confirm the diagnosis sera LH, FSH and estradiol levels were obtained. Very surprisingly the sera LH and FSH were < 1.0 mIU/ml and the serum estradiol was < 5 pg/ml. This prompted a measurement of prolactin which was very elevated at 975 ng/ml. Serum thyroid and cortisol levels were normal.

Computerized axial tomography revealed a large pituitary mass with suprasellar extension into both the sphenoid sinus and left middle fossa. Surgical and radiation therapy consultations concluded that the tumor had grown too large for either treatment. She lost her vision in the meantime. There had been some early reports that bromocriptine (at that time known as CB154) might shrink macroprolactinomas. Indeed, 5 mg of bromocriptine per day did shrink the tumor by 50% allowing a transphenoidal hypophysectomy to be performed. Her vision returned.

Following surgery she remained on 5 mg bromocriptine per day. Though her serum prolactin levels were still elevated (ranging between 400-600 ng/ml) no growth of the macroprolactinoma was noted two years following surgery.

The woman returned at age 37 stating that she was now ready to try to conceive. She was advised that with the persistence of high serum prolactin that there was a good chance that the tumor could grow and that at that time the safety of taking bromocriptine during pregnancy was not known. Furthermore, she would require expensive gonadotropin injections (her insurance did not pay for them) and the likelihood of these drugs stimulating ovulation after 20 years of menopause was quite small since she probably had no more follicles left. Nevertheless, she wanted to give treatment a try. She stated that she had been told by the neurosurgeon and the radiation therapist that she was going to die. Though she was hoping that a pregnancy would not kill her she was willing to risk death again to have a baby.

She failed to ovulate or even respond to the first two treatment cycles. She still wanted to try a third cycle and surprisingly she did ovulate. Finally it took 4350 IU of human menopausal gonadotropins (hMG) to achieve ovulation. With high-dose hMG therapy she ovulated in five of her next six stimulation cycles. She conceived on her ninth treatment cycle but had a first trimester miscarriage after showing fetal viability on ultrasound at seven weeks. She conceived again her next cycle and successfully delivered a baby boy at 31 weeks. The boy was deemed healthy and was discharged from the hospital. Unfortunately, however, at four months of age while strapped in a car seat, the baby died from sudden infant death syndrome.

The woman had averaged 3950 IU of hMG per treatment cycle in her ten cycles of gonadotropin stimulation. Despite the continuation of bromocriptine during the pregnancy the pituitary tumor grew to cause a bitemporal hemianopsia (but it regressed again after delivery). Nevertheless despite the risk and the expense she elected to try again.
She conceived again on cycle 11 but had another miscarriage. She conceived in her next attempt, had a live fetus through the first trimester, but unfortunately had fetal demise in the second trimester.

In the next cycle she again conceived and delivered a full-term baby girl. The girl is now a very healthy teenager who is an Olympic quality ice skater.

This case was allegedly a woman in ovarian failure who 20 years later developed a macroprolactinoma that suppressed her elevated serum gonadotropins either by a direct effect of the markedly elevated prolactin levels and/or damage to the sensitive gonadotropin producing cells. However, with her response to gonadotropins so many years after apparent menopause, I favor that she originally had a gonadotropin and prolactin secreting tumor which eventually secreted prolactin exclusively. I do not believe that such a case has ever been previously reported.

Case 6

A 33-year-old woman presented with a history of primary infertility with oligomenorrhea. Her medical history was significant in that she had hypothyroidism treated with L-thyroxin replacement but she also had Graves’ ophthalmopathy [8].

She was treated with clomiphene citrate and progesterone vaginal suppositories in the luteal phase and became pregnant. She was discharged from our practice after successfully completing the first trimester.

She called the office when she was six months pregnant stating that her obstetrician disagreed with our estimated date of confinement. She stated that ultrasound showed she was only five months along. I informed her that I knew the precise date of conception and that she was showing signs of intrauterine growth restriction (IUGR). She was advised to inform her obstetrician and to come into the office to have plasma long-acting thyroid stimulator (LATS) tested. My assumption was that she had thyroid stimulating immunoglobulins which were unable to stimulate her own thyroid gland because of damage from Hashimoto’s disease. However, the antibodies would still be able to cross the placenta and stimulate the fetal thyroid causing fetal thyrotoxicosis and IUGR.

Unfortunately the LATS test, which uses mouse thyroid membranes in the assay, came back negative. I was still convinced that she had human thyroid stimulating immunoglobulins but at that time the assay was still experimental. Serum was sent to Dr. D. J. MacKenzie’s laboratory in Canada. Unfortunately I was advised that the lab was having some technical problems with the assay and results would not be available for months.

At 32 weeks the patient went into labor. However, the obstetrician insisted that she was only 28 weeks by fetal biparietal diameter and tried to stop labor. At 33 weeks she had a cesarean section for fetal distress, amnionitis and prolonged spontaneous premature rupture of the membranes. A female infant weighing 1,446 g with a developmental age of 33 weeks died at 30 hours of life of group B streptococcal septicemia. A serum thyroxin of the baby obtained four hours after birth was markedly elevated at 24.5 μg/dl (normal cord serum 10.9 μg/dl + 1.6) and the T3 serum triiodothyronine level by radioimmunoassay was 230 ng/dl (normal 48 ± 1.6 ng/dl) [8].

The maternal levels of thyroid stimulating immunoglobulins came back extremely high from the MacKenzie laboratory. Dr. MacKenzie actually advised sterilization of the woman because of the risk of severe IUGR and premature synostosis.

The patient was advised of the recommendation. However, I told her that I had an idea, that to my knowledge had never been tried before, and that was to give her an anti-thyroid drug despite the presence of hypothyroidism to cross the placenta and thus treat the fetus. Otherwise her options were to adopt or true surrogacy.

The couple chose to try again with clomiphene citrate and progesterone in the luteal phase. She conceived and was started empirically on 150 mg propylthiouracil per day. At 36 weeks gestation amniocentesis revealed a lecithin:sphingomyelin ratio greater than 2:1. An elective repeat cesarean section was performed with a delivery of a live-born male with an apgar score of 8 and 8 at 1 and 5 min. The infant’s weight was 2,530 g, head circumference was 33.5 cm and had a total length of 45 cm. There was no evidence of a thyroid goiter.

At four days of life the infant developed tachycardia and elevated serum T4 and T3 (> 32 μg/dl and 630 μg/dl, respectively). The infant responded within three days to treatment with methimazole and lugoliodine solution as evidenced by shrinkage to normal size of the goiter, and the tachycardia ceased. All medications were discontinued at four months.

This case illustrates that this woman, though advised that her next child could have serious complications, was willing to take a chance on a treatment that had theoretical merit but had never been tried before. We could say she was rewarded for her bravery.

Discussion

These cases illustrate successful pregnancies despite low odds of success. They also show that couples are willing to take some chances on their health or the baby’s for the chance of the gift of life.

Obviously, since we attempted to help these cases, my own view is that if the risks and odds are meticulously explained to a couple, but they want to proceed with infertility therapy, they should be given the opportunity. Of course this should be done only if the couple seems to have a clear understanding of the risks and there is at least some chance for success even if the odds are very low. A physician has the right to deny a patient therapy if that physician is concerned about future lawsuits. However that physician should at least be honest and explain the reason for refusal to treat, and encourage the couple to seek another opinion.

References

A 59-year-old woman gives birth to twins - when should a fertility specialist refuse treatment?


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Summary

Placenta percreta complicating pregnancy in the first trimester is extremely rare, and only a few cases have been reported in the literature. We recently reported on a patient with risk factors for placenta percreta that presented as first trimester fetal demise, unresponsive to medical management with prostaglandin. The patient required an emergency hysterectomy to control the bleeding after uterine curettage, and was complicated by severe consumption coagulopathy. This rare entity can lead to significant mortality and morbidity, particularly in the background of increased prevalence of the disease and its associated risk factors, and the large number of spontaneous and induced abortions performed worldwide. Therefore, we also reviewed all reported cases of first-trimester placenta percreta in the literature to increase the awareness of physicians and to highlight the clinical features and essentials of the management.

Key words: Placenta accreta; Percreta; First trimester; Early pregnancy.

Introduction

Although maternal mortality associated with placenta accreta has been greatly reduced with modern obstetric practice, obstetric haemorrhage still accounts for a significant proportion of maternal deaths [1]. It is therefore very important that regular reviews of the rarer causes of obstetric haemorrhage appear in the literature to emphasise their clinical features and aspects of management.

Placenta accreta is defined as abnormal adherence of the placenta to the myometrium, first characterised in modern times by Irving and Hertig in 1937 [2]. In general, placenta accreta is an abnormally firm attachment of placental villi to the uterine wall in the partial or complete absence of the normal intervening decidua basalis and fibrinoid layer of Nitabuch. Three variants of this complication can be histologically distinguished, according to the degree of invasion. In the most common form, placenta accreta, the placenta is attached directly to the underlying myometrium. Less commonly, chorionic villi may extend into the myometrium (placenta increta) or through the entire myometrial thickness to the serosa (placenta percreta). In placenta percreta, rupture into the peritoneal cavity and infiltration into the bladder and neighboring organs may occur.

The incidence has variously been reported between 1/540 to 1/93,000 pregnancies, with an average incidence of about 1/7,000. The highest incidence is reported from Thailand, which may reflect the increased prevalence of trophoblastic disease in the Far East. It is estimated that approximately 15% of these cases are increta and 5–7% are percreta [1, 3, 4].

In a normal pregnancy, the placenta is formed at the implantation site by a combination of the chorion frondosum and the decidua basalis. When the decidua is partially or completely absent, abnormal placentation may occur, and an absent or poorly developed decidua is the constant pathologic feature in all reported cases of placenta accreta. The Nitabuch fibrinoid layer, on the other hand, may or may not be present [3]. Therefore, Fox hypothesized that any condition that adversely affects the endometrium and the decidua basalis may predispose to placenta accreta, resulting in an invasive placenta upon implantation at that site [4]. Predisposing risk factors include a uterine scar usually from a caesarean section or myomectomy, uterine curettage, history of manual removal of the placenta, endometritis, Asherman’s syndrome, submucous fibroids, and adenomyosis, and all have been associated with endometrial injury [1, 4–7]. This theory can be further supported by another report from Bevan et al., where dilatation and curettage in the first trimester failed to terminate a pregnancy that was later complicated by placenta percreta [8].

The development of placenta accreta is also strongly associated with advanced maternal age and high parity [1, 7, 9]. Increasing age alone may lead to progressive insufficiency of the decidua, accounting for an increased risk among these patients. Importantly, Miller et al. demonstrated that 89% of women with placenta accreta had coexisting placenta previa [7]. The risk for any type of placental disorder among women with placenta previa further increases linearly with the number of previous...
caesarean sections, from 15-24% in women with one previous caesarean section, to 48% with two previous sections, and to 67% with four or more previous sections [10]. The further increase in the incidence of placenta accreta, among women with placenta previa and a previous caesarean section, when the placenta was implanted over the scar, supports the theory that trophoblast adherence is enhanced when the scant decidualisation of the lower uterine segment is further impaired by previous myometrial disruption [7]. However, Fox reported that 7% of the patients with placenta accreta had no contributing factors identified [4].

Most cases of placenta accreta present during the delivery of a term or near-term fetus, when the placenta fails to separate spontaneously, and upon attempts of manual removal no plane of cleavage is recognised. Postpartum haemorrhage can be severe, and hysterectomy is usually necessary. Uncommonly, occasional cases have been reported, presenting in the second or third trimester as antepartum haemorrhage and/or uterine perforation or rupture leading to intraperitoneal or intravesical haemorrhage [11-14]. Many second-trimester cases occurred in the setting of severe postabortal haemorrhage [13, 14].

### Table 1. — Reported cases of confirmed placenta percreta/increta in the first trimester.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Maternal age</th>
<th>Gravidity</th>
<th>Parity</th>
<th>Gestational age (weeks)</th>
<th>Placental abnormality</th>
<th>Clinical presentation</th>
<th>Risk factors</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veridiano et al., 1986</td>
<td>23</td>
<td>4</td>
<td>1</td>
<td>14</td>
<td>Percreta</td>
<td>Missed miscarriage, D&amp;C followed by uterine perforation and vaginal haemorrhage</td>
<td>1 caesarean section</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Woolcott et al., 1987</td>
<td>34</td>
<td>3</td>
<td>2</td>
<td>10</td>
<td>Percreta</td>
<td>Incomplete miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>2 caesarean sections, second followed by PPH and postpartum curettage</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Harden et al., 1990</td>
<td>34</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>Increta</td>
<td>Incomplete miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>3 caesarean sections</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Haider, 1990</td>
<td>35</td>
<td>6</td>
<td>5</td>
<td>12</td>
<td>Percreta</td>
<td>Missed miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>1 caesarean section</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Ecker et al., 1992</td>
<td>32</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>Increta</td>
<td>Missed miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>3 first trimester induced miscarriages, 1 vaginal delivery followed by PPH and postpartum curettage</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Gist et al., 1996</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>Increta</td>
<td>Blighted ovum, D&amp;C followed by vaginal haemorrhage</td>
<td>1 caesarean section</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Gherman et al., 1999</td>
<td>27</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>Increta</td>
<td>Missed miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>1 caesarean section, 1 first trimester spontaneous miscarriage completed by D&amp;C</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Walter et al., 1999</td>
<td>30</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>Increta</td>
<td>Delayed hemorrhage, occurring 17 weeks after uncomplicated D&amp;C for an 11-week missed miscarriage</td>
<td>1 caesarean section</td>
<td>Hysterectomy (angiographic embolization was also offered)</td>
</tr>
<tr>
<td>Chanrachakul et al., 2001</td>
<td>38</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>Increta</td>
<td>Missed miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>1 caesarean section</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Carlton et al., 2001</td>
<td>32</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>Percreta</td>
<td>Missed miscarriage, D&amp;C followed by uterine perforation and vaginal and intraperitoneal haemorrhage</td>
<td>1 caesarean section</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Höpker et al., 2002</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>Percreta</td>
<td>Missed miscarriage, D&amp;C followed by vaginal haemorrhage</td>
<td>1 caesarean section, 1 diagnostic D&amp;C</td>
<td>Hysterectomy</td>
<td></td>
</tr>
<tr>
<td>Liu et al., 2003</td>
<td>40</td>
<td>6</td>
<td>1</td>
<td>9</td>
<td>Increta</td>
<td>Induced surgical miscarriage, followed by vaginal haemorrhage</td>
<td>1 caesarean section</td>
<td>Bilateral uterine artery embolization</td>
</tr>
<tr>
<td>Esmans et al., 2004</td>
<td>40</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>Percreta</td>
<td>Uterine perforation presenting as intraperitoneal haemorrhage</td>
<td>1 vaginal delivery, complicated by manual removal of the placenta and uterine curettage due to a placenta accreta</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Balkanli-Kaplan et al., 2006</td>
<td>33</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>Percreta</td>
<td>Delayed haemorrhage, occurring 8 months after uncomplicated D&amp;C for a 7-week termination of pregnancy</td>
<td>1 caesarean section</td>
<td>Localised resection, Hysterectomy</td>
</tr>
</tbody>
</table>
Materials and Methods

Reports of placenta accreta presenting in the first trimester are exceedingly rare. Using the key words “placenta accreta”, “placenta percreta”, “early gestation”, and “pregnancy”, a total of only 14, histologically proven, first-trimester cases of placenta increta and percreta (Table 1) [15-28]. Placenta percreta was identified in seven cases, including our recent case. The most common clinical manifestation has been severe haemorrhage, precipitated by curettage for spontaneous or induced miscarriage. Two cases presented as delayed post abortion haemorrhage, 17 weeks and eight months following D&C [22, 28]. In three cases, spontaneous or iatrogenic uterine perforation occurred [15, 24, 27], complicated by intraperitoneal haemorrhage in two of them [24, 27]. In all cases, the definite management was total abdominal hysterectomy, except one that was managed with bilateral uterine artery embolisation [26]. Three additional cases of first-trimester placenta accreta have been reported in the first trimester in association with a cervical pregnancy [29-31]. Finally, Thorp et al. diagnosed one case of placenta percreta in the first trimester, which was confirmed histologically at 32 weeks of gestation [32].

Our case presented as a missed miscarriage, as most of the reported cases, and it can be postulated that retention of products of conception may be caused or enhanced by placenta percreta. Additionally, the patient failed to respond to prostaglandin treatment, which is an effective method of management of missed miscarriage. Olsen and Gonzalez-Ruiz reported a case of failed prostaglandin abortion in a second-trimester termination of pregnancy associated with placenta accreta, and they postulated that placenta accreta may have played a role in the failure of prostaglandin to induce abortion [33].

While most cases of placenta percreta are diagnosed at or near term, our case along with this review, highlight the fact that placenta percreta does not develop in later months as a result of the secondary disappearance or absorption of the decidua, but rather early during the process of implantation, enabling it to cause problems at any time thereafter. It is important to recognise that placenta percreta can cause severe uterine bleeding at any gestational age, particularly when considering the large amount of dilatation and curettage performed for induced or spontaneous miscarriages. It can be assumed that there may be numerous undiagnosed cases of partial placenta accreta in patients with early incomplete miscarriages that do not become clinically apparent and can not be diagnosed histologically. Similarly, it is probable that a proportion of so-called difficult removal of placenta at term could have a component of partial placenta accreta.

The incidence of placenta accreta should increase steadily over the next decades, as the number of caesarean sections and maternal age at delivery increase. There is a need for reliable antenatal diagnosis, since placenta accreta encountered unexpectedly can lead to massive blood loss following its detachment, multiple complications and death. It has been suggested that the single most important factor affecting the outcome of placenta percreta, which still carries a maternal mortality rate from 2 to 7%, is the antenatal identification of abnormal placentation [34]. If these pregnancies can be identified, the blood loss can be minimised by the accurate planning of labour, the availability of blood products and earlier resort to hysterectomy. Additionally, the patient and her family should be informed of her increased risk of placenta percreta and the resulting severe haemorrhage, for which hysterectomy might be required. Anticipating this rare but potentially catastrophic complication of pregnancy at any gestational age is of primary importance. The first and most significant factor is the role of the obstetrician in identifying the patient at risk of abnormal placentation, and clinical history combined with a detailed imaging evaluation is often, though not always, useful in diagnosis. However, it should be kept in mind that placenta percreta can also develop in an unscarred uterus [12, 35].

Several diagnostic modalities have been used to detect placental abnormalities upon clinical suspicion, with varied success. The role of ultrasound (US) examination in the antenatal diagnosis of placenta accreta is unresolved. In one study by Giechinsky et al. [36], US succeeded in diagnosing placenta percreta in only 45% of cases, in contrast to other studies by Levine et al., and Finberg and Williams, where a sensitivity of 86-100% and a specificity of 92% were demonstrated [37, 38]. Sonographic findings include the absence or thinning of the usually dark line seen between the myometrium and the placenta that represents the decidua basalis, the presence of lacunar vascular spaces within the placental parenchyma (“swiss cheese” appearance), and thinning, irregularity, or focal disruption of the normally smooth hyperechoic interface between the bladder and myometrium [38, 39]. At present, color flow Doppler sonography has not been shown to have superior sensitivity over B-mode. However, Levine et al. found that power Doppler can increase the level of confidence in identifying the myometrial zone [37]. When prominent placental vessels can be identified extending from the placenta into the myometrium, then the diagnosis of placenta percreta should be suspected [39]. Finally, magnetic resonance imaging (MRI) can be useful as a complementary technique, particularly in assessing bladder involvement and in cases with a posteriorly implanted placenta [32, 37].

During the first trimester, US does not well define the decidua space in the lower uterine segment, and its value in early pregnancy is debatable. However, by nine to ten weeks the diffuse granular echotexture of the placenta is clearly apparent with US. Comstock et al. showed that in a patient with a previous caesarean delivery, a sac lying in the lower uterine segment on a scan at ten weeks or earlier suggests the possibility of placenta accreta [40]. Chen et al. diagnosed a case of placenta accreta at nine weeks’ gestation based on the absence of a retroplacental clear space, in association with hypervascularity of the lacunar spaces between the placenta and myometrium [41]. Our patient’s US revealed no placental abnormalities. As already mentioned, Thorp et al. managed to diagnose a case of placenta previa percreta with bladder involvement with the use of MRI at 9 weeks’ gestation [32].

An elevated maternal serum creatine kinase was reported to be a biochemical marker of placenta percreta in two cases [42]. Zelop et al. and Kuperminc et al. found a significant association between an otherwise unexplained elevation of maternal serum alpha-fetoprotein and placenta percreta [43, 44]. If macroscopic haematuria is present or there is a sonographic suspicion, a preoperative cysotoscopy could aid in making the diagnosis of bladder involvement and help the surgical team to prepare for a more extensive operation [39]. However, biopsy should be avoided because it may cause severe haemorrhage. The treatment of choice is hysterectomy at all stages of gestation [1, 4]. This is based on the belief that conservative management gives a much higher mortality rate. This is supported by Fox in 1972, when he concluded that the conservatively treated patients had a four times higher mortality rate than those treated with immediate hysterectomy. In cases of suspected abnormal placentation, catheterisation and occlusion of the anterior divisions of the internal iliac arteries with balloon
catheters prior to planned surgery, can significantly decrease the uterine blood flow to reduce intraoperative blood loss and control postpartum haemorrhage. It also allows for eventual embolisation of the hypogastric arteries during surgery using absorbable gelatin particles [45, 46]. Conservative management of placenta percreta is also possible, and various methods have been employed with varying degrees of success [1, 5, 34, 47]. Conservative management is beneficial in preserving future fertility, and may reduce the need for transfusion [34]. It can be further categorised into conservative abdominal surgery and non-surgical conservative management. The former includes: bleeding control by bilateral uterine or internal iliac artery ligation, localised excision and uterine repair, and oversewing of the placental bed. Non-surgical measures include: systemic and intracervical injections of oxytocin, ergometrin, and prostaglandins, uterine curettage with vaginal or uterine packing, use of an intruterine inflated Foley catheter, angiographic uterine artery embolisation, and leaving the placenta in situ with adjunctive chemotherapy. The choice between hysterectomy and conservative therapy depends on the severity of the placental percreta, the desire to preserve fertility, and the degree of haemorrhage or additional complications.

Experience in the management of first-trimester placenta percreta is limited because of its rare presentation in early gestation, and the difficulty in making such an early diagnosis. In 13 out of the 14 reported cases, as well as in our case, the definitive treatment consisted of a hysterectomy, despite an initial effort to control the bleeding with local measures. In only one case [26] was placenta increta successfully managed by bilateral uterine artery embolisation (UAE). The authors also reported successful treatment in three additional cases of suspected placenta accreta with UAE, although they were not histologically confirmed. Therefore, they recommend UAE as conservative management in the first trimester when future fertility is desired, as soon as local measures fail to control the bleeding, or if the patient shows shock symptoms. On the contrary, other studies with longer gestation times showed that the success rate of UAE for postpartum bleeding is significantly lower in cases of abnormal placentation, due to a significant venous component of the bleeding, and suggest an alternative conservative treatment [48, 49].

Methotrexate has also been used in the management of invasive placenta, and in some cases it has been possible to avoid hysterectomy, providing that the patient is haemodynamically stable [47]. The earliest pregnancy described concerned a 15-week gestation, in which methotrexate treatment was unsuccessful [50].

No matter which initial management is used, if it is unsuccessful in controlling the bleeding rapidly, there should be early resort to hysterectomy. In our case, the diagnosis of placenta percreta was not considered in such an early gestation despite the presence of multiple risk factors. The delay in resorting to laparotomy led to the development of severe consumption coagulopathy, which was fortunately managed successfully with vigorous resuscitation.

Conclusion

Although rare, patients who have had previous uterine manipulation, including caesarean section, uterine curettage, manual removal of the placenta, uterine infection, and other pregnancy-associated complications are at risk for placentation abnormalities, as early as in the first trimester. Because of the difficulty in accurately diagnosing these conditions preoperatively, particularly in early gestation, it is of paramount importance that the obstetrician is aware of the possibility of placental abnormalities, the possibility of severe haemorrhage, and the need for hysterectomy. This is imperative for proper preoperative and intraoperative planning, regarding especially the availability of blood products and the early resort to hysterectomy, as well as for the proper counseling of the patients. A high index of suspicion is still required for these patients, until hopefully in the future, improvements in imaging techniques enable a more accurate preoperative diagnosis.

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102

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Intrauterine devices and extrauterine pregnancy.  
A literature review

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Summary
The incidence of ectopic pregnancy has been high over the last decades. Many risk factors are potential causes, among them IUDs use which might have a significant role. According to the current thinking, the use of IUD does not increase the risk of ectopic pregnancy. However, IUDs are more effective in protecting from intrauterine rather than ectopic pregnancy. Our review focuses on current and past IUD use, duration of its use, type of IUD and the associated risk of ectopic pregnancy. Fertility after IUD removal regarding the incidence of ectopic pregnancy is also discussed. Conflicting results regarding the association of ectopic pregnancy risk with the use of intrauterine devices exist.

Key words: Intrauterine devices; Ectopic pregnancy; Fertility; IUD removal; Contraception.

Introduction
An ectopic pregnancy occurs when the fetus develops outside the uterus. The most common site is the fallopian tube (97.7%) and 80% of these are ampullar [1, 2]. There has been a dramatic increase in the number of ectopic pregnancies over the last decades. The incidence increased from 4.5/1,000 pregnancies in 1970 up to 19.7/1,000 pregnancies in 1992. It should be pointed out that ectopic pregnancy is the major cause of maternal mortality during the first trimester of pregnancy [3, 4]. The main risk factors of ectopic pregnancy are pelvic inflammatory disease (PID), previous ectopic pregnancy, previous tubal surgery, endometriosis, IVF, and in utero diethylstilbestrol exposure [5-9]. Use of an intrauterine device (IUD) as a method of contraception is supposed to be another significant risk factor. Marchbanks et al. [5] tried to evaluate the association of ectopic pregnancy with 22 potential risk factors. They found high risk in four possible factors: history of infertility (relative risk - RR: 2.6), history of PID (RR: 3.3), prior tubal surgery (RR: 4.5) and current IUD use (RR: 13.7).

Intrauterine devices are one of the world’s most popular methods of reversible birth control. Worldwide, a hundred and six million women use medicated or non-medicated IUDs. Medicated IUDs releasing copper or steroids are used in Europe, North and South America [10], whereas nonmedicated IUDs (single or double steel rings) are widely used in China. It should be mentioned that 30-40% of women in reproductive age in China use IUDs, but only 1-2% of women using contraception in the USA use an IUD [11]. The acceptability of IUD use in the USA was initially higher but decreased [12] because of the consumer’s fear of IUD-related pelvic infection (due to the problems caused by Dalkon Shield IUD) [13, 14]. Most types of IUDs have a plastic T-shaped frame that is wrapped with copper and/or has copper bands. The presence of an IUD in the uterus prompts an inflammatory response by the endometrium and increases the spermicidal effect. Furthermore, an IUD can also change the lining of the uterus preventing implantation. An IUD is usually used for three to five years because it increases the rates of PID (Chlamydia infection, actinomycosis) with longer duration of use. Although, IUD use provides protection against intrauterine pregnancy, many studies have tried to find the association between ectopic pregnancy and IUD use.

IUDs and ectopic pregnancy

The perception about the role of IUD use in the increase of ectopic pregnancy risk is conflicting. In 1975, Beral et al. [15] in their epidemiological study showed that the increasing use of IUDs as a method of contraception may be a significant risk factor the increased ectopic pregnancy rates. Savolainen et al. also found a relation between ectopic pregnancy and IUD users [16]. In 1985, a multinational case-control study of ectopic pregnancy organized by the WHO showed an elevated RR (6.4) of ectopic pregnancy when IUD users were compared to pregnant controls [17]. The suggested mechanism of this elevation was that although an IUD provides greater protection against intrauterine pregnancy it predisposes women to PID and tubal damage [17]. Mol et al. in 1995 [18] in his meta-analysis showed that current use of an IUD elevates ectopic pregnancy risk whereas oral contraceptives have a protective role [18].

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Parazzini et al. in 1995 [19] and Raziel et al. in 2004 [20] found a strong relationship between IUDs and ectopic pregnancy. On the contrary, Edelman et al. [21] suggested that current and past IUD users do not have an increased risk of ectopic pregnancy and furthermore no relation was found with the longer duration of IUD use [21]. The same results have been shown by numerous authors [12, 22-24]. In 1986, Sandmise et al. suggested that former IUD users presented a 2.35% ectopic pregnancy rate and 2.7% remained infertile after IUD removal [25]. Regarding the role of past IUD use, Makenin et al. [26] implied that an IUD has a predisposing role in ectopic pregnancy only in users and not in previous users. Furthermore, this was also reported by Randic et al. [27] and Xiong et al. [28] in their meta-analyses showed that past IUD use mildly increased ectopic pregnancy. The same authors [28] implied that women with current IUD use compared to pregnant controls presented elevated ectopic pregnancy risk, but no correlation was found when compared with non pregnant women.

The role of duration of IUD use

Many authors tried to investigate the role of duration of IUD use in elevating ectopic pregnancy risk. Ory [29] suggested that IUD users for over 25 months were 2.6 times as likely to have ectopic pregnancy than those with less than 25 months of use and furthermore this difference persisted for one year after the IUD removal. Kalandidii et al. [30] showed that past use of IUDs was associated with a RR of 3.89 for ectopic pregnancy and that this RR increased with longer duration of use. Rossing et al. [31] found that IUD use for more than three years compared to non-users has a RR of 2.5 and this elevated risk remained for many years after removal. Parazzini et al. [19] also found such a correlation. The differences in study design regarding the control group, sample size, and recall bias might possibly contribute to these inconsistencies. Further research is necessary to clarify the association between the risk of ectopic pregnancy and the duration of IUD use.

Ectopic pregnancy risk according to IUD type

There has been a reduced ectopic pregnancy rate associated with IUD use in recent years [22] due to the use of more effective and safe medicated (copper-containing) IUDs. The currently used copper-containing IUDs have lower failure rates than the nonmedicated IUDs (used in the 1960s and early 1970s) [10, 21]. Many studies indicate that the risk of ectopic pregnancy is higher in Dalkon Shield, Lippes Loop or even TCu-200 users compared to users of other IUD types except the Progestasert IUD [10, 21, 31]. However, there are no statistically significant differences in the risk of ectopic pregnancy between the other types of copper-containing IUDs [10, 21].

Many authors have tried to find out the role of IUD type regarding ectopic pregnancy rates. Ory [29] suggested that the likelihood of ectopic pregnancy was independent of the IUD type (copper containing or inert plastic), a finding that Sandmire et al. [25] also suggested. However, Chow et al. [32] found a very elevated RR (2.5) of ectopic pregnancy in former users of the Dalkon Shield IUD versus other IUD types (RR: 1.7). Sivin et al. [10] showed that the less copper an IUD contains, the higher is the incidence of ectopic pregnancy over the time. Sivin et al. [10] have estimated that current users of copper IUDs with a surface area of 350 mm² have a 91% lower ectopic pregnancy risk than non-users, whereas the risk is even lower when the copper surface is 200 mm². Finally, Ganacharya et al. [33] reported that between non-medicated and copper IUDs there was no difference in ectopic pregnancy rates after one year of use but elevated risk in copper IUDs was found after ten years of use.

Fertility response after IUD removal

Many studies are reassuring for IUD users regarding their future fertility [34, 35]. It has been shown that fertility in women with an IUD in situ [22, 23, 25] or in women with an ectopic pregnancy while using an IUD [6, 17, 23] is excellent, which means that tubal inflammation is immediately reversible after IUD removal, independent of the reason for the removal.

However, many questions have been raised regarding fertility response after IUD removal. Pyorala et al. [34] found no statistically significant difference in the return of fertility in women who used either Nova T or Copper T200 IUDs. They also found no significant effect regarding the duration of IUD use and fertility return, and the cumulative probability of pregnancy per 100 women after the IUD removal was 77.3 at one year, 88.9 at two years and 92.4 at three years. Skjeldstad and Bratt [35] found no significant differences in fertility return related to the type of IUD, duration of use, parity or maternal age while checking other IUD types (Nova T, MLCu250 and MLCu375). Sandvei et al. [36] after analysing 304 women with ectopic pregnancies also reported that in women with a previous history of ectopic pregnancy, fertility rates are better in IUD users than non-users. Similarly, Wilson et al. [37] showed a favourable return of fertility and good pregnancy outcome after IUD removal. In the same study, 91.5% of the nulligravid and 95.7% of the gravid women, respectively, had conceived within 48 months after IUD removal. However, Wilson et al. [37] found a difference in ectopic pregnancy rates after IUD removal regarding the reason for removal (0.7% among women who removed the IUD due to complications, e.g., infection vs 0.5% for those that removed it to achieve pregnancy [37]. Furthermore, Andersson et al. [38] found that 96% of pregnancies occurred in the first year after IUD removal. In contrast, Bouyer et al. [39] showed that the recurrence rate of ectopic pregnancy was higher in women who had had an IUD in place at the time of previous ectopic pregnancy than in those without contraception. Recently, Palladine et al. [40] suggested that IUD use less than 3.5 years is not associated with infertility.
On the other hand, Chow et al. [32] implied that recent IUD users (< 3 years after removal) still had an elevated risk for ectopic pregnancy. Basuki et al. [41] also suggested that discontinuation of IUD use results in a 70% elevation in ectopic pregnancy risk, especially in women with more than three years duration of use. This elevation in ectopic pregnancy risk was also mentioned by Mol et al. [18].

Ectopic pregnancy rates and contraceptive methods

Franks et al. [42] investigated ectopic pregnancy rates among women who used different contraceptive methods. In this study the ectopic pregnancy rate was: 0.005/1,000 women years for oral contraceptives or vasectomy, 0.1/1,000 women years for condoms, 0.15/1,000 women years for diaphragms, 0.318/1,000 women years for tubal sterilisation, 1.02/1,000 women years for IUDs and 2.6/1,000 women years for no contraception. Rossing et al. [31] showed that ectopic pregnancy was more likely to occur among IUD users than oral contraceptive users or in women surgically sterilised, but ectopic pregnancy was less likely to occur when compared with non-contraceptive users. Zhang et al. [43] in a retrospective study found that according to different contraceptive methods the incidence of ectopic pregnancy varied as follows: 0.18/1,000 women for female sterilisation, 0.21/1,000 women for oral contraceptives, 0.57/1,000 women for condoms or spermicides, 0.65/1000 women for IUD users and 2.43/1000 women for rhythm or withdrawal method. Basuki et al. [41] also found that women develop ectopic pregnancy more frequently without contraception than using contraceptive methods. Finally, Skjeldestad et al. [44] in a retrospective analysis showed that relative to non-users of contraception, current IUD users have a 91% protection against ectopic pregnancy, while women with tubal sterilisation had a 60% elevated risk of ectopic pregnancy.

Conclusion

Conflicting results regarding the association of the ectopic pregnancy risk with the use of intrauterine devices exist. A pregnancy with an IUD in place is more often ectopic than a pregnancy with no IUD. A slight increase occurs with current IUD use. The role of duration of the use of an IUD to the elevated risk of ectopic pregnancy should be further investigated. Many studies are reassuring for IUD users regarding their future fertility, but further investigations should also be done in this field. Further meta-analyses should be carried out combining the old and the new data regarding the role of IUDs in ectopic pregnancy risk.

References


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Analysis of perioperative morbidity according to whether the uterine cavity is opened or remains closed during abdominal myomectomy - results of 423 abdominal myomectomy cases


Semmelweis University, 1st Department of Obstetrics and Gynaecology, Budapest (Hungary)

Summary

For women who desire pregnancy or who wish to retain their uterus, myomectomy is the standard approach for the treatment of fibroids. Abdominal myomectomy seems to be the best choice when there are large subserosal or intramural fibroids (> 5-7 cm), or submucosal fibroids > 3 cm or when multiple fibroids (> 3) are to be removed. When submucosal myomas are present or multiple fibroids are to be removed, opening the uterine cavity during the surgical procedure is more likely to happen. There is lack of published evidence about whether there is any difference in perioperative morbidity and management of those cases where the uterine cavity is opened during the surgical procedure compared with those where the uterine cavity remains closed. Methods: We undertook a retrospective review of 423 abdominal myomectomies via either an opened or closed uterine cavity. As a primary outcome we assessed the overall perioperative morbidity rate and as a secondary outcome we compared the necessity of pre and postoperative transfusions, intraoperative bleeding, febrile morbidity, unintended surgical interventions, life-threatening events, need for relaparotomies and duration of hospital stay between the opened and non opened uterine cavity groups. Results: The overall perioperative morbidity rate was significantly higher in those cases where the uterine cavity was opened during surgery; however the difference was caused only by the increased risk of intraoperative bleeding. All the other variables, such as febrile morbidity, number of relaparotomies, unintended surgical procedures and life-threatening events did not differ between the two groups. Conclusion: Although there is an increased risk of intraoperative bleeding it seems that entering the uterine cavity during abdominal myomectomy can be considered as safe a procedure as in those cases where the uterine cavity remains closed.

Key words: Abdominal myomectomy; Opened uterine cavity; Perioperative morbidity.

Introduction

Uterine fibroids are benign monoclonal smooth muscle tumors of the uterus. Reports of prevalence rates in the literature range from 20% to 50% based on post mortem studies [1]. There are some data from careful pathological examinations which suggest that the prevalence is as high as 77% [2]. Uterine fibroids are clinically apparent in about 25% of women [3]. Myomas have been reported occasionally in adolescents, but most women are in their 30s or 40s when the fibroids become symptomatic, and at the time of the menopause symptoms are relieved in many women. Race is an important epidemiological risk factor as black women are significantly more likely than white women to have myomas [4]. Parity is also an important factor, as having one or more pregnancies decreases the chance of fibroid formation [5, 6]. The exact prevalence of asymptomatic fibroids is unknown. Symptoms attributable to myomas can be abnormal uterine bleeding, pelvic pressure and pain, and reproductive dysfunction [7]. The most characteristic bleeding pattern of myomas is menorrhagia. Those myomas which are located in or intruding into the uterine cavity are more likely to cause menorrhagia. Increased uterine size can cause pelvic pressure symptoms, such as urinary symptoms or constipation. Very rarely when degeneration occurs or when there is torsion of a pedunculated fibroid acute pain arises. The influence of myomas on reproduction has been clearly demonstrated and the appearance of uterine fibroids has been linked to infertility. Fibroids were implicated as the sole factor of infertility in < 10% of infertility cases, and 43% of women presenting uterine leiomyomas were found to have had a history of infertility for at least two years [8]. Fibroids of > 5 cm in diameter and those located near the cervix or near the tubal ostia are more likely to cause a problem. Fibroids are also associated with miscarriage. The miscarriage rate is likely to be higher if implantation occurs over a submucosal fibroid or if the fibroid is close to the placenta [9]. The location of the fibroid in relation to the placenta appears to be more important than its size [10, 11]. Several factors determine treatment, such as the presenting symptoms, size and type of fibroids, age and reproductive desires of the patient and the skill of the gynaecologist. Many surgical and non-surgical interventions are available, and although several surgical methods...
are used the most favourable technique worldwide is still abdominal myomectomy. Many studies have confirmed that abdominal myomectomy is not associated with a clinically significant elevated risk of morbidity with respect to abdominal hysterectomy for the same diagnosis [12, 13]. However there is minimal published evidence about whether there is any difference in perioperative morbidity and the consequently required management of those cases when the uterine cavity is opened or remains closed during abdominal myomectomy.

We undertook a retrospective review of 423 women who underwent abdominal myomectomy at our Institute between 1990 and 2004 either with an opened or closed uterine cavity to compare perioperative morbidity and to define the safety of those cases where the uterine cavity is opened during the surgical procedure.

Materials and Methods

Hospital charts were reviewed for all women who had undergone abdominal myomectomy at the 1st Department of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary from 1990 through 2004. Patients were identified by manually going through the operating theatre and medical records under the procedure code for abdominal myomectomy. In all of these cases the removal of fibroids via laparotomy was the route of choice because the patients had either large subserosal or intramural fibroids (> 5–7 cm), submucosal fibroids (> 3 cm) or multiple fibroids (> 3) to be removed. Patient age, indications for surgery, type, size and number of removed fibroids, entry into the uterine cavity during the procedure, perioperative complications, and duration of hospital stay were recorded and analysed.

The most frequent indications for myomectomy were determined; these included menorrhagia, pelvic pain, infertility, recurrent spontaneous abortion, size larger than 16 weeks and/or growth of the fibroid and asymptomatic fibroids diagnosed by routine bimanual or ultrasound examination in which cases surgery was performed based on the desires of the patients.

The type (submucosal, intramural, subserosal or intraligamental) of each fibroid was determined. If multiple fibroids were present and located in different layers, the position of each fibroid was determined. If multiple fibroids were removed, indicating a 26-fold increase.

From the 423 abdominal myomectomies the uterine cavity was entered during the surgical procedure in 92 (21.7%) cases and in 331 (78.3%) cases the uterine cavity remained closed.

The patients who underwent myomectomy were between 20 and 55 years of age. There was no significant difference in the mean age between the opened and non-opened uterine cavity groups, 34.8 vs 34.3 years, respectively.

Analysing the indications for surgery and the likelihood of entering the uterine cavity during surgery we found that in case of menorrhagia significantly more surgical procedures were associated with opening the uterine cavity, whereas in other types of indications no significant difference was found (Table 1).

The largest removed myoma was subserosal in 128 cases, intramural in 338 cases, submucosal in 19 cases and intraligamental in five cases. Sixty-seven patients had more than one type of fibroid in the uterus. In cases of subserosal and intramural fibroids the uterine cavity remained closed in a significantly higher percentage of the cases (85.2% vs 14.8% and 79.3% vs 20.7%, respectively), whereas in cases of submucosal fibroids the

### Table 1.

Mean age and indication pattern of abdominal myomectomy in the opened and non-opened uterine cavity groups

<table>
<thead>
<tr>
<th>Indication</th>
<th>Non-opened uterine cavity</th>
<th>Opened uterine cavity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>34.3</td>
<td>34.8</td>
<td>0.4563</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>65/331 (19.6%)</td>
<td>41/92 (44.6%)</td>
<td>&lt;0.0001$^*$</td>
</tr>
<tr>
<td>Pain</td>
<td>100/331 (30.2%)</td>
<td>25/92 (27.2%)</td>
<td>0.5721$^*$</td>
</tr>
<tr>
<td>Infertility</td>
<td>97/331 (29.3%)</td>
<td>28/92 (30.4%)</td>
<td>0.8336$^*$</td>
</tr>
<tr>
<td>Habitual abortion</td>
<td>3/331 (0.9%)</td>
<td>3/92 (3.3%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Size and/or growth</td>
<td>12/331 (3.6%)</td>
<td>1/92 (1.1%)</td>
<td>0.3144</td>
</tr>
<tr>
<td>Other</td>
<td>113/331 (34.1%)</td>
<td>25/92 (27.2%)</td>
<td>0.2074</td>
</tr>
</tbody>
</table>

$^*$Pearson’s χ²-square, $^*$Fisher’s exact test, Student’s t-test.
Analysis of perioperative morbidity according to whether the uterine cavity is opened or remains closed during abdominal etc.

The uterine cavity was opened in a significantly higher percentage of the procedures (63.2% vs 36.8%). In all cases of intraligamental fibroids, the uterine cavity remained closed (Table 2).

We formed four groups according to the size of the largest removed fibroid (size of the dominant removed fibroid < 30 mm, 30-50 mm, 50-70 mm, and > 70 mm) and compared the percentage of those cases where the uterine cavity was opened during the procedure or remained closed. None of the groups showed any significant difference in this regard (Table 2).

There was no significant difference in the number of removed fibroids between the opened and non-opened uterine cavity groups (1.9 vs 2.2).

Analysing the complications we found that in the opened uterine cavity group significantly more bleeding occurred during the surgical procedure (220 ml vs 180 ml mean intraoperative blood loss) and significantly more patients needed postoperative blood transfusions (23.9% vs 6.7%). No patient needed a preoperative blood transfusion due to low haemoglobin levels in the non-opened uterine cavity group and only one patient required a pre-

Figure 1. — Removal of submucosal myoma with opening of the uterine cavity.

Figure 2. — Site after enucleation of submucosal myoma.

Figure 3. — Position of the tennis racket shaped drain in the uterine cavity.

Figure 4. — Suturing of the endometrial layer above the drain.

Figure 5. — Suturing of the outer layer of the myometrium with continuous stitches.
operative blood transfusion in the opened uterine cavity group, thus there was no significant difference between the compared groups in this regard (Table 3).

There was also no significant difference in febrile morbidity between the compared groups. Febrile morbidity was defined based on the criteria used by Sawin et al. [13] as occurrence of infection after surgery which was not present on admission or initiation of antibiotics > 24 hours after surgery (Table 3).

There were no unintended surgical procedures in either group. An unintended surgical procedure was defined based on the criteria used by Sawin et al. [13] as unplanned removal, injury or repair of an organ during the operative procedure. The percentage of relaparotomies did not differ significantly between the compared groups (Table 3). In all cases the indication for relaparotomy was postoperative bleeding. Surgery included steps to reach haemostasis and none of the cases required hysterectomy.

No life-threatening events were observed in either group. Life-threatening events were defined according to the definition of Sawin et al. [13] as cardiopulmonary arrest, resuscitation, unplanned admission to intensive care unit or death (Table 3).

The length of hospital stay (9.3 vs 6.9 days) and the overall morbidity rate (23.9% vs 11.2%) were significantly higher in those cases where the uterine cavity was opened during the surgical procedure. The results are summarised in Tables 1, 2 and 3.

### Discussion

Many surgical and non-surgical interventions are available for the treatment of uterine fibroids. Medical treatment has an inconsequential role in managing patients with uterine fibroids. However gonadotrophin releasing hormone (GnRH) agonists produce a significant reduction in uterine size and after discontinuation of the medication there is a rapid resumption. In addition the consequent severe hypo-oestrogenism can cause significant symptoms, and most importantly bone loss which can lead to osteoporosis with long-term use.

Surgery has long been the main mode of therapy. For women who have completed childbearing hysterectomy offers a good treatment option as data suggest that women are satisfied with symptom relief and experience improved quality of life after hysterectomy [15, 16]. Hysterectomy also prevents the chance of recurrence. However the number of women who wish to retain their uterus for other reasons (concerns about sexual dysfunction and dyspareunia [12]) is increasing, as well as for those who desire future pregnancies myomectomy is the route of choice. For multiple myomas or a significantly enlarged uterus the abdominal route is the best choice. For women with submucosal fibroids hysteroscopic myomectomy may be performed. For women with a uterine size of 16 weeks’ gestation or less and a small number of subserosal or intramural fibroids 8 cm or less in diameter, laparoscopy may be an option [7, 17].

Myolysis is a variation of the laparoscopic or hysteroscopic technique in which the fibroid tissue is destroyed by the use of cryotherapy, laser or electrical energy rather than removed [18].

Women whose primary problem is bleeding and who have completed childbearing can be treated by endometrial ablation alone or in combination with hysteroscopic myomectomy. Uterine artery embolisation with polyvinyl alcohol microspheres positioned by a catheter passed through the right femoral artery is a novel technique and further long-term studies need to be done to assess the role of this method among the therapeutic options.

Although several surgical methods are available the most favourable technique worldwide is still abdominal myomectomy. During abdominal myomectomy difficulty achieving haemostasis can occur and may result in the formation of postoperative adhesions. Bleeding can be sufficiently heavy as to require hysterectomy. For many years it was believed that abdominal myomectomy was associated with greater operative blood loss, longer surgical time and higher risk of postoperative haemorrhage than hysterectomy [19]. Today many studies have confirmed that abdominal myomectomy is not associated with a clinically significant elevated risk of morbidity with respect to abdominal hysterectomy for the same diagnosis [12, 13].

We assumed that when submucosal myomas are present or multiple fibroids are to be removed opening the uterine cavity during the surgical procedure is more likely to occur. Although several studies have compared

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### Table 2. — Analysis of opened and non opened uterine cavity cases according to location, size and number of removed fibroids.

<table>
<thead>
<tr>
<th>Size (no./all cases (%))</th>
<th>Non-opened uterine cavity (mean ± SD)</th>
<th>Opened uterine cavity (mean ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 mm</td>
<td>0/331 (0%)</td>
<td>0/331 (0%)</td>
<td></td>
</tr>
<tr>
<td>30-50 mm</td>
<td>22/331 (6.7%)</td>
<td>22/331 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 mm</td>
<td>79/331 (23.5%)</td>
<td>30/331 (9.1%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. — Perioperative morbidity associated with opened and non opened uterine cavities during abdominal myomectomy.

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Non-opened uterine cavity (no/all cases (%))</th>
<th>Opened uterine cavity (no/all cases (%))</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative transfusion</td>
<td>0/331 (0%)</td>
<td>192/331 (58.2%)</td>
<td>0.2174</td>
</tr>
<tr>
<td>Postoperative transfusion</td>
<td>22/331 (6.7%)</td>
<td>22/331 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Life-threatening events</td>
<td>0/331 (0%)</td>
<td>2/331 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Length of stay in hospital</td>
<td>6.9 ± 2.4</td>
<td>9.3 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>Overall morbidity</td>
<td>37/331 (11.2%)</td>
<td>22/331 (6.7%)</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

*Pearson’s χ²-square, Fisher’s exact test, Student’s t-test.*
the perioperative morbidity of abdominal myomectomy and hysterectomy cases there is minimal published evidence about whether there is any difference in perioperative morbidity and the consequent required management of those cases when the uterine cavity is opened or remains closed during the surgical procedure. To determine perioperative morbidity and safety of the opened uterine cavity cases we undertook a retrospective review of 423 women who had undergone abdominal myomectomy at our Institute between 1990 and 2004 with either an opened or closed uterine cavity.

Of the procedures 21.7% were associated with opening the uterine cavity. It is a little bit less than what was observed in the study of Sawin et al. who analysed 197 abdominal myomectomies and found that the uterine cavity was opened in 29% of the cases [13].

Opening the uterine cavity occurred significantly more often when the indication for surgery was menorrhagia. Other types of indications did not cause any differences in the likelihood of opening the uterine cavity. This may be explained by the fact that the type seems to be the most important factor in determining bleeding symptoms. Submucosal myomas, those in or partially intruding into the endometrial cavity, are most likely to cause menorrhagia [7]. This association is supported by our results as in cases of submucosal fibroids significantly more procedures were associated with opening the uterine cavity. In cases of intramural, subserosal and intraligamental fibroids the uterine cavity remained closed in a significantly higher percentage.

Interestingly, the size of the major removed fibroids did not affect the likelihood of opening the uterine cavity. We even found in the > 70 mm group that in a significantly higher percentage of the procedures the uterine cavity remained closed.

Analysis of perioperative morbidity patterns is the most important consideration in determining whether those cases where the uterine cavity is opened during surgery can be considered as procedures as safe as those cases where the uterine cavity remains closed. Moreover our overall morbidity rate in both groups was much lower (11.2% and 23.9%) than was reported for abdominal myomectomy in the study of Sawin and colleagues as they reported a 38% overall perioperative morbidity rate [13].

In the opened uterine cavity group the intraoperative bleeding and postoperative transfusion rate was significantly higher whereas febrile morbidity and the number of relaparotomies did not differ between the two groups. However the hospital stay was significantly longer in cases when the uterine cavity was opened, mostly because removal of the metroplasty drain was performed on the ninth or tenth postoperative day.

The overall morbidity rate was significantly higher in the opened uterine cavity group, but the difference was due only to the higher intraoperative bleeding and postoperative transfusion rate. Taking into consideration all the other factors the perioperative morbidity rate did not differ between the groups.

Conclusion

For women who desire future pregnancies or who wish to retain their uterus for other reasons, myomectomy is the standard approach for the treatment of uterine fibroids. Previously hysterectomy was considered a safer procedure than myomectomy, but a number of studies analysing the perioperative morbidity of these procedures have shown that myomectomy should be considered as safe as hysterectomy. The type, number and size of the fibroids may all influence management options. In our opinion abdominal myomectomy should be the route of choice when there are large subserosal or intramural fibroids (> 5-7 cm), submucosal fibroids > 3 cm, when multiple fibroids (> 3) are to be removed or when entering the uterine cavity is to be expected. In those cases where the uterine cavity is opened during the surgical procedure we recommend to place a “tennis racket” shaped drain into the uterine cavity to avoid postoperative intrauterine adhesions. It seems that entering the uterine cavity and suturing the endometrial layer basically does not affect perioperative morbidity, although an increased risk of intraoperative bleeding and higher necessity of postoperative transfusion should be taken into consideration. In those cases where the uterine cavity is expected to be opened during surgery it would be useful to prepare for the need of either an intra or postoperative transfusion. Except for the increased haemorrhagic risk, cases where the uterine cavity is opened during the surgical procedure can be considered as safe as for those cases where the uterine cavity remains closed during surgery.

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Autofluorescence reveals menstrual phase in the endometrium

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Summary

Objective: Tissue contains fluorophores that autofluoresce without additional dye or photosensitizer with the appropriate light excitation. This technique has been widely applied for discrimination between normal and precancerous tissue. The aim of this study was to explore the capability and reliability of autofluorescence phase determination in samples of human endometrium. Methods: A total of 70 measurement sites from 31 endometrial tissue samples from hysterectomy were enrolled. Xenon light (330 nm) was directed at the endometrial tissue and the resultant autofluorescence intensity recorded. Spectra were then grouped according to the proliferative and secretory phase, with multivariant analysis, partial least square (PLS) and analysis of variance (ANOVA) used for evaluation of the statistical significance of phase determination. Results: Both proliferative and secretory autofluorescence spectra showed a similar characteristic triple-peak curve shape pattern, however, each of the intensities at the three peaks between the two phases varied markedly (p < 0.01). PLS analysis confirmed that collagen, NADH and FAD autofluorescence were the principle determinants of endometrial spectrum; the sensitivity and specificity of phase determination by autofluorescent was 100% and 97%, respectively. Conclusion: Autofluorescence measurement provides real-time information on endometrial phase status and, based on our results, it appears reasonable to suggest that it may be promising as a clinical tool for prompt phase interpretation.

Key words: Autofluorescence; Menstrual cycle; Endometrium.

Introduction

The menstrual cycle is a physiological reflection of the estrogen effect at the proliferative phase and progesterin-dominant effect at the secretory phase on the endometrium. An ultrasound endometrial study is still the most convenient and practical method of determining the menstrual cycle phase [1]. An additional serum hormone level offers an alternative study for women who have irregular menstrual cycles, especially those with polycystic ovarian syndrome [2, 3]. Although the role of endometrial sampling for menstrual cycle dating remains controversial, the method remains the standard, especially in cases involving luteal phase defects [4, 5]. Unfortunately, of these modalities, only sonography can provide instant endometrial phase information in a clinical setting; however, thorough training and experience is required.

Autofluorescence measurement is a distinct diagnostic tool, allowing direct collection of biological data from the tissue using appropriate light excitation without the need for dyes or photosensitizers. This investigative modality has been used to provide instant discrimination between normal and precancerous tissue, including cervical intraepithelial neoplasms [6, 7]. The subtle change of the two kinds of autofluorescence emitted by collagen and reduced-nicotinamide-adenine-dinucleotide (NADH), at 390 and 470 nm wavelengths, respectively, determines if the tissue is normal or precancerous. Minute variations in tissue architecture and metabolic changes are reflected in variations in autofluorescent spectral intensity, also referred to as optical biopsy [8].

The investigative focus of this pilot study was to test the discriminative capability of autofluorescence for physiological endometrial cyclic change, and to determine the corresponding reliability in phase determination.

Material and Methods

Patient selection and sample preparation

In vitro endometrium immediately after hysterectomy from patients without endometrial polyps, malignancy and pre-hysterectomy curettage were obtained from the Department of Gynecology, Taipei Veterans General Hospital from January through April 2004. Once the corpus uterus was detached from a patient, the endometrium was exposed and rinsed using normal saline to remove blood clots and extra mucus. The specimen was then secured on a tissue stand in preparation for subsequent testing. Randomized one to five sites of each hysterectomy endometrium were chosen for the following autofluorescent measurement. To avoid intra-observer error, each measurement was repeated three times within four hours of extraction, to ensure that the tissue fluorophores had not decayed [9]. Additional specimens were obtained at each measuring site and sent for further pathological evaluation.

Equipment setup and environmental setting

In our study, a xenon lamp (Jobin-Yvon Optics and Spectroscopy, France) was used as the light source, with a specific wavelength (330 nm) produced using a monochromator (Jobin-Yvon H10 UV, grating 1200 g/mm). The light was output to the surface of the endometrium via a Y-shape optic fiber containing 18 output and 19 input sub-fibers. With the aid of a tissue stand, the terminal end of the Y-shape fiber was placed in vertical contact with the endometrial surface. The input sub-fibers simultaneously transmitted emission autofluorescence through another monochromator (Jobin-Yvon DH10 VIS, grating 1200 g/mm) in the range of 370-540 nm in 2-nm increments, with the discrete outputs amplified by an R928 photo multiplier tube (Hamamatsu, Japan; rise time < 2.2 ns). The resultant data were managed using a program based on LabVIEW6i (Laboratory Virtual Instrument Engineering Workbench, National Instruments, Austria) run on a portable computer (ThinkPad, IBM Inc.).

The standard dye, Rhodamine solution, was used for device calibration at the beginning of measurement. Since autofluorescence is easily overcome by visible light, the procedure was conducted in a dark-room environment.

Data processing and statistical evaluation

Triple-repeat measurement data for each site were first averaged and then used to produce a raw autofluorescence spectrum. The extreme diversity of each spectrum resulted from several factors e.g., excitation-emission efficacy, signal-noise ratio, and fiber-tissue surface interaction. To eliminate such confounding effects, area normalization was performed.

The spectral data were categorized into proliferative (P) or secretory (S) phase group based on the pathological report. For advanced statistical discrimination between the two groups, a multivariate regression analysis algorithm, the partial least square (PLS), [10] which is widely accepted as a standard statistical tool in autofluorescence studies [11, 12] was applied. Through the PLS calculation, each spectrum was simplified as an integer digit, called cross-validation score. The score dispersion yields an index of the reliability of the diagnostic algorithm. The PLS also reveals the location of the significant autofluorescent wavelengths among the spectrum, named principle components. The principle components are the most representative elements of the spectra so that they can establish the statistical comparison between two groups with significance set at p < 0.05 by analysis of variance (ANOVA). Diagnostic accuracy was then evaluated by determination of diagnostic sensitivity and specificity using the receiver operating characteristics (ROC) curve.

Results

A total of 31 patients underwent total hysterectomy, with a total of 70 measurement sites enrolled in the study. The average age ± SD of the patients was 42.58 ± 13.40 years. The most common indication for hysterectomy was uterine fibroids (61.29%). There was no statistical significance comparing the two groups (P vs S) for age (42.34 ± 15.60 vs 36.16 ± 11.44 years).

All individual endometrial autofluorescence spectra demonstrated the characteristic triple-peak pattern (normalized group average spectra are shown in Figure 2) where the peaks corresponded to collagen, NADH and flavin-adenine-dinucleotide (FAD) autofluorescence. There was reciprocal change in these peaks comparing the two groups.

PLS analysis revealed three principle components affecting the pattern of endometrial autofluorescence at 395 ± 5, 470 ± 5 and 530 ± 5 nm, wavelengths identical to the triple-peak location. There was intensity statistical significance between the two groups on each of the three peaks (p < 0.01; Figure 3). All cross-validation scores of...
the 70 spectra by PLS algorithm are lined up in Figure 4. The sensitivity and specificity of the endometrial phase, as determined by autofluorescence, were 100% and 97%, respectively.

![Figure 4](image.png)

Figure 4. — Scatter plots of total cross-validation scores the using partial least square (PLS) method. Samples 1-32 and 33-70 on the horizontal axis are proliferative and secretory phases, respectively.

Discussion

First reported in 1924, tissue autofluorescence is a universal physical finding for different organ types [13]. The sources of autofluorescence are collagen NADH, FAD and other minor components [9]. Among the known fluorophores, collagen is the major supportive component of tissue, and NADH, FAD are the key coenzymes in the redox metabolic pathway. It has been demonstrated that autofluorescence studies provide an investigative alternative for discrimination between normal and abnormal cervical tissue, with comparable sensitivity and outstanding specificity relative to colposcopy performance [7, 14]. To our knowledge, however, endometrial autofluorescence performance is still the frontier to be explored. In this study, we found that in vitro endometrial tissue can also unexceptionally yield autofluorescence and the peak pattern is identical to other tissue [8, 12].

Both the proliferative and secretory endometrial autofluorescence spectrum show the triple-peak pattern, however, statistical comparison revealed significant differences between them. The satisfactory high sensitivity and specificity indicate the reliability of autofluorescence on phase discrimination. We attribute this advantageous discrimination to the entirely different dynamic, either structural or biochemical change of the endometrium which provides a favorable condition for the autofluorescent measurement approach. Cyclic endometrial change is the result of an ovarian hormonal synergistic effect. Collagen is the main supportive component of tissue architecture, however, the reported extent of endometrial collagen change during the menstrual cycle remains controversial, varying from 2% to 6.6% [15-17]. A descriptive transvaginal sonography study has demonstrated that endometrial thickness increases from the day of menstruation to ovulation, with a transition in crescent echogenicity revealing the change in thickness increase [18]. After the ovulation event the endometrial echogenicity becomes enhanced. It is postulated that the hyperchogenicity arises from the lengthening and coiling of the endometrial glands [19]. This indicates that the endometrium is more compact in the secretory phase relative to the proliferative analog. Condensation accounts for the increased collagen autofluorescence intensity in the secretory phase demonstrated in our study.

As is known, the endometrium recovers soon after the menstrual flow and proliferous cells pile up from the stratum basalis. Cell proliferation is related to the elevation of serum estrogen levels. It has been observed that direct estrogen administration to the endometrial cells evokes increasingly cellular nucleotide uptake and marked RNA synthesis in 15-30 minutes [20]. The subsequent glycogen, phospholipid and fluid increases contribute to protein synthesis, promoting cell growth in the next two hours [21]. The latest evidence supports the proposition that estrogen-mediated cell proliferation is accomplished via activation of the mitochondria [22]. NADH and FAD are the key coenzymes in the cellular redox pathway of respiratory chain reaction and they are the markers of mitochondrial bioactivity [23]. This expectably dramatic redox activity is compatible with the statistically significant increase in NADH and FAD autofluorescence in the proliferative phase shown in this study.

In comparison to the gold standard of pathology, an outstanding phase correlation is achieved for specimens categorized with autofluorescence. By contrast, Forrest et al., reported an overall accuracy for sonographic endometrial phase interpretation of 93% [24]. Ultrasound generates information with respect to tissue texture via sonic waves, which are received by a transducer and then transformed into dynamic images, so this is a physical diagnostic tool. Autofluorescence uses the fluorophores photo emission to portray the pathological or physiological status of tissue, which is also a kind of physical approach. PLS assay in this study has demonstrated the reliability of phase discrimination determined by autofluorescence. Such excellent performance is likely because autofluorescence reflects not only tissue architectural changes but also bioactivity events at the time of measurement. The combined information promotes the autofluorescent diagnostic efficacy and leads to the high accuracy.

Conclusion

This pilot study has generated autofluorescence data from in vitro endometria. Autofluorescence is a physical phenomenon that occurs when tissue fluorophores luminesce in light in a dark environment. The endometrial cavity is a naturally enclosed compartment in the corpus uterus that provides an ideal field for autofluorescence measurement. Herein, we have demonstrated that autofluorescence is an alternative measurement tool that can instantly and quite precisely reveal two major endometrial phases. Given these preliminary results, it appears reasonable to suggest that its potential capability will be confirmed by more detailed analyses of phase discrimination in the near future.
References


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Study of pubertal development in Abruzzo (Italy) and analysis of factors implicated in puberty variability

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Department of Obstetrics and Gynecology, University of L’Aquila (Italy)

Summary
The aim of the study was to confirm whether there is a secular trend towards the early onset of puberty without an early onset of menarche. The study included a total of 1,266 subjects, 771 females and 495 males, with an age range between 5.9 and 18.2 years. In all subjects height, percentile of height, weight, percentage of overweight, bone age and pubertal stages were evaluated. On the basis of pubertal stage the population was subdivided into Tanner’s corresponding classes. The obtained data for the female population showed a stabilized onset of puberty compared to the last decades and prolonged length of the pubertal period. Pubertal development in males, instead, did not appear to have changed over the last decades. The study is in line with American studies; the earlier onset of puberty verified in the last decades has slowed prolonging the length of the pubertal period. The specific mechanisms implicated in sexual maturation are not yet well known and need further studies.

Key words: Puberty; Menarche age; Tanner scale; Thelarche; Sexual maturation.

Introduction
Puberty is a transition period from childhood to adulthood characterized by important changes in hormones, secondary sex characteristics and behavior. During this period anatomic-functional maturation of the gonads occurs and individuals are able to procreate, while at the same time growth and somatic structure, intelligence and psychological and social attitudes are being modified [1]. The beginning of puberty is in relation to the total level of maturation of all somatic and visceral structures of individuals, but in spite of numerous studies and knowledge up to now, the mechanism that unhooks the onset of puberty still remains unclear.

A peculiarity of sexual maturation in the human species is the four to five years of physiological variations in age at onset of puberty observed among normal individuals despite relatively similar life conditions [2]. Furthermore, whereas reference data seemed to have stabilized in most industrialized countries during the last century, two fairly recent American studies [3, 4] highlighted an unexpected and unexplained advance in physiological age at the onset of breast development. Results obtained in these studies are very close to the data obtained in most European countries.

The survey of those data raises the issue of whether or not the onset of puberty has shifted toward earlier ages. The mean age of menarche found in the PROS study [3] did not show the same shift as age at the onset of breast development because age at menarche (12.9 years) was unchanged when compared with data reported earlier. Moreover in the NHANES III study [4] menarche occurred at 12.5 years, similar to that reported in the PROS study. It appears that mean menarche age is almost stable, whereas age at beginning of breast development has a trend to be earlier.

On the basis of data obtained by American studies the need arises to demonstrate that the age of pubertal development has changed in Italy and, in particular, to confirm whether or not there is a secular trend towards early onset of puberty without an early age of menarche. In addition to purely scientific reasons, clinical postulates also exist and therefore it is important to confirm these data. What is simply the onset of puberty should not be considered precocious puberty and, in particular, therapeutic treatment with the aim of stopping early onset puberty should be avoided.

Materials and Methods
The study was carried out on a healthy population at the Auxologic Center and Gynecology Adolescent Ward of “San Salvatore” Hospital, L’Aquila to monitor growth in the period between January 1999 and September 2005.

A total of 1,266 subjects (771 females and 495 males) ranging in age from 5.9 to 18.2 years for females and from 7.3 to 17.9 years for males were included.

All subjects were evaluated for height, percentile of height, weight, percentage of overweight, bone age and pubertal stages. Height was measured with a Holtain stadiometer with Tanner’s standards as the reference [5, 6]. Weight was precisely measured and the percentage of overweight was determined on the basis of Tanner’s standards. Bone age was determined by a radiograph of the left hand, also according to Tanner’s methods.

Determination of pubertal stages was carried out by expert staff based on the Tanner and Marshall criteria [5, 6]. In particular testicular and breast development, and the onset of pubic hair were evaluated. For testicular development an increase of testicular size of more than 4 ml, corresponding to Tanner’s
stage G2, was the only significant event that was connected to the beginning of male sexual development.

The pubertal female stage was assessed primarily through evaluation of breast development, because menarche, another marker generally used for determining pubertal development, represents the endpoint of a complex sequence of maturation events, while breast development results more simply from the onset of estrogenic action.

On basis of pubertal stage (pubic hair - P, testicular development - G, and breast development - B), males and females were subdivided into Tanner’s corresponding classes (Tables 1 and 2). For each pubertal stage the mean and standard deviation of chronological age were calculated. Statistical analysis was performed using STATA 8.2 (StataCorp, College Station, Texas, USA).

Results

Results of the data with means and standard deviations of age for males are reported in Tables 3 and 4 and for females in Tables 5 and 6.

Discussions

In 1997 a study of the American Academy of Pediatrics (PROS) [3] on more than 1,700 girls demonstrated a mean age of stage B2 to be ten years in white American girls and 8.9 years in African-American girls with lower limits of 6.3 and 5 years, respectively. In another large cross-sectional American study, the National Health and Nutrition Examination Survey (NHANES III) [4] found a similar early median age of 9.7 years for B2. These data are similar to data obtained in our study where stage B2 was attained at a median age of 9.2 years.

In 1970 Tanner obtained a mean age at stage B2 of 11.9 years [5]; if we compare this result with the reference value of 9.2 years in our study, we can see that in the last decades earlier onset of breast development has been occurring. This early onset, however, does not correspond to early menarche since stage B4 corresponds to 13.25 years and stage B5 corresponds to 14.15 years, values that have not changed when compared with Tanner’s values of 1970 (B4 at 13.11 years and B5 at 15.23 years). Therefore, our results are in line with American studies. It thus appears that the average menarche age has almost stabilized, whereas age at onset of breast development is much earlier. The increasing difference between trends in

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### Table 1. — Number of male subjects examined.

<table>
<thead>
<tr>
<th>G</th>
<th>Observed</th>
<th>Pubic hair</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2</td>
<td>148</td>
<td>P2</td>
<td>138</td>
</tr>
<tr>
<td>G3</td>
<td>164</td>
<td>P3</td>
<td>172</td>
</tr>
<tr>
<td>G4</td>
<td>100</td>
<td>P4</td>
<td>100</td>
</tr>
<tr>
<td>G5</td>
<td>83</td>
<td>P5</td>
<td>83</td>
</tr>
</tbody>
</table>

### Table 2. — Number of female subjects examined.

<table>
<thead>
<tr>
<th>Breasts</th>
<th>Observed</th>
<th>Pubic hair</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
<td>250</td>
<td>P2</td>
<td>238</td>
</tr>
<tr>
<td>B3</td>
<td>297</td>
<td>P3</td>
<td>301</td>
</tr>
<tr>
<td>B4</td>
<td>138</td>
<td>P4</td>
<td>140</td>
</tr>
<tr>
<td>B5</td>
<td>86</td>
<td>P5</td>
<td>92</td>
</tr>
</tbody>
</table>

### Table 3. — Genitals: mean age and SD on basis of puberty stage in males (Tanner and Marshall criteria).

<table>
<thead>
<tr>
<th>Genitals</th>
<th>Observed</th>
<th>Mean</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2</td>
<td>148</td>
<td>11.39</td>
<td>1.35</td>
<td>11.17-11.60</td>
</tr>
<tr>
<td>G3</td>
<td>164</td>
<td>12.43</td>
<td>1.15</td>
<td>12.25-12.60</td>
</tr>
<tr>
<td>G4</td>
<td>100</td>
<td>13.70</td>
<td>1.66</td>
<td>13.37-14.02</td>
</tr>
<tr>
<td>G5</td>
<td>83</td>
<td>15.90</td>
<td>1.40</td>
<td>15.59-16.20</td>
</tr>
</tbody>
</table>

SD = standard deviation; CI = confidence interval.

### Table 4. — Pubic hair: mean age and SD on basis of puberty stage in males (Tanner and Marshall criteria).

<table>
<thead>
<tr>
<th>Pubic Hair</th>
<th>Observed</th>
<th>Mean</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>138</td>
<td>11.74</td>
<td>1.76</td>
<td>11.44-12.03</td>
</tr>
<tr>
<td>P3</td>
<td>172</td>
<td>12.21</td>
<td>1.42</td>
<td>11.99-12.42</td>
</tr>
<tr>
<td>P4</td>
<td>100</td>
<td>13.65</td>
<td>1.57</td>
<td>13.33-13.96</td>
</tr>
<tr>
<td>P5</td>
<td>83</td>
<td>15.90</td>
<td>1.48</td>
<td>15.57-16.22</td>
</tr>
</tbody>
</table>

SD = standard deviation; CI = confidence interval.

### Table 5. — Breast: mean age and SD on basis of puberty stage in females (Tanner and Marshall criteria).

<table>
<thead>
<tr>
<th>Breasts</th>
<th>Observed</th>
<th>Mean</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
<td>250</td>
<td>9.20</td>
<td>1.79</td>
<td>8.97-9.42</td>
</tr>
<tr>
<td>B3</td>
<td>297</td>
<td>10.20</td>
<td>1.63</td>
<td>10.01-10.38</td>
</tr>
<tr>
<td>B4</td>
<td>138</td>
<td>13.25</td>
<td>1.38</td>
<td>13.01-13.48</td>
</tr>
<tr>
<td>B5</td>
<td>86</td>
<td>14.25</td>
<td>1.79</td>
<td>13.86-14.63</td>
</tr>
</tbody>
</table>

SD = standard deviation; CI = confidence interval.

### Table 6. — Pubic hair: mean age and SD on basis of puberty stage in females (Tanner and Marshall criteria).

<table>
<thead>
<tr>
<th>Pubic hair</th>
<th>Observed</th>
<th>Mean</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>138</td>
<td>9.10</td>
<td>1.66</td>
<td>8.88-9.31</td>
</tr>
<tr>
<td>P3</td>
<td>301</td>
<td>10.10</td>
<td>1.49</td>
<td>9.93-10.26</td>
</tr>
<tr>
<td>P4</td>
<td>140</td>
<td>12.95</td>
<td>1.50</td>
<td>12.69-13.20</td>
</tr>
<tr>
<td>P5</td>
<td>92</td>
<td>14.25</td>
<td>1.72</td>
<td>13.89-14.60</td>
</tr>
</tbody>
</table>

SD = standard deviation; CI = confidence interval.

The data showed stabilized onset of puberty for females compared to previous decades with a prolonged length of the puberty period based on findings of earlier thelarche.

Pubertal development in males, instead, does not appear to have changed in the last decades. Our study showed that boys reach stage G2 at a mean age of 11.39 years which is in line with results obtained by other studies: in the USA (11.5 years) [7], in Sweden (11.6 years) [8], in the Netherlands (11.5 years) [9], and in Switzerland (11.2 years) [10].
age at B2 and menarche involves an inverse correlation between age at onset of puberty and duration of puberty. Therefore, we can affirm that a secular trend towards early onset of puberty has stopped due to the early beginning of thelarche. The question arises as to the possible mechanisms involved in determining variability of the pubertal period and the early onset of puberty found in females. Numerous hypotheses have been proposed, some of which are still under study.

Factors related to the environment such as nutrition, light, stressors, and endocrine disruptors might impinge on the hypothalamic signalling network directly or through peripheral signals. Each variable – hypothalamic, peripheral and environmental – makes a possible contribution to the differences in timing of puberty and to the early activation of the hypothalamic-pituitary-gonadal system. Thus, intrauterine alterations are possibly associated with disorders of puberty and reproduction, but their role in the physiological variations in puberty remain uncertain.

A direct relationship between body weight and age at onset of puberty was suggested by Frisch and Revelle [11], with a study in which a critical amount of body fat was needed for the onset of puberty. The Frisch and Revelle hypothesis has triggered a number of studies that have either confirmed [7, 12, 13] or not [14, 15] a significant relationship between menarcheal age and fat mass estimated through the body mass index (BMI) or the sum of skinfold thickness.

The question is really complex because, even if a significant correlation between body fat and menarcheal age has been assessed, we have to understand whether this relationship is causal or consequential. The link between the two parameters can only be indirect because they share similar genetic determinants. With this aim, numerous studies found that a link between nutritional status and physiological variations in timing of puberty could be significant but not particularly strong, suggesting that the relationship is indirect or partial and superseded by other factors [16-19].

Nutritional factors take on an important role in the quality of foods assumed in the diet because a high animal versus vegetable protein ratio at the ages of three to five years has been associated with early menarche [20]. Phytoestrogens in the diet might play a role in the regulation of puberty both directly and indirectly, because they interact with estrogen receptors, having either agonistic or antagonistic effects depending on the endogenous hormonal balance [21]. This could also explain why children from developing countries (where there is a high consumption of soybean or cassava), after migration to European countries and undergoing nutritional changes, can have early puberty.

Endocrine disrupting chemicals (EDCs) are widespread environmental substances that have been introduced by man and may influence the endocrine system in a harmful manner [22]. EDCs account for several disturbances in wildlife and may also play a role in human disorders of sex differentiation and the reproductive organs and functions [22, 23]. The possible relationship between sexual precocity and fetal or perinatal exposure to EDCs is raising the issue of length of exposure during development. Although the mechanism underlying such an association is unclear, it indicates the importance of long-term studies. This is a complex question because the number of potential EDCs in the environment has drastically increased and isolation of responsible agents is not usually possible.

Conclusion

The main intent of our study was to attempt to understand if pubertal development has changed in Abruzzo (Italy), confirming whether or not the results of American works that hypothesized a longer pubertal period due to early onset of breast development but with menarcheal age remaining more or less constant. This conclusion shows a secular trend towards early puberty which in the last decades has really been due to better quality of life, but which now seems to have stabilized.

From American studies [3, 4] it emerged that the age of thelarche is in line with our results since the mean age of stage B4 for girls in our region is 9.2 years. If we compare this current value of 9.2 years with Tanner’s values obtained in 1970, in which stage B corresponded to 11.69 years, we can understand that earlier breast development has occurred in the last decades. However, this early development does not correspond to early menarcheal age since stage B corresponds to age 13.25 years and stage B, corresponds to age 14.25 years, values which are not different if compared with Tanner’s values of 1970 (B, at 13.11 years and B, at 15.33 years).

Results obtained from our study are in line with American studies; thus we can assert that the early onset of puberty verified in the last 30 years has really been arrested due to a longer pubertal period based on early thelarche. Instead for males pubertal development has not changed significantly over the years.

The possible mechanisms that cause variability in the pubertal period and early onset puberty in girls are still under study. Certainly genetic factors play a role but also others can significantly influence the maturation process, including nutrition, intrauterine conditions, the light-darkness cycle, climate conditions and exposure to different chemical substances.

In conclusion mechanisms that bring about early onset puberty and the different factors implicated in sexual maturation are still not clear and need further study.

References


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An objective measurement to diagnose micrognathia on prenatal ultrasound

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Summary

Purpose: We introduce the frontal naso-mental angle as an objective measurement for the prenatal detection of fetal retrognathia. The aim of this study is to present normal values for the frontal naso-mental angle from 18 to 35 weeks gestational age.

Materials and methods: In 81 patients between gestational ages 18 and 35 weeks the frontal naso-mental angle was measured on a profile view of the foetal face. The values were compared with four cases of proven Pierre Robin syndrome.

Results: The frontal naso-mental angle is not dependent on gestational age, the mean value is 146.74°, standard deviation 2.7°; 5th percentile 142°, 95th percentile 151°. All four cases of Pierre Robin syndrome demonstrated a significantly lower frontal naso-mental angle below the 5th percentile.

Conclusion: The frontal naso-mental angle represents an objective way to diagnose retrognathia.

Key words: Retrognathia; Pierre Robin syndrome; Prenatal diagnosis; Foetal face.

Introduction

The prenatal ultrasound diagnosis of micrognathia, characterized by a small mandible and receding chin, is usually made on a subjective basis. On sagittal images of the foetal face a small receding chin and a lower lip residing posterior to the upper lip may be detected [1]. Charts of normal sonographic measurement of the mandible have been published [2, 3]. True posterior replacement of the chin with a mandible of normal dimension is known as retrognathia, and by definition is not diagnosed by measuring the mandible. Different approaches to the prenatal diagnosis of retrognathia and micrognathia have been published [4, 5].

In several cases involving more subtle degrees of micrognathia-retrognathia, we have been involved in discussions on the subjective interpretation of the foetal profile. Therefore we aimed at developing a simple and objective measurement that allows easy identification of micrognathia and/or retrognathia in the more doubtful cases.

Methods

We introduce the frontal naso-mental angle on a midsagittal view of the foetal face which is defined by two lines (Figure 1): one from the most prominent point of the bony part of the foetal forehead (os frontale) to the tip of the visible soft tissues of the nose, and the other from the most prominent point of soft tissue of the foetal chin (mandible) to the tip of the visible soft tissue of the nose. The measurement is performed with the head in a neutral position (no extension or flexion of the neck) and the mouth closed.

All ultrasound examinations were performed with an ALOKA SSD 1700 and a 5 MHz curvilinear abdominal probe. A printout was made of the midsagittal image of the foetal face and the frontal naso-mental angle was measured manually with a graduated arc after drawing the two lines on the printout. To have an impression on intraobserver variability one observer measured the frontal naso-mental angle twice with a 5-10 min interval in ten foetuses. To study interobserver variation, ten foetuses were measured independently by two examiners.

Ultrasound examinations were performed between 18 and 35 weeks. After 35 weeks a correct foetal profile can only rarely be obtained.

Data for normal foetuses were plotted and compared with four cases of postnatally proven Pierre Robin syndrome.

Calculations were performed with SPSS 12.0. For intra- and interobserver variation the mean difference between measure-
ments and the standard deviation were determined. The mean, standard deviation, 5th and 95th percentiles were calculated.

**Results**

An overview of the frontal naso-mental angle measurement in 81 foetuses between 18 and 22 weeks is shown in Figure 2. It is clear from Figure 2 that the frontal naso-mental angle does not significantly change with gestational age (in linear regression p = 0.58 for gestational age).

The mean frontal naso-mental angle was 146.4°, standard deviation 2.77°, 5th percentile 142°, 95th percentile 151°. The values in four foetuses with postnatally proven Pierre Robin syndrome were 115° (at 27 weeks), 123° (at 22 weeks), 119° (at 19 weeks) and 120° (at 21 weeks); all clearly below the 5th percentile of 142°.

The mean difference between measurements for intraobserver variation was 2° (standard deviation 1.15°) maximal difference 4° and for interobserver variation 2.5° (standard deviation 1.19°), maximal difference 4°.

**Discussion**

The Online Mendelian Inheritance in Man (OMIM) database at the National Library of Medicine includes 211 genetic conditions with micrognathia and/or retrognathia [6]. Affected foetuses are at increased risk for an abnormal karyotype and amniocentesis should be offered.

Possible complications of micrognathia-retrognathia include hydramnios, neonatal respiratory obstruction, difficult infant feeding and the need for several surgical repair procedures.

Care should be taken to obtain a correct midsagittal profile; an oblique sagittal view will result in a false impression of micrognathia or retrognathia. It has been suggested that three-dimensional multiplannar imaging facilitates the realisation of a true midsagittal view [7].

Subjective interpretation of 2-D images that are mentally interpreted by the sonologist can result in discussion on whether micrognathia-retrognathia is or is not present.

Some have advocated mandibular measurements for this assessment [2], while others have applied a newborn parameter, the jaw index, to foetal ultrasound [8]. This method improved the detection rate of micrognathia as compared to subjective evaluation (sensitivity rises from 72.7% to 100%).

It is possible that the frontal naso-mental angle as we propose it is influenced by ethnic factors but our data do not allow for this analysis.

There is certainly need for a prospective study to compare the detection rate of micrognathia by subjective evaluation of the facial profile versus the frontal naso-mental angle and/or the jaw index.

**Conclusion**

Measurement of the frontal naso-mental angle seems to be a simple and reproducible method for an objective diagnosis of micrognathia.

**References**


An objective measurement to diagnose micrognathia on prenatal ultrasound


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Laparoscopic treatment of ovarian dermoid cysts

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Summary

Dermoid cysts are the most common germ cell tumors of the ovary in women of reproductive age. We report 67 cases of patients with dermoid cysts (mean age, 31.31 years) originating from the ovary treated from 1994 to 2006 at the Obstetrics and Gynecology Department of Aschaffenburg Hospital-Clinic in Germany. Most patients (60) underwent cyst removal. In two patients salpingo-oophorectomy was performed and in five partial oophorectomy was performed. Additional surgery ensuing laparotomy was never necessary. None of the patients had long-term postoperative complications. Two patients were at nine and 15 weeks of gestation and postoperatively were well following termination of pregnancy. In a group of 43 women, who desired pregnancy, 37 pregnancies resulted. The overall intrauterine pregnancy rate was 83.7%; one patient had an ectopic pregnancy (2.32%). To receive more information on this disease, treatment should be performed according to international protocols.

Key words: Dermoid cyst; Surgical; Postoperative treatment; Follow-up.

Introduction

Mature cystic teratomas (dermoid cysts), which arise from the germinal cells of the ovary, are one of the most common germ cell tumors in women. Ovarian cystic teratomas are the most common (95%) germ cell neoplasms. Germ cell tumors make up 15% to 20% of all ovarian tumors whereas dermoid cysts account for 21.8% of all ovarian tumors [1]. Teratomas comprise a number of histologic types of tumors, all of which contain mature or immature tissues of germ cell (pluripotential) origin. Benign or mature cystic teratomas (MCT), also known as dermoid cysts, are composed of mature tissues which can contain elements of all three germ cell layers. Typically they contain mature tissues of ectodermal (skin, brain), mesodermal (muscle, fat), and endodermal (mucinous or ciliated epithelium) origin. In monodermal teratomas, one of these tissue types (e.g., thyroid tissue in struma ovarii, neuroectodermal tissue in carcinoid tumor) predominates. Benign ovarian tumors affect all age groups, while malignant tumors are more frequent among elderly women [2]. Dermoid cysts are recognized as one of the most common tumors in women during the reproductive years [3]. The period of maximum incidence of these tumors is between 30 and 40 years of age [4, 5]. In approximately 10-15% of cases, the tumors present on both sides [6]. Several primordials can appear in one single ovary. Benign cystic teratomas are the most frequent ovarian tumors discovered during pregnancy (24-40%) [7]. Ninety-nine percent of teratomas are benign malignant transformations which occur in approximately 1% of cases [8-10]. Squamous cell carcinoma is the most commonly associated malignancy, though any constituent can undergo malignant change giving rise to a variety of tumors [8, 11]. Adenocarcinoma and the carcinoid form are much less frequent [12]. The tumors often grow slowly and cause minimal symptoms until very large, or there are complications as dermoid cysts. Usually dermoid cysts are slow-growing, even in premenopausal women. They are usually asymptomatic until they reach considerable size. The clinical course of dermoid cysts of the ovary is asymptomatic, and torsion or spontaneous rupture (followed by acute chemical peritonitis) only occurs in 16% and 3-7% of patients, respectively [13]. Diagnosis is based on clinical examination and ultrasonographic indications, confirmed by radiological evidence of solid cystic residues in the ovaries [14]. Ovarian dermoid cysts are relatively frequent ovarian lesions that can be easily diagnosed by transvaginal ultrasonography. Endovaginal ultrasound with Doppler enhancement is the best imaging technique to establish the nature of cysts and to distinguish cysts suspicious for malignancy which require more invasive investigation. MRI and endovaginal sonograms appear to be useful tools in the preoperative selection for this surgery. Tumor markers are definitely indicated for postmenopausal patients whereas they appear less useful in young patients. With adequate preoperative selection, both conservative and minimally invasive surgery can be applied with a clear benefit for the patient. Pelvic laparoscopy is the surgical approach of choice for the treatment of non-functional benign ovarian cysts. Dermoid cysts are benign tumors affecting young patients that can derive benefits from conservative and minimally invasive surgery. Conservative treatment to shell out the cyst and preserve functional ovarian tissue should be reserved for women desirous of future preg-
nancies. The surgical management of germ cell tumors of the ovary is based on the premise of preserving fertility. Ovarian germ cell tumors occur in young women in whom fertility preservation is of great concern. In the recent years, transvaginal sonographic diagnosis of ovarian dermoid cysts together with the laparoscopic approach have greatly improved the treatment of this benign lesion. Cystectomies with preservation of the ovarian remnant should be the routine surgical treatment of benign cystic teratomas. Laparoscopic surgery has almost totally replaced laparotomy in the management of benign adnexal conditions. We retrospectively reviewed the outcome of laparoscopic surgery for ovarian dermoid cysts, complications, and postoperative follow-up.

Materials and Methods

The charts of 67 patients who underwent laparoscopic removal of dermoid cysts from March 1994 until October 2006 at the Department of Obstetrics and Gynecology of Aschaffenburg Hospital-Clinic in Germany were reviewed retrospectively. All the patients had preoperative CA-125 antigen evaluation and transvaginal sonography with Doppler assessment of the ovarian pathology. Transvaginal sonography was carried out by one of the investigators using a 5-6.5 MHz transducer. Reliability of the recordings was usually confirmed by a single trained clinician and in difficult cases a second opinion was sought from one of the consultants involved in the study. The sonographic characteristics as well as the expected histological diagnosis were evaluated preoperatively. An inhomogeneous mass with irregular hypoechoic and hypeerechoic areas with posterior shadowing not separated by septa, or a homogeneous hypeerechoic mass with a regular capsule and posterior shadowing was categorized as a typical dermoid cyst [15]. This diagnosis was compared with the histopathological diagnosis. All the women with tumors less than 12 cm in diameter qualified for laparoscopic management. Lararoscopy was conducted under general anesthesia. Peritoneal fluid from the pouch of Douglas and pelvic washing fluid were examined. In all cases, surgery was performed by puncture of the ovarian tumor followed by removal of the bulge of the cyst, in such a way as to avoid spillage of cyst fluid into the abdominal cavity. The abdominal cavity was abundantly flushed during the procedure and before closure. The cysts were aspirated to reduce spillage and removed via a laparoscopic salvage bag inserted in a 10-mm trocar. Salpingo-oophorectomy and partial oophorectomy were performed in two and five cases respectively, by using scissors and cautery during laparoscopy. The women undergoing salpingo-oophorectomy were postmenopausal while the other five who had partial oophorectomy were perimenopausal. Enucleation of the dermoids cysts in toto with preservation of the ovary was the set therapeutic goal for younger women in 60 cases. In ten cases (5 having partial oophorectomy and 5 with cystectomy) the wound in the ovary was closed with repair sutures, initially using PDS 4/0 and later on either PDS 2/0 or 4/0. After satisfactory hemostasis in 40 cases the ovarian bed was not sutured. Cefalosporine (1 g) was given intravenously as a prophylactic antibiotic in the operating room and repeated at 8-h intervals in three doses.

The size of the tumor, patient's age, gestational age at the time of surgery, pregnancy-rate, pregnancy outcome, duration of the operation, hospital stay, intra- and postoperative complications following a laparoscopic approach were evaluated.

Results

A total of 67 women with ovarian tumors were included consecutively and treated laparoscopically. The characteristics of patients are presented in Table 1. The mean age of patients was 31.31 years (± 6.99; range 15-44). Among the 67 patients, 51 were multiparous and 16 nulliparous.

Table 1. — Characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean 31.31 years (± 6.99; range 15-44)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.31 years (± 6.99; range 15-44)</td>
</tr>
<tr>
<td>Parity</td>
<td>51 multiparous, 16 nulliparous</td>
</tr>
<tr>
<td>Previous laparotomy</td>
<td>22</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>32</td>
</tr>
<tr>
<td>Chronic</td>
<td>21</td>
</tr>
<tr>
<td>Acute symptoms</td>
<td>14</td>
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<tr>
<td>Acute symptoms</td>
<td>10</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Ovarian cyst torsion</td>
<td>1</td>
</tr>
</tbody>
</table>

Twenty-two women had a history of previous laparotomy for various causes. Routine assay of CA-125 was normal (< 35 U/ml) in all patients, confirming that the ovarian tumors were benign. In all study women a preoperative diagnosis with the help of transvaginal ultrasonography was that of teratoma. The correlation of preoperative sonographic imaging and intraoperative macroscopic assessment was evaluated. Preoperative transvaginal sonography led to the correct laparoscopic diagnosis in 59 (88.05%) cases. In the remaining 12% of operated patients diagnosis of an ovarian tumor was made after the results of the intraoperative frozen section. The sonographic appearance of tumor size > 5 cm was observed in 58 (86.56%). Mean cyst diameter size was 9.24 cm (± 2.68; range 4.5-14.2). Thirty-two patients (48.1%) were asymptomatic. In these cases the cysts were discovered by chance during gynecological and/or ultrasonographic examination.

Twenty-one patients sought medical advice because of chronic pelvic pain (23.8% = 16 cases) or menstrual irregularity (7.4% = 5). Acute symptoms were the indication in 14 (20.89%). Clinical presentations were abdominal pain and frequent swelling in ten cases (71.44%), abnormal vaginal bleeding in three (21.44%), and ovarian torsion in one (7.12%).

Two patients (2/14 = 14.28%) presented acute symptoms and had their surgical intervention performed during the first and second trimester of pregnancy in the 9<sup>th</sup> and 15<sup>th</sup> week, respectively. The immediate postoperative course was uncomplicated. No miscarriages occurred. Postoperatively they seemed to do surprisingly well following termination of pregnancy.

Dermoid cyst enucleation was the most commonly applied procedure, while total salpingo-oophorectomy and partial oophorectomy were the least frequent. Tumors 10-12 cm in size were the most frequently torsioned. Patient age and size of cyst did not differ between those with left and right lesions.
Surgery included cystectomy (89.55%), total (2.98%) or partial oophorectomy (7.46%). In 60 cases there were cystectomies performed sparing fragments of healthy ovarian tissue, in two cases salpingo-oophorectomies and in five partial oophorectomies were carried out. The whole gonad was removed in two postmenopausal patients (2.98%) generally because of total loss of functional ovarian tissue surrounding the cyst. In five cases partial oophorectomies were performed because the cyst borders with the rest of the ovarian tissue were indistinct due to the infections that these women had mentioned in their history.

Dermoid cysts were bilateral in 4.6% of cases, and associated with cysts of other histotypes homolaterally in 5.1% and contralaterally in 11.7%. Associated cysts were of a functional nature (89.2%), endometriotic (4.5%), serous cystadenomas (5.3%), and mucinous cystadenoma (1%). Unilateral cysts occurred more frequently in the right ovary (52.8%) than in the left. The surgical parameters in our study patients are shown in Table 2. The mean duration of the operation was 53.48 min (± 20.61; range 35-120 min). Mean blood loss was 53.13 ml (± 23.84; range 22-110 ml). The total number of days in hospital excluding the period of preoperative examination (generally 1 day) was 2.54 days (± 1.02; range 1-4).

Table 2. — Surgical parameters in women operated on for dermoid cysts by laparoscopy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range (in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyst diameter</strong></td>
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</tr>
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<td>2.54 days (± 1.02)</td>
<td>range 1-4</td>
</tr>
</tbody>
</table>

**Intraoperative complications**
- Injury of superior epigastric artery: 2
- Injury of inferior epigastric artery: 2

**Postoperative complications**
- Temperature above 38°C: 3
- Wound infection in umbilicus: 1

Cytological examination of the peritoneal fluid recovered from the Douglas cavity and presurgical wash-out with saline solution were negative for tumors.

All the extracted material was submitted for a prefinal histopathological examination frozen section at the time of surgery. The final histological diagnosis of mature ovarian cystic teratoma was received a few days postoperatively and confirmed in 100% of cases. All removed lesions histologically appeared as benign cystic ovarian teratomas without any signs of malignancy. During cyst extraction, minimal spillage occurred in 32.5% of the cases and none developed chemical peritonitis.

Postoperative complications included two cases of excessive bleeding from the extended incision, and one case of wound infection in the umbilicus. The two patients had an inferior epigastric artery injury during insertion of the 10-mm trocar in the right lower abdomen. The bleeding was controlled with bipolar coagulation. In these two cases we observed a drop in hemoglobin levels below 8 g%. In another two cases bleeding following injury of the superior epigastric artery in the left upper abdomen was controlled by suture ligature with an emergency needle. No case of postoperative peritonitis was recorded. Postoperatively we found that the menopause and fertility of post-enucleation patients were better than those who underwent salpingo-oophorectomy. During follow-up after laparoscopic treatment, we performed the following examinations on a 3, 6 and 12-month basis: CA125 level measurement and clinical examination by transvaginal sonography. Two years post-operatively study patients had no any clinical symptoms. Over a follow-up period of up to 24 months, ovarian folliculogenesis was confirmed ultrasonographically. During this period we did not find any recurrence of dermoid cysts in the treated or the contralateral ovary.

Our overall intrauterine pregnancy rate was 83.7% (36/43) in women aged from 19 to 34 years; one 37-year-old patient had an ectopic pregnancy (2.32%; 1/43). Thirty-six had intrauterine pregnancies and one patient had an ectopic pregnancy. All of the intrauterine pregnancies [36] went to term and no fetal abnormalities or other problems were reported.

**Discussion**

Laparoscopic removal of dermoid cysts has increased in the last few years [16]. Clinical studies in large patient populations show that most ovarian masses can be successfully treated by laparoscopy [17]. However, proper early qualification, based on medical history, gynecological and sonographic examination is of great importance. The risk of unexpected malignancy of the masses is reduced by accurate presurgical staging and an absence of spillage in expert hands [18, 19]. The reliability of transvaginal ultrasonographic diagnosis associated with negative CA125 and clinical oncological examination provide a highly certain diagnosis of benign ovarian swelling and hence dermoid cysts [20-22]. However serum CA125 concentrations are an unreliable indicator of malignancy, producing high rates of false-positive and false-negative results [23]. Benacerraf et al. reported a 15% failure rate in the ultrasonographic diagnosis of malignant cysts [24]. Miaman et al confirmed that in fact 31% of malignant tumors in their sample had similar features to benign ones [25]. Malignancy is rare and malignant transformation of an originally benign teratoma, which occurs mostly only in women in postmenopause, occurs even less often [26]. Each dermoid cyst, in which there is possible malignant potential, should be totally removed according to the standards set in oncosurgery taking care to avoid rupture [27-29]. Dermoid cysts are characterized by continuous growth. Due to this and possible complications, namely rupture, torsion, infection,
malignancy or malignant degeneration, respectively, dermoid cysts should be surgically removed. It bears some disadvantages. The standard practice is to avoid spillage of the cystic content. Spillage can be as high as 80% in laparoscopic procedures [29]. In our experience, spillage occurred in 32.5% of the laparoscopic procedures. Contents of dermoid cysts cause chemical peritonitis. A review of the literature reveals a 0.2% incidence of chemical peritonitis following laparoscopic removal of dermoid cysts [30]. It is obligatory to undertake extensive rinsing of the abdominal cavity with sodium chloride solution at body temperature until no fatty particles can be detected in the lavage [31]. Only in a few cases has bacterial peritonitis been reported following treatment for dermoid cysts during laparoscopy [31, 32]. To avoid this complication, it is important to not allow the cyst contents to spread from the lower pelvis to the intestinal loop with the aid of a salvage bag. Following extirpation of dermoid cysts the adhesion rate versus no adhesions on the adnexes in second-look laparoscopies has been variously reported [33-37]. Some adhesions are inevitable because of the very large ovarian incision that is necessary to remove the cyst intact. Adhesions can impair reproductive function and cause postsurgical pain. The use of specific anti-adhesion agents, such as barrier methods, or as fluid ingredients reduce the frequency of this complication [38-40]. Dermoid cysts do not occur often during pregnancy, but their high-risk complications (torsion, rupture and malignancy) demand immediate surgical intervention [40, 41]. In the first trimester of pregnancy, ovarian cysts are often functional without complications. After 16 weeks of gestation, frequency of ovarian cysts has been reported between 0.5-3.0% [42]. Approximately 2-5% of ovarian tumors in gravid women are malignant [43-47]. Immediate treatment of symptomatic masses permits conservative, fertility-preserving surgery and has no adverse effect on pregnancy outcome [48]. Tawa and White reported that the frequency of dermoid cysts surgically resected in gravid women was 21.1 and 40.3%, respectively [49, 50]. Laparoscopic management of dermoid cysts is a safe and beneficial method in selected patients when performed by an experienced laparoscopic surgeon. For the laparoscopic approach strict adherence to guidelines for selecting patients for preoperative clinical assessment and intraoperative management are obligatory. In approximately half of the non-malignant ovarian cysts, transvaginal ultrasound is capable of distinguishing between the different histopathological diagnoses of non-malignant ovarian masses [51]. Women older than 40 years of age with uncertain ultrasonographic parameters and high tumor marker levels should be evaluated with great care. In these cases it is absolutely obligatory to perform a frozen section during the operation. When laparoscopy is not possible or inadvisable, laparotomy is still irreplaceable [52]. Where malignancy is suspected, laparoscopy is contraindicated and a median laparotomy is appropriate for radical extirpative surgery. Laparoscopy should be considered the method of choice for the removal of benign ovarian cystic teratomas as it offers the advantages of fewer postoperative adhesions, shorter hospital stay, and better cosmetic results in comparison to classical surgery. It should be performed by surgeons with considerable experience in advanced laparoscopic surgery. Laparoscopy is a safe approach to adnexal masses and may decrease the rate of unnecessary laparotomies for benign cysts, which give no suspicious ultrasonographic signs [53]. Our evaluation of laparoscopic surgery showed that removal of the enucleated cyst from the abdominal cavity using a plastic bag is advantageous in terms of operating time and postoperative complications as well as in cosmetic results compared to extraction of the cyst through an extended abdominal incision. In most cases we have successfully dissected all ovarian cysts without breakage and preserved the ovary with a reproducible laparoscopic technique. Whether the ovary needs to be closed after cystectomy is controversial. After laparoscopy the ovary was left open to allow healing by secondary intention. According to some authors ovarian closure is unnecessary after laparoscopic cystectomy for cystadenomas and dermoid cysts because the postoperative adhesion rate appears to be minimal [54-57]. Suturing of ovarian tissue may increase adhesion formation [58]. However, this opinion is controversial for endometriotic cysts [58-60]. Laparoscopic cystectomy is effective in treating large endometriomas. However, operative difficulties may be encountered, explaining persistent endometriomas and postoperative adhesions [61]. Important surgical and postoperative complications were not observed. The fertility following laparoscopic treatment of adnexal cysts appears to be normal In our patients the pregnancy rate was 86.04%. According other authors the overall pregnancy rate is high (64.46% - 94.6%) [62, 63]. Sergent et al. reported that the discovery of an ovarian cyst has become relatively common in the beginning of pregnancy. After 16 weeks of pregnancy, organic cysts are the most frequent, mainly dermoid cysts. Their prevalence is estimated between 0.5 and 2 per thousand of pregnancies [64]. The ideal period for scheduled surgery is probably the beginning of the second trimester and the rate of abortion is minimized. The rate of complications (rupture, torsion, obstruction of labor) resulting from dermoid cysts in pregnant women can be as high as 22%. Removal by laparoscopy has been reported as being safe and free of obstetric complications [65]. We conclude that laparoscopic dermoid cyst enucleation was the most commonly applied procedure. Salpingo-oophorectomy or partial oophorectomy is the safest treatment for dermoid cysts, however it is justified only in women in perimenopause or postmenopause, respectively. We suggest this surgical procedure for women in reproductive age only when malignancy is suspected.

References

Laparoscopic treatment of ovarian dermoid cysts


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Summary

Aim: The aim of our study was to verify with the use of ultrasound (US) scanning the effectiveness of misoprostol in medical abortion.

Materials and Methods: The study population included women with a medical miscarriage attending the 2nd Department of Obstetrics and Gynecology, University of Athens in Aretaieion Hospital, Athens, Greece. All women < 49 days since their last menstruation received 800 μg vaginal misoprostol. The diagnosis of complete abortion was possible by the US measurements as endometrial thickness of 15 mm by transvaginal US was used as a cutoff level for successful abortion.

Results: The mean age of the study population was 27 years (ranging from 19 up to 37 years). Complete evacuation with misoprostol was performed in 149 women. The success rate was 85.2% (127/149). Twenty-two women experienced intrauterine echogenic structures with a diameter > 15 mm and all of them underwent surgical evacuation (14.8%). Vaginal bleeding was present in 17 patients after the procedure (11.4%). Less usual reported side-effects included nausea, vomiting, pain, or diarrhea.

Conclusion: Misoprostol use is an effective, safe and acceptable method of medical abortion for women.

Key words: Misoprostol; Miscarriage; Medical abortion; Transvaginal ultrasound.

Introduction

One out of four women will face at least one miscarriage in her reproductive life. Furthermore, about 10-20% of pregnancies end in miscarriage [1]. Dilatation and curettage has been the usual treatment for early pregnancy failure. The most effective method of abortion is surgical curettage, however expectant management of incomplete miscarriage is effective and associated with lower rates of infection than surgical management. It is shown that the risk of infection is low (2-3%) after expectant, medical or surgical management of a miscarriage [2]. The advice from the Royal College of Obstetricians and Gynecologists is that expectant or medical management should be offered only in units where patients have access to 24-hour telephone advice and immediate admission [3].

Medication abortion (mifepristone-misoprostol) is used worldwide by millions of women [4]. The success rates of such a nonsurgical method range from 72 to 93% depending on the dose, the route of administration and the type of miscarriage [5-11].

Method

This was a retrospective study carried out at Aretaieion Hospital, Athens, Greece from January 2005 to December 2006. Written informed consent was given by each patient to participate in our study. Transvaginal ultrasound (TVS) was performed to confirm pregnancy. The upper limits for treatment were either crown-rump length (CRL) of 10 mm or 49 days amenorrhea. The patient received misoprostol in a dose of 800 μg vaginally. One week later, TVS was performed to investigate whether all fragments compatible with a complete expulsion were discharged. Complete expulsion was the absence of intrauterine echogenic structures with a diameter more than 15 mm. In cases with a continuous evolving pregnancy or heavy vaginal bleeding, surgical evacuation was performed.

Results

From 160 women visiting our department, 11 did not agree to participate in our study. The mean age of the study population was 27 years (range 19 to 37 years).

Complete evacuation with misoprostol was performed in 149 women. The success rate was 85.2% (127/149). Twenty-two women experienced intrauterine echogenic structures with a diameter more than 15 mm and all of them underwent surgical evacuation (14.8%). Vaginal bleeding was present in 17 patients after the procedure (11.4%). Thirteen women experienced abdominal pain (8.7%), for which oral paracetamol was used. Nausea, vomiting and diarrhea were found in eight (5.4%), seven (4.7%) and five (3.4%) women, respectively. No cases of infection or blood transfusion were noted. Moreover no increase in uterine rupture was found in women with a previous cesarean section. The only factor that influenced the treatment efficacy was parity, as misoprostol affects uterine contractility and cervical maturation which could vary due to parity.

Discussion

"... I will not give to a woman a pessary to produce abortion...". This phrase from the Hippocratic oath was prohibiting the ancient Greek doctors to cause abortion in a pregnant woman [12].

Miscarriage is defined as an abortion due to accidental trauma or natural causes such as chromosome factors. Induced abortion (elective or therapeutic) is an abortion caused by use of medical or surgical management. The
Misoprostol use as a method of medical abortion

131

rates of abortions (missed, spontaneous or incomplete) could reach even 15% of all pregnancies [13]. Surgical uterine evacuation is traditionally used for the treatment of such cases. Although it is a safe method, there are also some complications such as uterine perforation or intrauterine adhesions. Historically many herbs, e.g., tansy, pennroyal, black cohosh or silphium were used as abortifacients [14].

Medical management of abortion became an accepted practice in the 1990s. The advantages of medical versus surgical abortion are no requirement for anesthesia and lower risk of infection or perforation [13]. In a Finish study, it was shown that although surgical treatment is associated with more infections, the patients were more satisfied and experienced less pain with the surgical management [15].

It was shown in a randomized trial that while using 800 mg vaginal misoprostol vs curettage for the treatment of early pregnancy failure, bleeding was heavier and more prolonged in the misoprostol group, however other interventions were rarely required [16].

Misoprostol is an FDA-approved drug for the prevention of NSAID-induced gastric ulcers. In other countries, it has also been approved for labor induction or as an abortifacient. In many countries, it is used in conjunction to mifepristone as an abortifacient.

These medical abortion regimens used in different studies include 600 mg oral mifepristone followed 48 hours later by 400 μg oral misoprostol. Many obstetricians use a regimen of 200 mg oral mifepristone followed by 800 μg vaginal misoprostol. Mifepristone is an antiprogestrone whereas misoprostol is a prostaglandin analogue. Misoprostol (Cytotec, Searle AG, USA) is a synthetic prostaglandin E1 analogue [17, 18]. It is used as a method of medical abortion for early pregnancies up to 49 days as later on it is less effective. It is more practical to be used orally, however fewer gastrointestinal side-effects are mentioned when used vaginally.

The protocol used in our institution is 800 μg vaginal misoprostol as a method of medical abortion for early pregnancies up to 49 days.

Vaginal misoprostol is more effective than vaginal prostaglandin E in avoiding surgical management. Furthermore, it has been found that vaginal misoprostol is more effective than oral misoprostol and it was shown that sublingual misoprostol has equal efficacy to the vaginal regimen, although it was associated with more episodes of diarrhea [19, 20]. It has been revealed that successful misoprostol treatment is significantly more likely in nulliparous women with localized lower abdominal pain or active vaginal bleeding within the previous 24 hours or with Rh-negative blood type [21]. It has also been shown that long-term conception rate and pregnancy outcome after misoprostol use is similar to that after surgical management [22]. Misoprostol treatment of miscarriage seems to be the least expensive method (1000 US dollars) when compared with expectant (1,172 US dollars) or surgical management (2,007 US dollars) [23]. Minimal side-effects have been noted such as light bleeding, diarrhea, vomiting or headaches, something which was also found in our study with the exception of headaches.

Serum beta-hCG is used to discriminate abortion status after misoprostol use; hCG measurement can detect a persistent gestation or an incomplete medical abortion. Specifically, a cutoff level of 20% of the initial value might lead to a diagnosis of complete expulsion in 98.5% of pregnant women, whereas the sensitivity of ultrasound reaches 89.8% [24]. In our study, we preferred to use US scanning as a criterion of effective abortion instead of the hCG measurement because the initial values of hCG were not available in the majority of the women as the first measurement was done in other hospitals.

Although Fiala et al. showed that measurement of hCG before treatment and at follow-up is more effective than US to confirm a successful medical abortion, there is still no agreement in the verification of medical abortion outcomes [24].

US on the other hand is easier to perform and could exclude the possibility of ectopic pregnancy. US can often reveal an inhomogeneous endometrial thickness leading to unnecessary surgical interventions [24].

Endometrial thickness of 15 mm by TVS was used as a cutoff for successful abortion, although many disagree with this cutoff level because it could cause unnecessary interventions [25]. Furthermore, absence of the gestational sac is of course necessary [26]. The US criterion used by El-Rafaey et al. [27] to define complete abortion was the absence of an intrauterine gestational sac, whereas Chung et al. [28] used the criterion of a choriodecidual reaction 5 cm² and 6 cm² in the transverse and sagittal planes, respectively. Leung et al. used stricter criteria for defining an “empty uterus” after medical abortion. Patients with a homogeneous intrauterine dimension of less than 11 cm² in combined transverse and sagittal planes were regarded as having complete expulsion [29]. We preferred to use the US cutoff measurement of 15 mm of endometrial thickness as a criterion of successful abortion. The success rate was 85.2% in our study.

Conclusion

Misoprostol use is an effective, safe and acceptable method of medical abortion. The diagnosis of complete abortion was possible by the US measurement of endometrial thickness of 15 mm by TVS and was used as a cutoff for successful abortion.

References


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“Chromohysteroscopy” for evaluation of endometrium in recurrent miscarriage

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Summary

Purpose: “Chromoendoscopy” results in 34 recurrent miscarriage (MR) patients in whom conventional hysteroscopy did not show any apparent endometrial pathology. Method: 5 ml of 1% methylene blue dye was introduced through the hysteroscopic inlet. Results: The study group was classified according to the staining characteristics. Group I included 19 patients in whom focal dark staining was observed. Group II included 15 patients in whom diffuse light blue staining was observed. There was no significant difference between the two groups in age, smoking, status, BMI, number of miscarriages and in mean gestational age of the miscarriages. Time to hysteroscopy after the last miscarriage was shorter in Group I (63.9 vs 95.3 days). Then, the study group was classified according to the histopathology result. Group I included ten cases of endometritis while Group II included 24 cases with a normal histopathology. The mean number of miscarriages was higher in Group I (3.4 vs 2.5). Conclusion: Chromohysteroscopy improves the efficacy of hysteroscopy in RM cases and is warranted after three miscarriages in two cycles time.

Key words: Hysteroscopy; Chromohysteroscopy; Recurrent miscarriage; Endometrium.

Introduction

Recurrent miscarriage (RM), defined as the loss of three or more pregnancies earlier than 20 weeks of gestation, is of great concern to gynecologists. RM affects between 0.5 and 3% of couples [1]. Despite numerous studies the etiology of RM remains obscure, a causal factor can not be identified in half the cases [2, 3].

Known causes of RM fall into four categories: genetic, endocrinologic, immunologic and anatomic. Anatomical abnormalities can be congenital as Müllerian anomalies or can be acquired as adhesions and fibroids. Miscarriages because of uterine anatomical abnormalities are not due to the distortion of the shape of uterine cavity or to the lack of endometrial lining in the abnormal part. There is still an endometrial layer lining the abnormal part but the decidual transformation is not adequate due to inadequate vascularization [4, 5].

The diagnosis of uterine anatomical defects can be established using ultrasonography, hysterosalpingography and hysteroscopy and/or laparoscopy. Hysteroscopy has the advantage in its ability to diagnose intrauterine defects. When there is a macroscopic abnormality, it is hardly possible to miss the diagnosis, but when there is no apparent finding, the uterus is considered as normal, although endometrial function can still be defective.

Chromoendoscopy is a widely used technique in gastrointestinal imaging [6]. Over the last decade, endoscopic systems have acquired greater potency due to high resolution images owing to CCD chip technology and narrow band imaging techniques [7]. Besides imaging enhancement, gastroenterologic endoscopists use chemical agents either to identify specific epithelia, contrast or highlight subtle mucosal irregularities, or tattoo a specific mucosal site.

Unlike the gastrointestinal mucosa the endometrium is not an “absorbive” epithelium. The endometrium does not absorb any dye under normal circumstances. However, Marconi et al. reported that endometrium can be stained by methylene blue except in the periovulatory phase [8]. The reason for endometrial staining is explained with apoptosis. They noted that structural damage of the cells during apoptosis would allow passage of the methylene blue dye into the cell.

The aim of the current study was to assess the value of “chromohysteroscopy” (endometrial dying during conventional hysteroscopy) for enhancement and detection of subtle endometrial changes in RMs.

Material and Method

The current study was conducted between January 2005 and August 2007. Inclusion criteria were at least two consecutive miscarriages without a known cause. There was no age limit. Women were not included if they (or their husbands) had any chromosomal abnormality, endocrinological disease or antiphospholipid syndrome. Also, women with a known uterine abnormality were excluded. Applying these criteria 37 women were included in the study. As this was a preliminary study we did not calculate a sample size prior to the study. Institutional review board approval and written informed consents were obtained.

All hysteroscopic operations were performed in the early follicular phase. In three cases hysteroscopy revealed a uterine structural abnormality which was missed in ultrasonography and/or hysteroscopy (1 polyp, 2 adhesions), and they were excluded from the study. Conventional hysteroscopy did not show any apparent endometrial pathology in the remaining 34 patients. These were included in the analysis.

When no apparent abnormality was seen in the endometrial cavity, distending medium flow was stopped and 5 ml of 1%
methylene blue dye was introduced through the hysteroscopic inlet. After 5 min distending medium flow was started again to wash the endometrium. The uterine cavity was visualized for any staining pattern. Diffuse light blue staining was considered normal. Focal, dark blue staining above the internal cervical ostium, regardless of size and number of stained areas, was considered a positive finding (Figure 1). Biopsies were obtained from dark stained and light stained areas and sent to pathologic examination in separate bottles.

All procedures were performed in an operating room. The classic dorsal lithotomy position was employed for all hysteroscopic procedures and a 2.9 mm, 30° rigid telescope with an operative sheath of 3.5 mm was used for examination (Karl Storz, Germany). Neither speculum nor tenaculum was used in the "no-touch technique" as described by Bettochi et al. [9]. All patients were given intraoperative antibiotic prophylaxis with 1 g ceftriaxone (Rocephin, Roche, Istanbul).

Endometrial biopsies were obtained using hysteroscopic grasping forceps. With the jaws open, the forceps were pushed into the endometrium until sufficient tissue was grasped.

Time to hysteroscopy after the last miscarriage was between 33 and 205 days (mean 77 ± 40 days).

Results

The conventional hysteroscopy and chromohysteroscopy procedure were successful in all 34 patients. Prior to dying of the endometrium there was no apparent abnormality in any of the patients. With endometrial dying, focal dark staining areas were observed in 19 of 34 patients. Two biopsies were taken, one from the light stained area and another from the dark stained area and sent for pathological examination in separate containers. When no dark stained area was seen a single biopsy was obtained from the posterior fundal endometrium. The pathologist was blinded during the initial histopathologic examination. After completion of the study, specimens were rechecked by the same pathologist and the histopathologic diagnoses were confirmed.

The study group was classified according to the staining characteristics. Group I included 19 patients in whom focal dark staining was observed and Group II comprised 15 patients in whom diffuse light blue staining was observed. There was no significant difference between the two groups in age, smoking status, BMI, number of miscarriages and in mean gestational age of the miscarriages. There was a statistically significant difference in time to hysteroscopy (p = 0.030). Time to hysteroscopy after the last miscarriage was shorter in Group I (63.9 vs 95.3 days) (Table 1).

Table 1. — Classification according to staining.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 19)</th>
<th>Group II (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.4</td>
<td>27.2</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>26.3</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.75</td>
<td>22.54</td>
<td>NS</td>
</tr>
<tr>
<td>Time to hysteroscopy (days)</td>
<td>63.94</td>
<td>95.33</td>
<td>0.0030</td>
</tr>
<tr>
<td>Number of miscarriages</td>
<td>3</td>
<td>2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean gestational age of miscarriages</td>
<td>7.75</td>
<td>7.68</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group I: dark staining; Group II: diffuse light blue staining; NS: not significant. Comparisons were made by using the Mann-Whitney U-test.

Figure 1. — a) Conventional hysteroscopic view; b) Light staining area; c) Dark staining area.
Afterwards, the study group was classified according to the histopathology result. Group I included ten cases of endometritis while Group II included 24 cases with a normal histopathology. There was no significant difference between the two groups in age, smoking status, BMI, time to hysteroscopy and in mean gestational age of the miscarriages. This time, a statistically significant difference was found in the number of miscarriages (p = 0.008). The mean number of miscarriages was higher in Group I (3.4 vs 2.5) (Table 2).

Table 2. — Classification according to histopathology.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I</th>
<th>Group II</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.3</td>
<td>26.9</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>40</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.25</td>
<td>21.67</td>
<td>NS</td>
</tr>
<tr>
<td>Time to hysteroscopy (days)</td>
<td>71.50</td>
<td>80.42</td>
<td>NS</td>
</tr>
<tr>
<td>Number of miscarriages</td>
<td>3.4</td>
<td>2.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Mean gestational age of miscarriages</td>
<td>7.90</td>
<td>7.62</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group I: endometritis; Group II: normal histopathology; NS: not significant.
Comparisons were made by using the Mann-Whitney U-test.

Stratification of the patients according to the mean gestational age of miscarriage did not produce any significant difference (Table 3).

Table 3. — Stratification according to gestational age of miscarriages.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt; 7 weeks</th>
<th>≥ 7 weeks</th>
<th>&lt; 10 weeks</th>
<th>≥ 10 weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark staining (%)</td>
<td>58.3</td>
<td>54.5</td>
<td>0.832</td>
<td>56.7</td>
<td>50</td>
</tr>
<tr>
<td>Endometritis (%)</td>
<td>25</td>
<td>25.8</td>
<td>1</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

Comparisons were made by using Fisher’s exact test. Significance was a p value < 0.05.

Discussion

Ultrasonography, sonohysterography, hysterosalpingography and 3D ultrasonography can all show uterine and corresponding endometrial anatomy. However, the presence of an endometrial lining does not assure normal endometrial function. Hysteroscopic visualization is recommended for a direct and closer look at the endometrium in RM.

Although RM is often defined as three or more consecutive pregnancy losses some investigators have included women with two miscarriages in their series [10, 11]. Weiss et al. compared hysteroscopic findings after either two or three miscarriages [12]. The rate of uterine abnormalities was not significantly different and hysteroscopy might be justified after two miscarriages. Women with two miscarriages were also included in the current study.

The role of infection in first trimester RM is controversial. Associates of RM with high titers of IgG antibody to chlamydia have been reported [13]. Summers reported that infection is an occasional cause of sporadic spontaneous miscarriage and, consistent with statistical probability [14]. La Sala et al. reported an incidence of 2% endometritis among 100 women with two consecutive IVF failures [15]. The incidence of endometritis in our series was higher and was likely related to better targeting of the biopsy by endometrial dying, and/or examination of the tissues by a dedicated gynecopathologist. Zeyneloglu et al. reported that observation of micropolyps in hysteroscopy was a significant predictor of miscarriage after IVF-ET [16]. Although the incidence of endometritis was not reported, patients were treated by ciprofloxacin when endometritis had diagnosed. Micropolypsis is a common finding in endometritis [17].

Local damage to the endometrium, as in incomplete Asherman’s syndrome, produces patchy fibrosis without a significant amount of intrauterine adhesions [1]. Endometrial responsiveness to steroid hormones is reduced in affected areas. Those areas contain defective endometrial cells which allow methylene blue into the cell. Removal of those areas leads to replacement by healthy cells and responsiveness is restored, and eventually successful implantation is achieved. This theory is supported by the study of Barash et al. [18] who showed that local injury to the endometrium significantly increased the pregnancy rate in IVF. It can be speculated that local injury induced by a biopsy catheter might have removed the defective endometrium to be replaced by a new cell line.

Japanese medicine is expertised in chromoendoscopy for the early detection of gastrointestinal premalign/malign diseases. The current study was inspired from their approach to enhance subtle mucosal changes. Conventional hysteroscopy has its limitations in evaluating endometrial cell integrity. Chromohysteroscopy increases the effectiveness of the intervention. Structural endometrial cell damage as indicated by dark staining was seen in the majority of recurrent early miscarriage cases. This might prevent either adhesion or invasion of a blastocyst into the decidua properly. The majority of dark stained areas were diagnosed as endometritis in pathological examination. It has been shown that local endometrial defects can cause miscarriage. It has also been shown that septal endometrium or endometrium covering a submucous fibroid responds suboptimally to steroid hormones and shows defective development [5, 19].

In conclusion, chromohysteroscopy improves the efficacy of hysteroscopy in RM cases. The results of this study indicate that chromohysteroscopy is warranted after three miscarriages in two cycles time. Gestational age of miscarriages does not affect the results. Larger studies are needed to draw stronger conclusions and probable routine use of endometrial dying.

References


CA 19-9 can be a useful tumor marker in ovarian dermoid cysts

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Summary

Purpose: To evaluate the importance of CA-19-9 as an aiding tool in the diagnosis of mature cystic teratomas.
Methods: We found 43 cases of dermoid cysts that were operated on at our clinic, and whose tumor marker CA 19-9 was studied before the operation.
Results: Thirty-seven of 43 patients (86%) had elevated CA 19-9 levels. Using Pearson’s correlation, the average diameter and weight of the tumor had a strong positive correlation with the level of CA 19-9 (p < 0.01). Thirty-one out of the 43 (72%) cases had a dermoid cyst in the right ovary, nine (20.9%) in the left ovary, and three (7%) had bilateral dermoid cysts. Right predominancy was very high among the patients (p < 0.05).
Conclusion: We suggest that besides ultrasonography and computed tomography, serum CA 19-9 level could be a useful tumor marker in the diagnosis of dermoid cysts.

Key words: Dermoid cyst; CA 19-9 level; Gynecological tumors.

Introduction

Mature cystic teratoma (MCT), also called dermoid cyst, is the most common ovarian tumor, which is composed of well-differentiated tissues derived from the three germ cell layers (ectoderm, mesoderm, and endoderm) [1]. MCTs account for about 10-20% of all ovarian tumors and are mainly found in young women of reproductive age [1, 2].

The Lewis histo-blood group antigens Lewis a (Lea) and Lewis b (Leb) are carbohydrate structures that form epitopes on glycolipids and glycoproteins. The tumor marker, CA 19-9, which recognizes the sialylated Lea carbohydrate structure [3], has been used mainly for serological diagnosis and follow-up of gastrointestinal and pancreatic malignancies [4-7]. Currently, CA 19-9 is regarded as the most sensitive and specific marker in the diagnosis and follow-up of pancreatic cancer [4]. Additional associated malignancies are biliary tract, colon, esophageal, and hepatic cancers. However, the interpretation of CA 19-9 can be difficult because about 5-7% of the population that are Lewis-negative do not produce CA 19-9 and have undetectable concentrations of CA 19-9 regardless of the tumor mass, and several nonmalignant diseases like pancreatitis, biliary disease, cirrhosis have been associated with increased serum concentrations of CA 19-9 [4]. The level above which benign disease is unlikely is > 1,000 units per ml [4].

The relationship of CA 19-9 with ovarian dermoid cysts is not well established. The current data are insufficient and include few trials and mostly case reports [1, 8-10].

The aim of our study was to investigate the clinical value of CA 19-9 in ovarian dermoid cysts and to evaluate the average size, weight, and bilaterality of the tumor.

Materials and Methods

We found 43 cases of dermoid cysts that had been operated on at the Obstetrics & Gynecology Department of Kahramanmaras Women’s and Children’s Hospital between January 2004 and September 2007, and whose tumor marker CA 19-9 was studied before the operation. CA 19-9 was analyzed with Immulite 2000 autoanalyzer (USA). This method depends on a solid-phase, two-site chemiluminescent immunometric assay procedure. Test interassay precision was 5.8% (CV).

We noted data from the reports of the patients as age, gravida, parity, average diameter and weight of the tumor, the site of the tumor (right or left ovary), bilateral, and the level of CA 19-9. The cutoff value for serum CA 19-9 was accepted as 37 U/ml and tumor size and weight were determined by the pathology reports. Dermoid cyst cases whose CA 19-9 level was not measured were excluded from the study. Data were classified by using the SPSS 11.0 statistical package program and Pearson’s correlations were made.

Results

Forty-three patients were included to the study. Mean age at the time of operation was 32.3 ± 8.1. Mean and median gravida and parity numbers, average tumor diameter, average tumor weight and CA 19-9 levels are shown in Table 1.

Thirty-seven out of the 43 patients (86%) had elevated CA 19-9 levels. Using Pearson’s correlation, the average diameter (cm), and weight (g) of the tumor had a strong positive correlation with the level of CA 19-9 (p < 0.01). Thirty-one out of the 43 (72%) cases had a dermoid cyst in the right ovary, nine (21%) in the left ovary, and three (7%) had bilateral dermoid cysts (Table 2). Right predominancy was very high among the patients (p < 0.05).

CA 19-9 levels were elevated in patients who had bilateral MCTs (3/3). Elevation was observed in 85% of the unilateral dermoid cyst cases (34/40). This rate was...
higher in bilateral cases than unilateral ones (100% vs 85%), but the difference was not statistically significant (p > 0.05). Elevation rate of CA 19-9 for right and left side tumors was similar (p > 0.05) (Table 2).

**Discussion**

Dermoid cysts are the most common ovarian tumor, but there are few reports about tumor markers which are useful in the preoperative diagnosis [1]. Case reports of dermoid cysts of the mediastinum [11-16], adrenal gland [17], greater omentum [19], brain [20], and cervical area [21] with elevated serum or cyst fluid CA 19-9 levels have been published.

In some gynecologic tumors, especially ovarian dermoid cysts, elevated levels of CA 19-9 have been published. In some gynecologic tumors, especially ovarian dermoid cysts, elevated levels of CA 19-9 have been shown in a few trials [1, 8, 21, 22]. The mean age of the patients in the present study was 32.3 years which was similar to the literature [22].

In our study 31 (72%) cases had a dermoid cyst in the right ovary, nine (21%) in the left ovary, and three (7%) had bilateral dermoid cysts. Right predominancy was significantly high in our study (p < 0.05). Dede et al. [22] found the bilaterality rate to be 27.5% (22/80) which was higher than in our study.

Comerci et al. analyzed 517 cases of MCT and reported that the mean tumor size was 6.4 cm [23]. Kikkawa et al. reported the mean size of 92 MCTs as 8.8 cm [1]. Dede et al. found the mean tumor size of 80 cases to be 7.2 cm [22]. In our study the mean tumor diameter was 7.7 cm.

Kikkawa et al. found the mean level of CA 19-9 in ovarian dermoid cysts to be 217.6 U/ml in their trial which included 71 cases [1]. Ingec et al. reported a case of huge fallopian tube teratoma with elevated CA 19-9 [24]. Kikkawa et al. investigated 92 patients with MCT, and found that CA 19-9 was the only marker with the mean level above the cutoff value [1]. The ratio of CA 19-9 elevation among patients was found as 59% (42/71).

Kawai et al. and Mikuni et al. both reported elevation of CA 19-9 in nearly half of their patients [10, 25].

Ito et al. measured serum levels of CA 19-9 in 250 patients with MCTs, and they found 31 patients with serum CA 19-9 levels over 101 U/ml [26]. Dede et al. found CA 19-9 elevation in 31 out of the 80 patients (38.8%). The mean value of CA 19-9 was 101.2 in their report [22]. In our study the mean level of CA 19-9 was 109.1 and the ratio of the patients with elevated CA 19-9 was 86% which is the highest value reported in the English literature. Our study supports the findings of Dede et al. in the similarity of mean CA 19-9 levels, but we found a higher ratio of patients with elevated CA 19-9 which might be related to the geographical and socioeconomic differences between the regions where the studies were conducted.

Dede et al. [22] found an elevated ratio of CA 19-9 in bilateral cases of 73% (16/22), but we found this ratio to be 100% (3/3). However our sample size was not sufficient enough to comment on this data.

**Conclusion**

Being the most common ovarian tumor, mature cystic teratoma is a real problem for women of reproductive age. The preoperative diagnosis of this entity is an important issue and may give some clinical points to the surgeon before the surgery. Our study showed that serological preoperative diagnosis of this disease is possible. We suggest that in addition to ultrasonography and computed tomography, serum CA 19-9 levels could be a useful tumor marker in the diagnosis of dermoid cysts as a supporting diagnostic tool.

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CA 19-9 can be a useful tumor marker in ovarian dermoid cysts


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Neurofibroma of the vaginal wall

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Summary

Background: Von Recklinghausen’s disease is characterized by cutaneous manifestations but it is a systemic disease which may affect the genitourinary tract. Case: A 20-year-old woman with a history of type-1 neurofibromatosis attended our center due to a vaginal nodule. Surgical treatment consisted of an incisional biopsy of the nodule. The anatomopathological diagnosis was plexiform neurofibroma. Conclusion: Periodical check-ups are recommended in asymptomatic vaginal neurofibroma whereas its radical excision should be avoided as such surgery is highly aggressive.

Key words: Vaginal neurofibroma; Genital neurofibroma; Neurofibromatosis; Vaginal nodule.

Introduction

Von Recklinghausen’s disease or type-1 neurofibromatosis (NF1) is a hereditary disorder of autosomal dominant transmission that affects 1 in 3,000 people. It is characterized by a mutation of the NF1 gene and its main phenotypic feature is the presence of multiple skin neurofibromas and café-au-lait spots. Neurofibromas may affect any organ of the body, including the cardiovascular system, gastrointestinal tract and larynx [1]. Genitourinary involvement is less common, the bladder and vulva being the organs most often affected [2]; however, a few cases of vaginal involvement have been described [3-5].

This paper presents the findings from a single case and describes the typical features of neurofibromatosis (NF), an uncommon systemic disease, which nevertheless may be seen among women attending a gynecology clinic.

Case Report

A 20-year-old woman with no remarkable family history came under our care. She had menarche at 12 years of age with normal menstrual cycles. The patient had never had a gynecological check-up but had been diagnosed at ten years of age with type-1 NF; the genetic test was positive. The rest of her family tested negative. The patient presented skin manifestations (café-au-lait spots and a cutaneous neurofibroma on her chest), but without ocular involvement. She brought along the results of a cranioencephalic magnetic resonance imaging (MRI) scan performed seven years previously, which showed a homogeneous myometrial pattern; the adnexa were normal. However, in the upper third of the vagina, toward the left of the central area, there was a well-circumscribed and encapsulated nodule (probably intramural) measuring 47 x 41 x 27 mm which appeared not to be affecting the bladder or cervix. A color Doppler study showed the nodule had minimal vascularization. MRI also revealed an intramural vaginal tumor with irregular contours localized on the anterior wall of the vagina. This mass, which measured approximately 7 x 4 x 2 cm and extended from the vaginal dome to the vulvar region, was predominantly hypointense in T2 with small foci of greater intensity on the inside. No vesical involvement was observed (Figures 3 and 4).

The clinical diagnosis was an adenomyotic nodule versus neurofibroma with compromised micturition, and it was thus decided to intervene surgically. An incisional biopsy was performed, the outer portion of the tumor being excised by means of a wedge resection using the cold scalpel technique; the edges were then brought together and the urethra checked for permeability (Figure 5). The patient presented no post-operative complications.

Anatomopathological findings confirmed the diagnosis of plexiform neurofibroma.

The patient is currently being followed-up annually and has shown a satisfactory clinical evolution, and the micturition problems have disappeared.

Pathological anatomy

The macroscopic findings showed an irregular specimen consisting of shiny, moist tissue, light yellowish-gray in color, with a weight of 3 g and measuring 3 x 1.5 x 1 cm. Histopathological study using hematoxylin-eosin stains revealed a tumor consisting of tortuous nerve bundles and a plexiform pattern. The fibers presented mixoid changes of multiplex formal pattern. The fibers presented mixoid changes of multiplex pattern.
tifocal origin. These plexa were surrounded by NF tissue showing fusiform cells. No atypias or other signs of malignancy were found (Figure 6). The lesion was observed to be partially covered by normal vaginal mucosa and was in extensive contact with the resection margin. In terms of immunohistochemistry, the cells from the nerve plexa as well as some from the surrounding tissue expressed the S-100 protein. The diagnosis was a plexiform neurofibroma of the vaginal wall.

Discussion

NF is a hereditary disorder of the tissues derived from the neural crest, although tissues and organs of mesodermal origin may also be affected (2). It is characterized by the presence of progressive anomalies of the skin, central and peripheral nervous systems, skeleton, and internal secretion glands, and may occasionally affect other organs and systems such as the digestive, cardiovascular...
and genitourinary apparatus. Two types of NF have been described: type-1 neurofibromatosis (NF1) or von Recklinghausen’s disease, which affects 85% of patients, and type-2 or central neurofibromatosis (NF2), which affects 10-15%. Both types are the result of autosomal dominant inheritance with complete penetrance and variable expressivity, although 50% of cases are due to de novo mutations.

The NF2 gene is located on chromosome 22 and the disease is characterized by bilateral acoustic schwannomas in patients with little or no cutaneous signs of NF. However, patients with NF1 rarely develop neurinomas of the eighth cranial nerve [1].

NF1 affects one in every 3,000 people. Its gene is located on chromosome 17 and normally acts as a tumor suppressor gene encoding the protein neurofibromin, which is expressed in several tissues and functions as a negative regulator of intracellular ras-GTP signaling. The characteristic clinical features of the disease are café-au-lait spots and skin neurofibromas, which increase in size and number during childhood and especially following puberty. Extracutaneous manifestations occur in one percent of cases and are more likely to affect the bladder or the gastrointestinal tract [6]. Genital involvement is rare, the vulva and clitoris being the areas most commonly affected. The cardinal symptoms are highly variable, including metrorrhagia, dyspareunia and chronic pain, and depend, above all, on the area affected; thus, clitoral neurofibromatosis may be the cause of intersexual states [7]. The first case of vaginal NF was described by De Jorio and Belfiore in 1970 [3]. In recent years numerous cases of NF with vulvar or clitoral involvement have been reported, although the literature contains few reports of vaginal neurofibromatosis and those which have been published are not always related to NF1 [4, 5].

In our case the neurofibroma was NF1 and was confined solely to the vagina, with the only effect being alterations to micturition.

It is not usually difficult to diagnose a neurofibroma in a patient with skin neurofibromas and café-au-lait spots. Although US is usually the first imaging technique used to study the pelvic region, both computed tomography (CT) and MRI scans are necessary to accurately define the characteristics of the nodule and its limits. MRI is preferable to a CT scan as it offers a multi-plane view and is able to differentiate tissue; it is also useful for characterizing lesions and determining the extent of a tumor.

The current diagnostic criteria for NF1 are those approved in 1988 by the NIH Consensus Development Conference [8]. The differential diagnosis of a vaginal nodule includes adenosis (due to the mother being exposed to diethylstilbestrol or post-treatment of a condylomatosis with 5-fluorouracil), polyps, leiomyomas, rhabdomyomas, hemangiomas, neurofibromas and malign tumors (rhabdomyosarcoma, adenocarcinoma) [9].

The treatment for cases of genitourinary neurofibromatosis has yet to be established and may be conservative or surgical depending on the extent of the disease and the clinical features. Neither radiotherapy nor chemotherapy has proved beneficial [2].

As there is malign degeneration in approximately five percent of people with NF1 [2], it is necessary to perform a biopsy in those patients where this is suspected. In our case, an incisional biopsy was performed to confirm the diagnosis of neurofibroma and treat the altered micturition. After surgery the patient evolved favorably and the micturition problems disappeared. Complete excision of a vaginal neurofibroma requires highly aggressive
surgery and recurrence is common. Therefore, in asymptomatic women the advice is to monitor the situation through periodic check-ups involving a pelvic US and MRI to detect possible changes in the characteristics and size of the tumor.

In sum, the diagnostic procedures to be used when faced with a vaginal nodule are, firstly, a pelvic US (either vaginal or abdominal), followed by MRI to characterize and determine the extent of the tumor. When a vaginal neurofibroma is diagnosed, strict monitoring through imaging tests every six months is recommended in asymptomatic women to detect any changes in tumor consistency and size. If there is suspicion of malignancy or symptomatology it is advisable to perform an incisional biopsy to determine the diagnosis and resolve the clinical signs. However, radical excision of a vaginal neurofibroma should be avoided as such surgery is highly aggressive and does not offer significant benefits (neurofibromas frequently reoccur). Moreover, it may cause serious postoperative problems including painful hypersensitivity in the area of the incision, possible damage to nerve endings leading to hypostesia, and even constrictions which may hinder future sexual relations.

References


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Mucinous cystadenoma in a female patient with 45,X/46,XY karyotype

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Summary

The mosaic karyotype of 45,X/46,XY has a wide phenotypic spectrum and there are substantial differences between prenatally and postnatally diagnosed cases. The phenotype varies between normal male to classical Turner syndrome. There is a high risk of gonadal tumor development in the dysgenetic gonads of patients with sex chromosome mosaicism. We report a case of a 24-year-old patient with a pelvic mass and amenorrhea referred to our laboratory for karyotyping. Peripheral blood chromosome analysis showed a mosaic karyotype of 45.X[17]/46,XY[83]. The tumor originated from the left ovary and the right ovary was found to be a streak gonad. The uterus was intact. Pathologic examination of the tumor revealed mucinous cystadenoma. Physical examination of the patient showed signs of Turner syndrome, as short stature (145 cm), short neck and asymmetric shoulders. Her mental state was normal. Y chromosome microdeletion screening involving SRY and ZFY genes was performed and no deletion was found. The patient was informed about the condition during the genetic counseling session.

Key words: Mucinous cystadenoma; Chromosomal mosaicism; Turner syndrome.

Introduction

Numerical abnormalities of the sex chromosomes are among the most frequent abnormalities cytogeneticists encounter during routine studies. Among these, cases with sex chromosome mosaicism are probably the most heterogeneous condition. Especially in postnatally diagnosed cases of 45, X/46,XY mosaicism is well-known to exhibit a wide spectrum of phenotypes, ranging from typical Turner syndrome to normal male [1].

Mosaicism is defined as the presence of two or more cell lines in the same individual. In most cases of 45, X/46,XY mosaicism, the cause is considered to be the loss of the Y chromosome by nondisjunction after normal disomic fertilization [2]. Gonad tissues have been studied in these patients, as mosaicism in the lymphocytes does not always display the same percentage in the gonads [3]. Whatever the phenotype, the presence of the Y chromosome is considered as an indicator of increased risk for the development of tumors in the dysgenetic gonads.

Case Report

A 25-year-old woman with a pelvic mass and amenorrhea was admitted to the Gynecology Department of our university hospital for diagnostic procedures. She was a twin, had another pair of older twin sisters and two younger brothers. Her parents were non-consanguineous and pedigree analysis was noncontributory. She was 145 cm tall and weighed 60 kg. She had a short neck and asymmetric shoulders. Pubic hair was present and the breasts were normal in size. Her mental state was normal and she had attended university. Her twin sister appeared normal and had no complaints.

The patient had primary amenorrhea and the pelvic mass was found to have originated from the left ovary, thus first suspected to be dysgerminoma. During surgery, the uterus was visualized and the right ovary appeared as a streak gonad (Figure 1). Left salpingo-oophorectomy was performed and pathological examination of the tumor revealed mucinous cystadenoma (Figure 2).

Concurrently, the peripheral blood of the patient was sent to our laboratory for chromosome analysis. Lymphocyte cultures were set up and analysis of the G-banded chromosomes revealed a 45,X/17 46,XY/83 karyotype. Fluorescence in situ hybridization was performed with CEPX-Y probes (chromosome X (DXZ1), chromosome Y (DYZ3) cocktail probe (Kreatech) to confirm the presence of Y chromosome material. In addition, Y chromosome microdeletion screening involving SRY and ZFY genes was carried out and no deletion was found. The presence of a XY cell line was demonstrated in the tumor tissue as well by FISH analysis with CEPX-Y probes of paraffin-fixed samples from the cystadenoma, though with a lower ratio (36% X, 64% XY) (Figure 3).

The patient was informed about her karyotype in a counseling session and was referred to different departments for further examination. Her hormone profile showed hypergonadotrophic hypogonadism (FSH: 48.14 mIU/ml, LH: 16.28 mIU/ml, E2: 17 pg/ml). She was offered gonadectomy and allowed time for her decision on request.

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Mucinous cystadenoma in a female patient with 45,X/46,XY karyotype

**Discussion**

Mosaic individuals with 45,X/46,XY karyotype manifest a variety of gonadal dysgenesis phenotypes; the external genitalia may be female, male or ambiguous. Most patients with female external genitalia are clinically indistinguishable from Turner syndrome, while some are tall in stature, some may manifest virilization and some show no somatic abnormalities. After karyotyping, further studies like FISH or PCR are suggested especially for these patients, to demonstrate the presence of Y chromosome material [4-6]. This is of utmost importance in terms of approximately 20% risk of ovarian tumor development, especially gonadoblastoma [4]. Neoplasia often develops in the first and second decades of life and is thought to be caused by a cancer predisposing locus on the Y chromosome (gonadoblastoma) [7-8]. Currently it is recommended to perform an ovariectomy in these patients [8].

Mucinous neoplasms of the ovary are classified to surface epithelial tumors and may be grouped into benign, borderline or malignant categories depending on their histopathologic features. Approximately 80% of these tumors are cystadenomas, which are usually large, multicystic, characteristically unilateral and benign [9]. These tumors often are heterogeneous and may contain borderline or malignant elements. They are not expected to recur after being surgically removed, though malignant transformation has been described as a sequential process [9].

The case reported here had an unusual type of tumor development in the ovary which led to the diagnosis of the sex chromosome mosaicism she harbored. Mucinous cystadenoma has rarely been reported in patients with Turner syndrome or 45,X mosaic patients with a structurally abnormal Y chromosome [10-13]. To our knowledge this is the first report of mucinous cystadenoma in a patient with 45,X/46,XY karyotype.

The patient’s contralateral ovary was a streak gonad; the chromosome constitution of this tissue has not been studied since the karyotype was determined after surgery and the patient has not yet decided to undergo a second operation.

Streak gonads of some 45,X/46,XY mosaic individuals were found to contain a homogeneous 45,X complement, thus the absolute necessity for gonadectomy is being argued [3]. These authors deduced that absence of the Y chromosome in the gonad would reduce the probability of neoplasia and suggested further extensive studies to better determine the risk before surgery. The proportions of cell lines in different tissues of a patient may determine their normal or abnormal development; therefore gonad karyotyping seems to be valuable in this context.
Conclusion

The association of the presence of Y chromosome in 45,X individuals and gonadoblastoma formation has been studied and is thought to be a mechanism of oncogene activation on Y [8]. The development of a benign cystic tumor in this patient, though unexpected, may be attributed to the Y chromosome, as the tumor was also shown to contain Y chromosome material.

References


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Secondary amenorrhea with normal ovulatory cycles in a young virgin with normal follicle stimulating hormone levels – a case report

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Summary

Purpose: To determine if normal ovulation is possible despite amenorrhea in the absence of any obvious uterine abnormalities or adhesions. Methods: The study was conducted on a 17-year-old virgin with normal sexual development and normal secondary sexual characteristics whose menarche was at age 12 but whose menses ceased after two menstruations. She was first treated with medroxyprogesterone acetate 10 mg x ten days and then a cycle of oral contraceptives. Results: She failed to get menses following progesterone (P) withdrawal and following a cycle of oral contraceptives. All of her pituitary function studies were normal. Her serum follicle stimulating hormone (FSH) was 3 mIU/ml, luteinizing hormone (LH) 9 mIU/ml, estradiol (E2) was 107 pg/ml and the serum P was 3.9 ng/ml. These values were consistent with recent ovulation. However menses failed to ensue. Conclusions: This case confirms that in humans, similar to some non-primates, ovulation is possible without shedding the endometrium. Possibly she lacked spiral arterioles similar to ovulating mammals. Her virginal introitus and lack of any serious febrile illness made Asherman’s syndrome highly unlikely. Her normal menstrual cycle at age 12 not only excluded a Mullerian abnormality or imperforate hymen but led to speculation as to whether anovulatory bleeding from unopposed estrogen was possible but that somehow the presence of P inhibited the endometrial shedding process. In contrast to a previously reported study, this young woman almost had primary amenorrhea whereas the former case had more menses during her life but they ceased shortly after age 30.

Key words: Secondary amenorrhea; Ovulation; Normal uterus.

Introduction

Some animals, e.g., rabbits, sheep, and hamsters have hypertrophy of the luminal epithelium in response to estrogen followed by degeneration of the epithelium in response to estrogen and progesterone (P) exposure [1]. However, they do no menstruate because the atrophy of the endometrium is completely related to apoptosis of the cells [1]. From a histologic standpoint these animals lack the spiral arterioles that are responsible for the menstrual flow in primates.

A previous case was described of a 35-year-old woman who had developed secondary amenorrhea four years prior and in the year before treatment had only three episodes of “spotting” for two hours [2]. Her evaluation revealed that she was having evidence of normal ovulation but no menses. Hysteroscopy showed no evidence of scar tissue and she gave no history of any previous surgical procedures of the uterus or uterine cavity, or pelvic infections. Artificial estrogen followed by progestin therapy failed to induce menses. There was evidence that she had normal estrogen and progesterone receptors in the endometrium because an endometrial biopsy taken seven days after ovulation showed appropriate secretory changes [2]. The exact mechanism of why she developed secondary amenorrhea was not known but it was pondered whether it had something to do with fewer ovarian follicles since she was documented to have elevated serum follicle stimulating hormone (FSH) when the serum estradiol (E2) was < 50 pg/ml on three separate occasions [2]. In fact, she had been misdiagnosed by another physician as having premature menopause.

We present another case of secondary amenorrhea but in this case the secondary amenorrhea developed in a teenager with normal serum FSH and after having only two menstrual periods, which were most likely anovulatory.

Case Report

A 17-year-old female presented with secondary amenorrhea. She had normal sexual development and her menarche had started at age 12. After her very first menstrual cycle she had another one a month later but no menses since that time.

There was a lot of family stress at that time so her lack of menses over the next several years was attributed to a psychogenic amenorrhea from anovulation. However at age 17 she was given medroxyprogesterone acetate for ten days but she failed to get her menses with the withdrawal of the drug. A cycle of oral contraceptives with 35 μg of ethinyl estradiol also failed to induce menses.

She was then referred for evaluation. Upon examination there was a virginal introitus and she preferred to forego a pelvic examination or ultrasound. She did have adult-type secondary sexual characteristics. The following serum hormonal evaluations were obtained to check her pituitary functions: free thy-
roxin (T4) – 1.10 ng/dl (nl 0.83 to 1.44), thyroid stimulating hormone (TSH) – 0.92 uIU/ml (nl – 0.360 to 5.8), cortisol – 9.9 ug/dl (nl – 3.1 to 22.4) and her prolactin level was 18.8 ng/ml (nl 2.8 to 29.2).

She denied having monthly menses and any monthly abdominal pain or abdominal pain in general. Her serum E2 on the day of evaluation was 107 pg/ml, serum P was 3.9 ng/ml, serum FSH was 3 mIU/ml and her LH was 9 mIU/ml. These values were consistent with recent ovulation. However she once again failed to get spontaneous menses.

A repeat of her serum E2 and P and FSH taken 18 days later found a serum E2 of 47 pg/ml, P of 0.2 ng/ml, and the serum FSH was 3 mIU/ml.

Discussion

In a search of the world literature we could not find another case of amenorrhea despite ovulation and absence of Asherman’s syndrome since the one published in 1989 [2].

Though the first case was better studied including hysteroscopy and endometrial biopsy it left a few questions. One was whether this phenomenon could somehow be related to the decrease in egg reserve in the previous case as manifested by a high serum FSH.

In contrast this teenager had a perfectly normal serum FSH when the serum E2 was low. Sometimes a woman can have a heterophile antibody leading to a false increase in serum hormonal levels but this was not the case since her serum P dropped down to 0.2 ng/ml [3].

The first two periods of a young woman’s life are generally anovulatory. Clearly nothing happened from a physical standpoint to this young virgin, e.g., pelvic infection, undisclosed therapeutic abortion, D&C, etc. Whether the initiation of ovulation and the type of histologic changes that occur may provide a clue to this strange condition remains to be seen. This case is much closer to being the first report of primary amenorrhea despite normal ovulation in the absence of endometrial adhesions or Mullerian abnormalities. The fact that she did have two spontaneous menses at age 12 and does not have abdominal distention or cyclical abdominal pain fairly well excludes mullerian dysgenesis or an imperforate hymen.

Her history raises the question as to whether breakthrough bleeding by continuous estrogen exposure might be possible but that somehow changes induced by the progesterone thwart shedding of the stratum functionalis.

To prove that ovulatory amenorrhea is not due to the loss or down-regulation of estrogen and progesterone receptors could be easily determined in a non-invasive manner via ultrasound, by watching the endometrium thicken (an estrogen-related event) and then looking for the architectural changes induced by P (homogeneous hyperechogenic pattern) in the mid-luteal phase [4, 5]. Admittedly it would be best accomplished by transvaginal ultrasound which would not be possible because of her virgin status, but we thought possibly transabdominal sonography might also give us this information. However, the patient preferred not to even attempt this by transabdominal ultrasound at the time because of a previous traumatic experience [4, 5].

Bartelmez concluded that a marked reduction in the thickness of the endometrium is primarily due to loss of fluid and the resulting collapse of the corpus spongiosum [6]. McLennan and Rydell concluded that in most cases an appreciable fraction of the stratum spongiosum actually disintegrates but endometrial tissue superficial to the basal layer remains in situ at the end of menstruation [7]. They also concluded that endometrial tissue shedding is less extensive than many believe it to be and that the amount of shedding varies widely from one uterus to another [7].

It could be speculated that for some reason this young woman lacks spiral arterioles similar to non-primates and thus does not get a menstrual flow. However these animals are fertile. It remains to be seen in the future if this lack of endometrial shedding will be associated with infertility or not.

References

Tuberculosis of the cervix and infertility: report of a rare case

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Summary

Tuberculosis is a frequent bacterial infection in less developed countries. Lung and lymph node localisations are common, while the genital apparatus is less involved. In this work a rare case of cervical tuberculosis followed by some lesions causing infertility in a 20-year-old woman is reported. The diagnosis was confirmed by a histological examination from a biopsy of the cervix. The patient was offered six-month antituberculosis therapy which eliminated the cervical lesions. A few years later she came under our care for infertility due to uterine adhesions diagnosed by hysterosalpingography. Now the patient is being treated for infertility complicated by amenorrhoea.

Key words: Tuberculosis; Cervix; Infertility.

Introduction

Tuberculosis (TB) is a bacterial infection, particularly frequent in less developed countries where it rages in an endemic state. Through the years a substantial reduction in its incidence has been observed, but with the outbreak of the HIV/AIDS pandemic, there has been a recrudescence of TB, particularly in non-traditional sites. While pulmonary and lymph node localisations are frequent, an internal genital localisation is still rare: 2.5% to 7.7% according to different authors [1-4].

The aim of our work was two-fold:
– To describe a rare case of genital TB, by stressing the pitfalls that can present with cervical lesions.
– To reexamine, in light of the mainstream literature, the characteristics of this localisation, disease management, and factors influencing the prognosis.

Case Report

The 20-year-old unemployed patient, had been examined in January 2001 by the Service of Gynaecology of CHU Treichville (Abidjan-Ivory Coast) for vaginal bleeding of three months’ duration.

Physical examination showed absence of sexual intercourse, and the general examination highlighted weight loss (height 1.58 m-weight 48 kg), and clinical anaemia confirmed by bioas say (rate of haemoglobin to 9.8 g/dl).

Gynaecological examination revealed a budding cervical tumour of the cervix which was friable and bleeding on contact. Rectal examination found a normal sized uterus with supple parameters and rectovaginal wall.

Ultrasoundography (US) of the pelvis revealed an empty uterus of regular size and echo-structure. While the left ovary was normal, the right ovary contained a transonic formation with posterior reinforcement compatible with an organic cyst, measuring 52 x 49 mm. The right ovary measured 65 mm. The Douglas pouch was free of fluid. Pulmonary radiography and HIV serology showed normal values. Given the data cancer of the cervix was suspected.

Biopsy samples of the cervical tumour were collected and analysed. The typical histological aspect indicated cervical tuberculosis (Figure 1).

Medical treatment, based on antitubercular medications (rifampicin, isoniazide, pyrazinamide), was administered for six months by the Pneumology Department.

The evolution was favourable characterised by:
– rapid improvement of the overall condition.
– interruption of the bleeding after two months of treatment.
– a normal gynaecological examination (apparently healthy cervix) after six months of treatment.

The patient was discharged and readmitted six years later, at the age of 26, for infertility with amenorrhoea.

US examination of the pelvis was normal. Hysterosalpinography showed widespread adhesions of the uterus with fallopian tube involvement.

Hysteroscopy could not be done because the Gynaecology Department did not have the appropriate equipment.

The patient’s infertility is presently being studied.

Discussion

The literature review revealed that cervical tuberculosis has been the topic of a limited number of publications, which suggests the existence of a limited number of cases. The cervical localisation of this pathology is found with a frequency ranging from 2.5 to 7.7% for uterine lesions [1-4]. The frequency of genital TB is probably underestimated due to the fact that it normally spreads in endemic forms in less developed countries, but also because latent forms are frequent [1].
In developing countries this pathology usually affects sexually active young women in 72% of the cases [1, 2, 3, 5], while in developed countries genital TB is mainly found among older women, in 62% of the cases [1]. In our case the patient was just past adolescence (20 years).

Concerning the diagnosis, the literature review showed that the clinical signs revealing a cervical localisation of tuberculosis are not highly specific. Besides the pseudotumor presentation (most frequent), vegetating or papillary TB, milia TB (yellow and translucent granulations), interstitial TB (cervix penetrated in all its thickness by granuloma) and TB with intracervical polyps have also been described [1, 6, 7].

In our case all the signs – spontaneous vaginal bleeding, a budding cervical tumour, and bleeding on contact made us suspect cancer of the cervix. The diagnosis was obtained by histological study of a biopsy which highlighted the typical damage of cervical TB, like granuloma lymphocytes with giant multinucleate cells (Langerhans cells) associated with a central caseous necrosis.

Although this type of damage can also be found in other benign pathologies such as venereal granulomatosis, sarcoidosis, schistosoma and in reactions to external substances, its presence justifies the immediate administration of treatment without waiting for the certainty obtained through direct examination or after culture that highlights Mycobacterium tuberculosis [1].

In our case the clinical improvement after the beginning of the “trial” treatment confirmed the successive diagnosis. The extension of diseases estimated by pulmonary radiography and abdominal US resulted negative. Hysterosalpingography, carried out six years after the treatment, highlighted the lesions of the uterine cavity because the patient reported no sexual relations and did not present signs of defloration.

In our case, the medical treatment containing antitubercular medication led to an improvement in the state of the cervix with complete recovery after six months.

In genital localisations of tuberculous lesions, especially when the fallopian tubes are involved, the prognosis is characterised by infertility (44%) requiring reproduction techniques (ART) [1].

Sterility can be irreversible (from 10-15%) in case of widespread uterine lesions as intrauterine adhesions responsible for primary or secondary amenorrhoea, like in our patient.

Our case suggests that the patient would benefit from ART after treatment of the uterine adhesions, however due to the high cost of this technique in contrast to its poor results the situation is difficult [7].

### Conclusion

In less developed countries, cervical lesions in young women should lead to the consideration not only of cancer, but also TB of the cervix, even though this localisation is rare.

The diagnosis is provided in the majority of cases by cervical biopsy which makes it possible to start medical treatment containing antitubercular medications.

In young patients the prognosis is characterised by an elevated risk of infertility due to an complete attack on the genital tract.

### References


Irregular dental structures in a benign ovarian cystic teratoma (dermoid cyst): case report

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Summary

Mature cystic teratomas, often referred to as dermoid cysts, are the most common germ cell tumors of the ovary in women of reproductive age. The gross pathologic appearance of a dermoid cysts is characteristic. Hair follicles, skin glands, muscle, and other tissues lie within the cyst wall. We present a case of a dermoid cyst ovarian tumor in a 24-year-old patient with a tooth lying on each wall. The mass was laparoscopically removed by ovarian cystectomy.

Key words: Ovarian dermoid cyst; Teeth; Cyst wall.

Case Report

A 24-year-old woman, gravida 0, para 0, presented with a painful lower abdominal mass of eight months duration. She reported that she often went to the emergency department with the following complaints: sharp lower abdominal pain associated with anorexia, nausea, malaise and occasionally bloody stools. The abdominal pain was noted to be increased in the mid cycle. Her last menstruation was associated with moderate abdominal pain for the first three days, but she had a normal menstrual pattern with no vaginal discharge or bleeding. In the last two months she noted dyspareunia. She had no past medical history, no systemic symptoms, no previous operations, and took no medications. Her vital signs were normal with a body temperature of 36.8°C. On the tenth mid cycle the young woman was hospitalized with recurrent abdominal pain of low to moderate intensity. The gynecological examination was unremarkable except for the left lower abdominal quadrant. She had localized rebound tenderness in this area. A pregnancy test was negative. Her blood chemistry showed no abnormality and the serum levels of CA125 were within normal range. Transvaginal sonography (TVS) was performed and showed the presence of a large inhomogeneous cystic mass 6 cm in diameter in the left ovary with numerous round, intensely hyperechoic and hypoechoic masses contained within. Doppler assessment showed the presence of normal blood flow to both ovaries. The contralateral ovary showed the classic appearance of a polycystic ovary. During the laparoscopy that ensued the following findings were noted: 1) One cyst 6 cm in size was located in the left ovary and had the appearance of an unruptured dermoid cyst, free of vegetation and macroscopically unsuspicious; 2) Soft pelvic adhesions between the left tube and bowel; 3) The right ovary had the classic image of polycystic ovary; 4) The rest of the pelvis was otherwise normal.

Initially, the surgery was performed by tubal sigmoidal adhesiolysis and puncture of the ovarian tumor followed by removal of the bulge of the cyst as well as the solid cystic elements. The cystic mass was full of sebaceous material and the wall was lined by hair follicles, skin tissue and intraoperatively in the marginal area of the tumor two developing teeth were observed (Figures 1 and 2). The cyst contents were aspirated with a 10-mm aspiration device and the bulge of the cyst was enucleated completely using a 10-mm trocar device. The cyst was removed and sent for histological processing. Subsequently, the abdominal cavity was washed once more with sodium chloride solution (about two liters) at body temperature. Bipolar cautery was used for hemostasis and the rest of the left ovarian bed with normal ovarian tissue was not sutured.

The following chromoprerturbation was normal without resistance in either tube. Both fallopian tubes were inspected and found to be normal. A specific antiadhesions agent was used and placed intraoperatively into the left ovary. Particular attention was paid to carefully close the fascia and abdomen positions of the trocar incisions to avoid hernia development, incarceration of the small intestine, and local infections. A drainage was put into the Douglas pouch. The total duration of the operation was 90 minutes. All the extracted material was submitted for histopathological examination.

Postoperative histologic examination confirmed the preoperative suspicious diagnosis of a benign cystic teratoma (dermoid cyst) and showed an essentially normal formation of two dental structures. The teeth were closely situated near the cyst wall. Macroscopic examination of the teeth showed that they were premolars in form. The teeth did not change the cystic shape of the tumor. The macroscopic view of the teeth seemed to be normal and they appeared similar. However the histological examination showed several anomalies which affected the different mineralized dental tissues such as enamel hypoplasia and irregular cementum growth. The patient had an uneventful postoperative course and was released from the hospital two days after the operation. The first follow-up examination was scheduled three months postoperatively.

Discussion

Cystic teratomas are congenital tumors that contain derivates of all three germ layers. 1) Teratomas make up 5-25% of ovarian tumors in women of reproductive age; 2) Dermoid cysts consist mainly of ectodermal tissue with some mesodermal and rare endodermal derivatives. Mesodermal elements, which include hair follicles and sweat glands on the wall of dermoid cysts, differentiate them from simple epidermoid cysts; 3) Understanding the
atypical imaging manifestations of mature cystic teratomas permits a more specific and accurate diagnosis. Usually dermoid cysts grow slowly at an average rate of 1.8 mm each year [4, 5]. They are usually unilateral, unilocular swellings up to 15 cm in diameter. Most dermoid cysts are asymptomatic. Abdominal pain or other nonspecific symptoms occur in a minority of patients [6, 7]. Tooth-forming ovarian teratomas provide a unique opportunity to observe the effects of the tumor environment on developing dental structures. These structures in ovarian teratomas are products of normal genetic/epigenetic events modified to a greater or lesser degree by unknown factors in the tumor environment. Most teeth are not distinctly deciduous or permanent but have intermediate shapes [8]. The frequency of also single teeth or calcifications in dermoid cysts has been variously reported (31%-56%) [9, 10]. The simultaneous appearance of two teeth in dermoid cysts has not been reported. Operative laparoscopy is the technique of choice to remove most, if not all, ovarian dermoid cysts [11]. Particular strategies have been suggested to safely and easily dissect the cysts totally. Experienced laparoscopic surgeons should consider laparoscopy as an alternative to laparotomy in the management of ovarian tumors in selected cases [12]. Laparoscopic treatment of ovarian dermoid cysts is a safe method, offering many advantages in comparison to classical surgery. However, proper early qualification, based on medical history, gynecological and sonographic examination is of great importance [13].

References

Prenatal diagnosis of type I sacrococcygeal teratoma and its management

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Summary

Purpose: To report a case of type I sacrococcygeal teratoma (SCT) diagnosed prenatally and managed surgically successfully in the neonatal period. Case report: A gravida 2, para 1, woman at 32 week’s gestation was referred for suspected fetal anomaly. On US a 14 x 12 cm mass with solid and cystic components was detected in the sacral region of the fetus. On MRI the tumor had no apparent intrapelvic or intraabdominal extent, indicating type I SCT. Cesarean section was performed at 34 weeks’ gestation due to signs of deteriorating high output cardiac compromise in the fetus. In the neonatal period stabilization of the infant was achieved. At age ten days the mass was successfully excised surgically. Conclusion: Prenatal determination of SCT, follow-up with sonography, time, and mode of delivery are indicative factors for prognosis in SCT.

Key words: Doppler studies; Magnetic resonance imaging; Prenatal diagnosis; Sacrococcygeal teratoma.

Introduction

Sacrococcygeal teratomas (SCT) have an incidence of 35,000 to 40,000 live births and are therefore the most common tumors in newborns [1]. The male to female ratio is one to four [1]. The course of SCT’s are ultimately associated with prenatal and perinatal complications. The majority of SCT’s have low morbidity and mortality when diagnosed prenatally and managed during the neonatal period [1]. However, a certain subgroup with a large, predominantly solid and highly vascular formation has a poor prognosis due to high output cardiac failure, fetal hydrops and intrauterine fetal demise [1].

Successful management of SCT cases depends on an accurate prenatal diagnosis and classification of the tumor, time of delivery, and mode of delivery. According to the literature, when SCT is diagnosed earlier than 30 week’s gestation its prognosis is generally poor [2].

We report a case of type I SCT diagnosed prenatally at 32 week’s gestation by (2D) two dimensional-ultrasound (US) and fetal magnetic resonance imaging (MRI) evaluations. The patient was successfully managed surgically and during the neonatal period.

Case Report

A 25-year-old woman, gravida 2, para 1, was referred to our clinic at 32 weeks of gestation for suspected fetal anomaly, polyhydramnios and preterm labor. On initial transabdominal 2D-US examination we detected a mass with solid and cystic components measuring 14 x 12 cm in the sacral region of the fetus (Figures 1 and 2). There was no evidence of fetal hydrops, placentomegaly, or polyhydramnios. We confirmed the gestational age with breech presentation consistent with 32 weeks of gestation and observed normal female genitalia. Thus we made a presumptive diagnosis of SCT.

Further detailed investigations were performed to establish a definite diagnosis. Color Doppler sonography showed that the mass was well vascularized, with normal fetal vascular flow. Fetal MRI revealed a clear presentation of the tumor (17 x 12 cm in diameter) and its relationship to the sacrum which was without apparent intrapelvic or intraabdominal extent indicating type I SCT (Figure 3).

Serial sonograms done by her previous doctor up to 30 weeks’ gestation demonstrated no anomalies. Furthermore, α-fetoprotein and F-βhCG testing at 17th weeks’ gestation revealed a low risk of Down’s syndrome, open neural tube defects and Trisomy 18 (1.30 multiples of median (MOM) and 1.45 MOM, respectively). The patient’s history was uneventful except for the Rh incompatibility.

The patient was hospitalized and monitored with serial US, fetal Doppler studies and fetal echocardiograms, and external fetal monitoring. To prevent preterm labor and enable lung maturity, sedation and hydration were done and a course of betamethasone was administered to the patient. On serial US at 33th weeks’ gestation signs of placentomegaly and polyhydramnios were detected. Furthermore, fetal echocardiography and Doppler studies revealed dilated cardiac ventricles and a dilated inferior vena cava. Tricuspid valve regurgitation was detected on fetal echocardiography (Figure 4). To reverse polyhydramnios one liter of amniotic fluid was aspirated and the fluid was checked for fetal lung maturity. After the amniodrainage Rh prophylaxis was carried out for the protection of the mother against Rh isoimmunization.

Since the fetus was showing signs of deteriorating high output cardiac compromise and the L/S ratio indicated a mature lung profile, we decided to perform a cesarean section. Cesarean section was done with midline abdominal and vertical uterine incisions to minimize trauma to the SCT during delivery. A female infant with a 17 x 10 x 14 cm SCT was delivered...
Figure 1. — Midline sagittal view of the fetus showing a sacrococcygeal teratoma.

Figure 2. — Axial view of the fetus demonstrating a sacrococcygeal teratoma.

Figure 3. — Prenatal MRI of the SCT.

Figure 4. — Severe tricuspid regurgitation in the 34-week fetus with SCT.

Figure 5. — Postnatal view of the female fetus with the SCT.
with Apgar scores of 4 and 6, at 1 and 5 min, respectively (Figure 5). The combined weight of the infant and the tumor was 3100 g. Maternal postoperative recovery was uncomplicated. At age ten days, the female infant underwent excision of SCT.

The pathologic examination confirmed this mass as a mature cystic teratoma. The postoperative course was uneventful.

Discussion

Sacrococcygeal teratoma is a germ cell tumor, comprising elements from all three germinal layers; endoderm, mesoderm, and ectoderm [3]. The majority of these tumors are usually fully differentiated, mature and benign, as in our case [3]. However, 4%-20% have malignant tissue at delivery [3].

The American Academy of Pediatrics Surgical Section has classified SCT according to the amount of presacral and external tumor present, stage and timing of diagnosis, ease of resection and malignant potential based on MRI findings: Type I (47%) is predominantly external, with a minimal presacral component as in the case presented; Type II (35%) is external with significant intrapelvic component; Type III (8%) is apparently external but predominantly internal; Type IV (10%) is completely internal [4].

US has proven to be an important tool in the diagnosis and surveillance of fetuses with SCT. Moreover, US can also aid in determining the timing and mode of delivery.

MRI is a valuable adjunct to US in providing crucial information for the definitive diagnosis. It provides better visualization of the skeleton and pelvic bones and better contrast between the cystic and solid components of teratomas, and delineates the intrapelvic extent [4]. In the presented case, MRI was instrumental in counseling the parents and in describing the lesion to them.

Color Doppler can identify areas of increased blood flow through the tumor mass [5]. Serial evaluation of fetal Doppler velocimetry studies, especially of the descending aorta and inferior vena cava is useful to search for signs of high output cardiac failure. In the present case the signs of deteriorating high output cardiac compromise detected on serial Doppler evaluation were one of the reasons for an urgent delivery.

In SCT cases alfa fetoprotein (AFP) levels may be elevated during the second trimester. However, in the literature maternal serum screening and amniotic fluid markers result in inconsistent findings in pregnancies complicated by SCT [6]. The use of AFP as a tumor marker in the follow-up is well established, and persistently elevated levels may indicate a residual tumor or recurrence as well as malignant degeneration [7, 8]. Triple test results were in normal range in our case.

Cases diagnosed after 30 weeks of gestation generally have a good prognosis. However, earlier detection of tumor prior to 30 week’s points out early occurrence and a rapid growing pattern of the tumor which causes arterio-venous communications that subsequently develop high output congestive heart failure, placen-tomegaly, polyhydramnios, fetal hydrops, and fetal demise [9]. The prognosis of SCT ultimately depends on the gestational age at diagnosis.

Planned delivery and postnatal surgery is the management of SCT especially after 30 weeks of gestation. Timing and mode of delivery is essential to avoid complications during delivery such as prematurity, tumor rupture and dystocia. Prognosis is best in the cases diagnosed after 30 weeks’ gestation without complications like congestive heart failure, placen-tomegaly, and polyhydramnios. If any of these complications are present on the following serial US examinations urgent delivery is necessary. In our case we detected these signs except for the fetal hydrops on serial US examinations.

Midline transabdominal and vertical uterine incisions should be performed since they minimize the trauma to SCT. After delivery, the tumor should be resected as soon as possible to avoid malignant degeneration, which we did in our case [10].

In conclusion, the indicative factors for improving the prognosis in SCT cases are accurate prenatal determination of SCT with US and MRI, close follow-up with sonographic and Doppler evaluations of the possible complications, and the mode and time of delivery.

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Uterus didelphys with blind hemivagina and ipsilateral renal agenesis complicated by pyocolpos and presenting as acute abdomen 11 years after menarche: presentation of a rare case with review of the literature

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Summary

Background: Congenital anomaly of the Müllerian duct system can result in various urogenital anomalies including uterus didelphys with blind hemivagina and ipsilateral renal agenesis. The diagnosis of this condition is usually made after menarche, but its rarity and variable clinical features may contribute to a diagnostic delay for years after menarche. Case: A 24-year-old woman presented to the emergency room of the Department of Obstetrics and Gynecology complaining of severe worsening lower abdominal pain, vomiting and pus-like vaginal discharge. Physical examination revealed acute abdomen with diffuse lower abdominal tenderness, rebound and muscular resistance. Cervical and vaginal observation was impossible because of the patient’s discomfort. Bimanual gynecological examination showed high tenderness cervical motion. Transabdominal ultrasound scan was performed and the radiologist interpreted the ultrasonographic findings as existence of a pelvic mass with mixed echogenicity. The preoperative diagnosis was ruptured tubo-ovarian abscess and emergency laparotomy was performed. Free pus in the pelvis was found. Also, a double uterus with an elongated and inflammatory right fallopian tube with pus passing out of its fimbrial end was observed. Vaginal examination under general anesthesia revealed an obstructed right hemivagina with vaginal pus-like discharge from a small fistula hole on the septate vagina. The final diagnosis was uterus didelphys with unilateral imperforate right hemivagina and pyocolpos. Transvaginal resection of the vaginal septum was performed and a large amount of pus and blood was spilled out. Postoperatively, intravenous pyelography demonstrated agenesis of the right kidney. Conclusion: We demonstrated the difficulty in making a correct diagnosis of this rare congenital anomaly of the female genital tract, especially after many years since menarche. This condition should be considered to prevent misdiagnosis or suboptimal treatment and decrease morbidity and unnecessary surgical procedures.

Key words: Pyocolpos; Uterus didelphys; Genital malformation; Urogenital abnormalities; Renal agenesis; Obstructed hemivagina

Introduction

Uterine didelphys with blind hemivagina and ipsilateral renal agenesis is an extremely rare congenital malformation of the female genitourinary system, occurring between the 12th and 16th week of gestation [1, 2]. In neonates, the obstruction of the blind hemivagina blocks the outflow of the cervical mucinous discharge caused by maternal estrogens, resulting in hydrocolpos with or without hydrometra [3]. After menarche, the blockage of the menstrual cycle results in hematocolpos with or without hematometra and hemosalpinx. Reflux of the blood during menstruation into the peritoneal cavity might cause endometriosis [4]. The interval from menarche to the onset of symptom ranges from a few months to several years and the manifesting symptoms consist of dysmenorrhea, acute or chronic pelvic pain, fever, peritonitis and purulent vaginal discharge [4-6]. The most suitable management of this condition is excision of the obstructing vaginal septum as complete as possible [7].

We present the case of a blind hemivagina associated with uterus didelphys and ipsilateral renal agenesis in a patient who presented with acute abdomen because of pyocolpos and reflux of pus into the peritoneal cavity 11 years after menarche.

Case Report

A 24-year-old, sexually active, nulligravid Caucasian female presented to the emergency room of the Department of Obstetrics and Gynecology, “Tzaneio” General State Hospital, Pireaus, complaining of severe worsening lower abdominal pain. In addition, the patient was suffering from nausea and vomiting. Her past medical history was uneventful. She reported menarche at the age of 11 years. Menstruation had been regular and she was on day 16 of a 24-day menstrual cycle. She denied ever having had a cervical smear test, gynecological examination or abdominal surgery. She reported having desmenorrhea, dyspareunia and excessive chronic vaginal discharge. Physical examination revealed an acute abdomen with diffuse lower abdominal tenderness and rebound. Her abdomen showed muscular resistance. The patient was hemodynamically stable. Her...
Uterus didelphys with blind hemivagina and ipsilateral renal agenesis complicated by pyocolpos and presenting as acute etc.

Temperature was 38.4°C. Inspection of the external genitalia revealed no unusual findings. A sufficient amount of pus-like vaginal discharge was noted. Observation of the cervix and vagina was impossible because of the discomfort of the patient. Bimanual gynecological examination showed high tenderness cervical motion. Estimation of the uterus and adnexa was difficult because of the muscular resistance of her abdominal wall. Hemoglobin concentration was 11.7 g/dl, hematocrit 34.6%, and white blood count 21,000 cells/ml with 94.2% polymorphonuclear leukocytes. Serum beta-hCG was negative. Renal and liver function tests were normal. Transabdominal ultrasound scan was performed and the ultrasonographic findings were interpreted by the radiologist as the existence of a pelvic mass measuring 11 x 5.4 cm with mixed echogenicity. Free pelvic fluid was also seen (Figures 1, 2, 3).

The preoperative diagnosis was ruptured tuboovarian abscess and an emergency laparotomy through a Pfannestiel incision was performed. The main operative findings are summarized as follows: (i) free pus in the pelvis; (ii) grossly normal left uterus, left fallopian tube and left ovary; (iii) grossly normal right uterus, elongated and inflammatory right fallopian tube with pus passing out of its fimbrial end and normal right ovary; (iv) no obvious endometriosis; (v) no evidence of abscess formation; (vi) absence of adhesions (Figure 4). The abdominal cavity was copiously irrigated with sterilized normal fluid. The abdominal wound was closed in layers. A uterus didelphys with obstructed hemivagina was suspected. Vaginal examination under general anesthesia revealed a pus-like discharge from a fistula hole on the distended and obstructed right hemivagina. Also, using a needle and syringe, pus was aspirated from the right hemivagina (Figure 5). Drainage of the pyocolpos with transvaginal right lateral colpotomy was performed using conventional scalpel diathermy causing a large amount of pus and blood to spill out (Figures 6, 7). Almost complete resection of the vaginal septum was achieved; the edges of the septum were sutured with interrupted Vicryl sutures (Figure 8). The right cervix was clearly evidenced. Postoperatively, the patient did well and was afebrile 24 hours after surgery and treatment with antibiotics. Histopathologic examination of the removed septum demonstrated vaginal tissue and cervical epithelium on the open vaginal side. An ultrasound scan showed absence of the right kidney, while the left kidney was increased in size (longitudinal diameter 14.5 cm). Intravenous pyelography showed agenesis of the right kidney and hypertrophy of the left kidney (Figure 9). A diagnosis of double uterus with unilaterally unperforated right hemivagina (Figure 10) and ipsilateral renal agenesis was made. At postoperative examination six months after surgery, the patient was free of symptoms and had regular menses. An ultrasound scan showed no reaccumulation of fluid and a normal vagina, uterine bodies, cervices and adnexa. Additionally, the Papanicolaou test from each cervix was negative for cytologic abnormalities.

Discussion

The male and female genital systems are identical at six weeks of intrauterine development, formed by two pairs of symmetric genital ducts: the paramesonephric...
Figure 4. — Uterus didelphys was observed during laparotomy.

Figure 5. — Pus was aspirated from the right hemivagina using a needle and syringe.

Figures 6, 7. — A large amount of pus and blood was spilled out during the drainage of pyocolpos with conventional scalpel diathermy.

Figure 8. — Demonstration of the vagina after an almost complete resection of the right hemivaginal septum; the edges of the vaginal septum were sutured with interrupted Vicryl sutures.
Uterus didelphys with blind hemivagina and ipsilateral renal agenesis complicated by pyocolpos and presenting as acute etc.

(Müllerian) ducts and the mesonephric (Wolffian) ducts. In the male embryo, a factor associated with the SRY region or sex-determining region of Y chromosome is responsible for the differentiation of the undifferentiated gonads to testes. If testes differentiate normally, Sertoli cells produce anti-Müllerian hormones, which results in the loss of the Müllerian duct and Leydig cells produce testosterone, which promotes Wolffian duct development. In 46, XX individuals, in the absence of testosterone, the Wolffian ducts begin to degenerate. Also, the lack of anti-Müllerian hormones results in the synchronous caudal elongation of Müllerian ducts along the lateral aspect of the gonads reaching the urogenital sinus. The adjacent mesonephric ducts are responsible for the fusion of the paramesonephric ducts. Fusion of the paramesonephric ducts results in the formation of the uterine body, cervix and upper two-thirds of the vagina. The lower one-third of the vagina is of urogenital sinus origin. Failure of Müllerian duct fusion leads to uterus didelphys (2 uterine bodies, 2 cervices, and vaginal septum). Because the genital system arise from a common embryonic mesoderm and the development of the uterovaginal complex is derived from the mesonephric ducts, maldevelopment of the paramesonephric ducts also may disturb embryogenesis of the kidneys and ureters [8-11]. Therefore, the association of uterus didelphys with blind hemivagina and ipsilateral renal agenesis simultaneously affects the mesonephric and paramesonephric ducts [2, 7, 12].

Most patients with uterus didelphys and blind hemivagina present with abdominal pain that starts right after menarche. It is presumed that hematocolpos is responsible for abdominal pain [13]. Menstruals in patients with this syndrome are often regular [12]. The main diagnostic problem of this syndrome is its low incidence, which makes the preoperative diagnosis difficult, although the concrete presentation is quite typical: dysmenorrhea, severe abdominal pain and pelvic mass after menarche [5]. Very rarely pyocolpos caused by infected fluid collection within the obstructed hemivagina may occur, as in the current case. Reflux of pus into the peritoneal cavity causes salpingitis and acute abdomen and this is a life-threatening condition requiring emergency surgery. In young girls, after menarche the differential diagnosis of acute abdomen should include hematometra, hematocolpos/pyocolpos, pelvic inflammatory disease, pregnancy complications or torsion of an adnexal mass [14-19].

The treatment of patients with uterus didelphys associated with blind hemivagina is resection of the obstructing vaginal septum as complete as possible using scissors or scalpel or conventional scalpel diathermy or resectoscope.

Figure 9. — Intravenous pyelography 15 min after injection showed agenesis of the right kidney and hypertrophy of the left kidney.
Figure 10. — Illustration of the surgical findings: uterus didelphys with obstructed right hemivagina and a small fistula hole on the right vaginal septum.
[4, 7]. If the patient complains of cyclic abdominal pain after surgical treatment, a suspicious endometriosis should be studied and treated [5, 7]. This syndrome has the best prognosis in terms of alleviation of symptoms. Successful pregnancy rates range from 37% to 40% of cases [20]. Annual Papanicolaou tests are recommended for each cervix. In the current study, the preoperative diagnosis was not correctly made because of the rarity of this condition and its late clinical presentation 11 years after menarche. The most likely preoperative diagnosis was a ruptured tuboovarian abscess because of (a) the acute abdomen of the patient; (b) the pus-like vaginal discharge; (c) the patient’s fever; (d) the increased white blood cells; and, (e) the weakness of the radiologist to interpret the ultrasonographic findings. During surgery, the presence of a didelphys uterus and tuboovarian abscess or pyosalpinx made us consider the possibility of an obstructed vagina and avoid incomplete treatment.

In conclusion, obstetrician-gynecologists and the radiologists should keep in mind the very rare case of uterus didelphys with blind hemivagina and ipsilateral renal agenesis in order to avoid complications, diagnostic delay and incomplete management.

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