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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 practical approach to the prevention of miscarriage: Part 4 - role of infection
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The multiple uses of ethinyl estradiol for treating infertility

J.H. Check

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Summary

Purpose: To demonstrate the usefulness of ethinyl estradiol, a drug no longer commercially produced in most countries, in treating various fertility related issues. Methods: Twenty to 40 micrograms of ethinyl estradiol can be started on day 2 or 3 of the cycle and combined with exogenous gonadotropin can be useful in improving hostile cervical mucus or inducing ovulation in women with hypergonadotropic amenorrhea. It can be used from the day after stopping clomiphene citrate to help negate the adverse effect of this drug on cervical mucus. Results: Successful pregnancies have been achieved saving the couple the expense of intrauterine insemination (IUI) or using donor oocytes. Conclusions: This drug can be very helpful for those physicians who treat each infertile woman on an individual basis and carefully ascertain the couple’s input as to their preferences rather than a “herd” type of medicine.

Key words: Ethinyl estradiol; Postcoital test; Clomiphene citrate; Premature ovarian failure; Premature luteinization.

Introduction

Ethinyl estradiol is one of the most consumed estrogen products in the world since it is the estrogen part of almost all oral contraceptives. Ethinyl estradiol without the progestin was distributed worldwide but eventually commercial production ceased by most pharmaceutical companies. Today it is only available as a commercial product in Germany from Schering. The reason why production stopped was because of lack of use. However, it can still be compounded by pharmacies if ordered.

I have been using ethinyl estradiol for 35 years and find it a very useful tool in treating infertility and use it frequently. This editorial will expound the various clinical uses for this drug when treating an infertile couple.

Cervical factor

A meta-analysis by Griffith and Grimes concluded that the postcoital test has poor validity as a diagnostic test for infertility and encouraged physicians to abandon the test [1]. If the definition of a poor postcoital test is considered as the absence of sperm with progressive forward motion in the cervical mucus, we found only 10% of patients conceived over six months vs 74% who did demonstrate sperm with progressive forward motion in the mucus [2]. Similarly in natural cycles there was only a 3.4% pregnancy rate per cycle when there was no motile sperm in the mucus vs 21.2% with properly timed intrauterine insemination (IUI) [2]. Thus, I strongly believe that this simple inexpensive test should still be performed even though today the frequency of abnormalities in women not taking clomiphene citrate is low (approximately 3%) [3].

The most common cause of a poor postcoital test today is the use of clomiphene citrate. Clomiphene citrate acts predominantly like an anti-estrogen drug by binding to and eventually depleting nuclear estrogen receptor. The blocking of estrogen effect results in a lack of estrogen suppression of follicle stimulating hormone (FSH) which in turn causes ovulation. However, it also blocks the estrogen effect on cervical mucus. Sometimes this negative effect on mucus can be negated by adding estrogen after clomiphene is stopped for the following five to nine days until ovulation is achieved. The reason for using ethinyl estradiol over other estrogen preparations is that it does not measure in the serum assay for 17 beta-E2 and thus the effect of clomiphene citrate on follicular maturation can be better determined. Our group found in the first cycle of clomiphene citrate therapy that 69% (40/58) of the women failed to show any sperm in the cervical mucus with intercourse at least eight hours before in an appropriately timed postcoital test (based on ultrasound and serum E2 and progesterone criteria) [4].

In cycle 2, all 16 of the group of 18 who had a normal postcoital test in cycle 1 and did not conceive still had sperm with progressive motion in the cervical mucus, though half had ethinyl estradiol added as follicular maturation approached because of an obvious decrease in amount and quality of the mucus [4].
Of the 40 patients with poor postcoital tests, 34 were given ethinyl estradiol after the clomiphene was stopped in a dosage of either .02 or .05 mg until ovulation [4]. Only one of the six (16.7%) who did not have added supplemental estrogen showed sperm with linear progressive motion in the mucus vs 43.7% (7/16) taking .02 mg ethinyl estradiol and 55.5% (10/18) using .05 mg ethinyl estradiol [4]. There were no pregnancies achieved in cycle 1 in the 40 women who had poor postcoital tests (IUI was not performed) vs 11.1% (2/18) who demonstrated sperm with linear progressive motion.

Of course one might argue why worry about whether the cervical mucus kills the sperm or not and just do intrauterine insemination (IUI). In fact a common practice among infertility specialists is to perform an IUI each month without even checking a postcoital test. Some of these infertility specialists quote the aforementioned meta-analysis stating that the postcoital test has no validity [1], with the assumption that the test has no validity. Others, including our group, do not agree and believe that the postcoital test is a valuable fertility tool [3, 5].

Rather than “waste” such a high amount of money, as mentioned, many physicians treating infertility automatically do an IUI. If we assume that a postcoital test costs $100 and it usually needs to be performed only one to two times per patient, consider the immense costs of performing an IUI every month with prices ranging from $250 to $1,000 each month, not just per patient. Even if the IUI is paid for by insurance carriers, performing this procedure monthly (especially since the majority will not need it) increases the cost of the healthcare. As mentioned above, adding ethinyl estradiol after stopping clomiphene citrate until ovulation can improve cervical mucus in a significant percentage of women taking clomiphene citrate without interfering with the measurement of estradiol. This is important in determining if the use of clomiphene citrate has allowed the development of a mature follicle.

Clomiphene citrate is frequently prescribed by general gynecologists who do not have the facilities to perform an IUI. Adding ethinyl estradiol to the clomiphene citrate is even more important for these physicians since they could be creating iatrogenic infertility by inhibiting sperm getting to the uterine cavity. It is imperative that any doctor prescribing clomiphene citrate should perform an appropriately timed postcoital test. If poor, and IUI is an option, this procedure can be performed in this cycle. However, the woman should be given the option of continuing with clomiphene citrate and IUI or switching to gonadotropin injections which do not create poor quality mucus.

A woman may for various reasons have less sensitivity to estradiol so that poor quality mucus exists despite attaining an adequate mid-cycle serum estradiol. Of course the mucus glands are being exposed over a two-week course with a gradually rising serum estradiol. Ethinyl estradiol, as mentioned, is the component of the oral contraceptive that helps suppress ovulation by inhibiting the release from the pituitary of follicle stimulating hormone (FSH). If ethinyl estradiol is started from the early follicular phase in dosages of 20 to 40 μg the mucus glands will be exposed to a pharmacologic dosage of estrogen. This can sometimes improve the quality of the mucus. However, the follicular maturation would be thwarted by the ethinyl estradiol, but this could be counteracted by the concomitant use of gonadotropin stimulation [6]. Sometimes, the ethinyl estradiol can be added later in the follicular phase which may be too late to suppress follicular maturation but could still improve mucus so exogenous FSH is not needed [7]. Alternatively a short course of low-dose FSH could be added concomitant to the use of ethinyl estradiol which if the mucus abnormality is corrected allows a better chance of monofollicular recruitment [8, 9].

**Inducing ovulation in women with ovarian failure**

In 1984 our group demonstrated that the use of higher dosage estrogen of any kind can help to recruit follicular maturation in women in apparent premature menopause [10]. The mechanism is related to restoring down-regulated FSH receptors in the granulosa-theca cells by the chronic elevation of serum FSH. A reasonable pregnancy rate has been achieved [10-14]. Though all estrogens can restore sensitivity of gonadotropin-resistant follicles to either endogenous or exogenous gonadotropins, the advantage of using ethinyl estradiol is that it allows proper measurement of estradiol which aids tremendously in determining if a mature follicle has been attained.

**Extending the length of the follicular phase**

Sometimes for religious reasons, e.g., Orthodox Jewish women, intercourse is not allowed until one week after the cessation of menses, after a ceremonial bath referred to as a mikvah. Some of these women are very fertile but fail to achieve a pregnancy because they are ovulating before they can have intercourse. Sometimes they are actually ovulating on the day of the mikvah or even shortly thereafter, however the mucus may have receded several hours after the luteinizing hormone (LH) surge but before oocyte release.

There is evidence that a short follicular phase is associated with infertility even if a mature dominant follicle is attained [15, 16]. This seems to apply both to women whose short follicular maturation time may be related to diminished oocyte reserve and thus higher early follicular phase FSH driving follicular maturation quicker, and to women who appear to have adequate oocyte reserves [16]. This may be related to inadequate time exposure to estradiol with failure to generate sufficient endometrial progesterone receptors [16]. Lengthening the follicular phase with ethinyl estradiol has resulted in improvement of pregnancy rates [16].

Sometimes ethinyl estradiol can be used from day 2 to day 8 or so, then stopped, and follicular maturation ensues naturally or sometimes a low dose of gonadotropins is needed to stimulate the follicles.
Premature luteinization

A rise of LH before full maturation of the dominant follicle (i.e., 18-24 mm in size with a serum estradiol > 200 pg/ml) leading to a rise in serum progesterone above 2 ng/ml is referred to as premature luteinization [17]. In the normal ovulatory cycle in the late follicular phase estradiol has a positive feedback effect on LH release from the pituitary gland causing this hormone to rise. However, in pharmacologic dosages, estrogen will suppress LH. Thus frequently a condition, e.g., polycystic ovarian syndrome is treated with oral contraceptives to allow the pharmacologic dosage of ethinyl estradiol to lower the chronically elevated LH so as to reduce the production by the ovaries of excess androgens. Ethinyl estradiol can be used in cases of premature luteinization to keep the gonadotropins suppressed and then the follicle can be matured by using exogenous gonadotropins [18].

One could of course try to treat premature luteinization with GnRH agonists or antagonists. These agents are 100 times as expensive as ethinyl estradiol.

Final comments

Ethinyl estradiol has many uses in treating infertile couples. However, it is unlikely that any pharmaceutical company will rekindle an interest in commercial production because it is the common practice for most physicians to simply do IUI and not worry about postcoital tests. Furthermore, most physicians are not aware that apparent menopause can be temporarily reversed and will simply recommend donor oocytes. Nevertheless, for those treating physicians who have interests in these areas compounding pharmacies can easily make the ethinyl estradiol. I am not aware of another estrogen product that does not measure in the assay for estradiol.

References

A practical approach to the prevention of miscarriage

Part 4 - role of infection

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Summary

Purpose: To evaluate the role of infection as a cause of pregnancy loss. Methods: Studies concerning the risk factor of certain microorganisms for first trimester miscarriage and premature rupture of membranes are reviewed. The microorganisms especially considered were ureaplasma/mycoplasma, the potpourri of organisms causing bacterial vaginosis and chlamydia trachomatis. Results: The consensus is that all these microorganisms can on occasion lead to first trimester spontaneous abortion and second trimester loss especially related to premature rupture of membranes. Conclusions: Reactivation during pregnancy is possible so the best strategies involve giving a course of appropriate antibiotics prior to pregnancy but giving antibiotics at least intermittently during the first trimester. Similar antibiotic therapy could be considered for unexplained recurrent miscarriage where negative cultures exist.

Key words: Spontaneous abortion; Bacteria; Premature rupture of membrane; Antibiotics.

Introduction

In our large population of women who have conceived following in vitro fertilization-embryo transfer (IVF-ET) aged 39.9 and under, irrespective of their previous infertility or miscarriage history or their status of ovarian oocyte reserve, there is approximately a 10% chance that a woman showing ultrasound evidence of pregnancy at 6-8 weeks will have a miscarriage. Accidental aneuploidy is the most common cause of a given miscarriage [1]. It is debatable if a predisposition to aneuploidy exists or not but if it does it is uncommon [2-4].

Nevertheless by chance alone a younger woman could have had two consecutive first trimester spontaneous abortions or miscarried in two of three pregnancies related to two accidental aneuploid fetuses. Theoretically one in 100 women could lose two in a row from a factor that can not be controlled or prevented.

Prior editorials have discussed certain causes of spontaneous abortion that are remediable, e.g., progesterone deficiency. A woman presenting with frequent miscarriages could have been unlucky and have had several different etiologies to the various first trimester pregnancy losses. The frantic primary, secondary, or tertiary aborter wants to not only eradicate any of the causes of miscarriage that she may be prone to have, e.g., need of extra progesterone, but would like to prevent another loss from any new etiology, especially if it is remediable.

Recurrent miscarriage is defined as three or more consecutive miscarriages. It has been estimated to occur in 0.5% to 3% of women [5]. There is little evidence that pelvic infections are a cause of recurrent miscarriages. However, there are data suggesting that a first trimester miscarriage or a loss later in the pregnancy can be related to an infectious etiology. This editorial will present some of the data suggesting that certain infections could result in a loss of a pregnancy. As in most areas of medicine there will be studies not finding an association. Nevertheless after weighing the evidence I hope to present a strategy to cover the possibility of an infection leading to a miscarriage.

Microorganisms considered as possible causes of some miscarriages or pregnancy loss

There are studies suggesting that the following microorganisms may on some occasions lead to fetal loss: ureaplasma urealyticum, mycoplasma hominis, chlamydia trachomatis, a group of microorganisms responsible for causing bacterial vaginosis, streptococcus, several bacteria in the clostridiales order, genital tuberculosis, trichomonas vaginalis, neisseria gonorhoeae, listeria monocytogenes, cytomegalovirus (CMV), herpes simplex virus and toxoplasmosis [6].

Any one of these could cause a miscarriage but some are more likely candidates in any given miscarriage. The more likely microorganisms will be discussed because they are the ones that lead to my final suggested strategy. I will emphasize that infection and miscarriage is a highly controversial area and there is no one strategy that can be said to be the correct one. I will provide the studies that have led me to my particular strategy but it should be emphasized that it is personal. Perhaps after presenting the data and evidence the reader will decide on their own strategy different than mine.

Evaluation for infections

In all women coming to our practice for either infertility or history of miscarriage we culture the cervix for...
mycoplasma, ureaplasma, gonorrhea, and chlamydia. Moreover vaginal cytology for bacterial vaginosis is evaluated. For the subgroup of women who have a history of miscarriages, we also do a deep vaginal culture for Group B streptococcus.

**Culture positive for mycoplasma or ureaplasma**

Not only do we culture the cervical fluid but we also culture the semen specimen. If either the female or male partner tests positive we generally treat both partners with doxycycline 100 mg twice daily for two weeks.

We do not repeat the culture but instead with a positive pregnancy test begin treatment with either erythromycin 500 mg four times a day or azithromycin 250 mg a day for a week then skip a week then resume on an alternate week basis throughout the first trimester. I do not reculture after the initial two-week course of doxycycline because it is hard to eradicate, thus giving a more prolonged antibiotic course of therapy could lead to complications, e.g., toxic bacterial enterocolitis or thrush.

I do not reculture necessarily when pregnancy occurs because based on one positive culture I will nonetheless add a macrolide drug to keep the infection in check. If the repeat culture of the cervix was negative I could not be sure that it was still not present at the endometrial level. Also even if the cultures were negative at the moment in the pregnancy they were obtained one can never tell when the concentration will become high enough again to do damage. It is not practical to keep getting cultures on a weekly basis plus it may take ten days to grow *mycoplasma/ureaplasma*. The male partner is only treated once but is advised to use condoms during the first trimester.

One study found that in pregnant women with a vaginal discharge 49% cultured positive for *U. urealyticum* and an additional 14% were positive for *M. hominis* [7]. It is unlikely that all or even most women that culture positive for these organisms will lose a pregnancy. However there are data suggesting that women with enough concentration of these microorganisms to demonstrate a positive culture will have a greater pregnancy loss rate than those who are negative. Cervical colonization ureaplasma was found in 43% of normal pregnant women (n = 310), 42% of women undergoing voluntary termination (n = 89), 41.5% of normal fertile women (n = 65), 53% of women with spontaneous abortion (n = 122), and 69.5% of women with recurrent miscarriage (n = 76) [8]. Another study found *U. urealyticum* and *M. hominis* in 74.1% and 27.6% of 58 women with spontaneous abortion vs 48% and 10% of 50 women who had live deliveries [9].

Thus studies by Naessens *et al.* would suggest that treating women with antibiotics who culture positive for mycoplasma could reduce the risk of miscarriage [8].

One study did find an extremely high percentage (90%) of pregnancy loss in women whose cervical cultures were positive for mycoplasma [10]. Using doxycycline only prior to conception reduced the miscarriage rate to 48% whereas using erythromycin in addition during pregnancy reduced the miscarriage rate to 15% and pretreating with doxycycline then using erythromycin during pregnancy resulted in a loss rate of 16% [10]. This was a prospective study though it is hard to believe that untreated controls could have a 90% loss rate. Nevertheless, it is this study that has guided my decision to give only a two-week course of doxycycline rather than a prolonged course prior to pregnancy and not to re-culture for the microorganisms but always treat with a macrolide, e.g., erythromycin or azithromycin at least during the time that our practice is responsible for patient care, i.e., the first trimester.

**Bacterial vaginosisis (BV)**

Bacterial vaginosis is an interesting condition in which the normal predominant type of bacteria that populates the vagina, *e.g.*, lactobacilli, which reduces the vaginal pH by metabolizing squamous cell glycogen to lactic acid, is replaced by predominantly anerobic bacteria. Bacterial vaginosis is probably the most common cause of vaginal discharge; for some reason colonization with these microorganisms does not cause an inflammatory reaction so that is why it is given the name vaginosis rather than vaginitis. Actually sometimes mycoplasma and ureaplasma can be the cause of BV but other common bacteria include Gardnerella vaginales, various mobiluncus species, prevotella, porphyromonas, bacteroides and peptostreptococcus.

Most commonly I identify BV by observing a fishy vaginal odor and confirm it by a wet smear of cells taken from the lateral vaginal wall demonstrating the adherence of bacteria by a phase contrast microscope showing “shaggy” epithelial cells (so called clue-cells). Occasionally for borderline cases the diagnosis will be confirmed by the demonstration of a vaginal pH > 4.5 or eliciting a fishy odor from the vaginal fluid by adding potassium hydroxide.

Interesting, though the actual cause of BV is unknown, one study of infertile women undergoing IVF-ET found that BV was three times more likely to be present in women with tubal factor than women having IVF-ET for endometriosis, unexplained infertility or male factor [11]. When lactobacilli are the predominant vaginal microorganism of the vagina the acidic pH helps provide protection against infection. By replacing the flora with organisms associated with BV and raising the pH, the woman is at greater risk of infection whether BV vaginal microorganisms ascend and now inhabit the endometrial cavity (but since not evoking a host inflammatory response so-called endometriosis) and directly in some manner creates an adverse milieu leading to pregnancy complications, or merely allows a more serious pathogen to cause the problem, remains to be determined [12, 13]. For example women may have colonization with *chlamydia* from previous exposure but host defenses are keeping it in check. The presence of BV could activate the *chlamydia* which in turn leads to pregnancy loss. One study found that women with endometrial cultures that
grow out *chlamydia* had a 59% miscarriage rate whereas treatment with antibiotics reduced the miscarriage rate to zero [14, 15]. Normally the uterine cavity is considered relatively sterile. However, studies performing endometrial cultures have demonstrated the presence of pathogenic bacteria even in the presence of normal cervical cultures [16].

Intravaginal or oral clindamycin treatment will help to eradicate *BV* [17, 18]. Metronidazole therapy was found to be about as effective as clindamycin [19]. Metronidazole therapy vs placebo showed marked reduction in preterm labor and preterm births and also premature rupture of membranes [19, 20]. Not all studies concur that treating *BV* prevents pre-term deliveries. A Cochrane meta-analysis concluded that antibiotic treatment (better with oral than intravaginal) resulted in a trend for fewer births before 37 weeks gestation especially in those women with a previous history of preterm births [21].

As far as miscarriages related to *BV* a large study of 867 consecutive women undergoing IVF-ET found that there was no difference in the conception rate of the 25% demonstrating *BV* vs the 75% without *BV* [22]. However, the group with *BV* had a significantly higher miscarriage rate (32% vs 18.5%) with no obvious confounding variables. Another study found that the presence of *BV* significantly increased the risk of first trimester miscarriage with no obvious decrease in the conception rate of the 867 consecutive women undergoing IVF-ET found that there was no difference in the conception rate of the 25% demonstrating *BV* vs the 75% without *BV* [22]. However, the group with *BV* had a significantly higher miscarriage rate (32% vs 18.5%) with no obvious confounding variables. Another study found that the presence of *BV* significantly increased the risk of first trimester miscarriage rate if the sac size was found to be more than one week earlier for gestational age than the crown-rump length [28]. We considered the possibility that this phenomenon could be related to leakage of amniotic fluid by an infection. Our policy is to add a macrolide when we find clue-cells on vaginal cytology when metronidazole/mycoplasma or clue-cells are seen in the wet smear then one can hope that the pregnancy losses were related to an infectious etiology and the woman can be treated both before conception and during her first trimester.

However, what should the treating physician suggest if all cervical and vaginal cultures are negative? Can a physician and patient be sure that the endometrial cavity was not overgrown with these microorganisms? The answer is no. Some of these microorganisms are fastidious and may be present in the cervix but not grow out on culture explaining a negative culture. There is also the possibility that they have colonized the endometrial cavity but are not present in the cervix. As mentioned, molecular genetics has allowed the detection of many other types of bacteria in the vaginal flora and with cervical cultures for which there has not been developed as yet growth media [6].

Under these circumstances I will frequently empirically prescribe erythromycin or azithromycin intermittently during the first trimester. Since some studies have found ureaplasm and mycoplasma in about three-fourths of women with miscarriages and it can develop at any time I use the macrolides because they will cover the *mycoplasma* and Group B *streptococcus* and they are safe in pregnancy and generally well tolerated [9].

We previously found that when performing a fetal ultrasound during the first trimester there was a high miscarriage rate if the sac size was found to be more than one week earlier for gestational age than the crown-rump length [28]. We considered the possibility that this phenomenon could be related to leakage of amniotic fluid by an infection. Our policy is to add a macrolide when we see this occurrence even if repeat cultures for ureaplasm and mycoplasma are negative. The exception would be if we find clue-cells on vaginal cytology when metronidazole or tinidazole would be used instead. These agents would be given intermittently. Since instituting this policy we have found a marked reduction in miscarriages when a crown-rump length/sac size discrepancy is found. These data are unpublished because our ethics committee rejected a proposal for a placebo control or no-treatment control.
References
Acute intermittent porphyria in pregnancy: A common misdiagnosis

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Summary

Acute intermittent porphyria (AIP) is inherited in an autosomal dominant fashion. Only 10% to 15% of the gene carriers have the clinical syndrome. The prevalence of AIP in Europe is 1/20,000. Pregnancy represents an essential risk factor in patients suffering from AIP. The clinical syndrome in AIP presents mainly with acute attacks, especially during the first trimester. Misdiagnosis of AIP unfortunately is very common. Pregnancy in women with AIP is associated with higher rates of spontaneous abortion, hypertension, low birth weight infants and considerable mortality (2-42%). Pregnancy, despite the major hormonal alterations it causes, is seldom associated with porphyric symptoms. There are only limited reports supporting the use of hemin during pregnancy, but experience indicates that it can be safely administered in pregnant women. Until clinical improvement is achieved, symptomatic treatment is recommended. Despite the fact that pregnancy in women suffering from AIP is related to higher rates of morbidity and complications, close management throughout the pregnancy could ensure a good outcome.

Key words: Acute intermittent porphyria; Pregnancy; Hemin; Treatment; Acute attacks.

Introduction

Acute intermittent porphyria (AIP) is a rare metabolic disorder, inherited in an autosomal dominant fashion. Pregnancy represents an essential risk factor in patients suffering from AIP. There are only limited reports dealing with the incidence, the clinical presentation, the diagnosis, the differential diagnosis and the treatment of patients with AIP in pregnancy. It is this rarity that has resulted in the increasing number of misdiagnoses of AIP.

This review article tries to disentangle different modalities concerning the management of patients with AIP in pregnancy and to keep physicians alert.

Classification of porphyria

The term porphyria refers to a group of rare, heterogeneous, metabolic disorders arising from the reduced activity of any of the enzymes in the heme biosynthetic pathway. Porphyrias can be classified as hepatic or erythropoietic depending on the main site of the defect. They can also be classified as either clinically acute: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), ALA-dehydratase deficient porphyria (ADP), or cutaneous: porphyria cutanea tarda (PCT), hepatoerythropoietic porphyria (HEP), erythropoietic protoporphyria (EPP), congenital erythropoietic porphyria (CEP) according to their major clinical manifestations [1-3]. With the exception of porphyria cutanea tarda, all porphyrias are attributed to inherited enzyme deficiencies and all hepatic porphyrias are acute. Some acute porphyrias may also display cutaneous manifestations; however, cutaneous porphyrias never present acute neurologic manifestations, with the exception of erythropoietic protoporphyria in crisis [4].

Inheritance of AIP

AIP is inherited in an autosomal dominant fashion, caused by a deficiency in the enzyme uroporphyrinogen I synthetase, often called porphinobillinogen deaminase (PBG). The gene responsible for encoding this enzyme is located on chromosome 11q24, and the coding sequences are spread over 15 exons. So far, 301 mutations in the PBGD gene have been described [5]. The mutations reported include single base substitutions, splicing defects, insertions, and deletions that lead to structural impairment or loss of function of PBGD. As a consequence, the defect is unable to convert PBG to uroporphyrinogen I [6-10].

The outcome of a mutation is a 50% decrease in enzyme activity. This explains the rarity of homozygotes, as a failure to produce hemin in this condition is incompatible with life [1-11]. The remaining activity of the enzyme is usually sufficient. This could possibly justify why only 10% to 15% of the gene carriers have the clinical syndrome. Moreover, almost 33% of patients are reported with a family history of the disorder [12, 13].
Incidence of AIP

The prevalence of AIP in Europe is estimated to be one in 20,000 people. However, the frequency rates between different populations, ranging from 1.5 per 100,000 Swedish people living in the USA and 3 per 100,000 people in Finland and Western Australia, to 1 per 1,000 people in Lapland Sweden, with clinical disease manifesting in approximately 10% of these carriers. Peak age of presentation is in the third decade [14-19]. Pregnancy represents an essential risk factor in patients suffering from AIP. Acute attacks have been reported as being more common during pregnancy (24-95%), especially during the first trimester [20, 21].

Clinical presentation of AIP in pregnancy

The clinical syndrome in AIP presents mainly with acute attacks. Acute attacks are expected in cases where there is an increased demand for hepatic heme; commonly when a precipitating factor occurs. In response, there is an induced synthesis of -aminolaevulinic acid (ALA) and overproduction of porphyrin precursors following the synthetic pathway to the point at which the partial enzyme deficiency becomes restrictive. Intermediates, which have no known useful physiologic function, accumulate in the body. Precipitating factors that can induce symptoms can be categorized as drugs, starvation, infection, and hormonal factors.

Endogenous hormones have been described as a vital factor in the induction and severity of acute attacks in patients with AIP [22]. During pregnancy, there is a major increase in sex hormone levels and on that basis, pregnancy has been thought to represent an essential risk factor in patients suffering from AIP.

In fact, acute attacks have been reported as being more common during pregnancy (24-95%), especially during the first trimester, but pregnancy is generally well tolerated. However, pregnancy in women with AIP is associated with higher rates of spontaneous abortion, hypertension and low birth weight infants [20, 21]. Furthermore, it is associated with considerable mortality (2-42%) [20]. Additionally, it has been reported that smoking may be related to a worse outcome of pregnancy in women with AIP. Smoking, which increases hepatic cytochrome P450 enzymes and presumably heme synthesis, has also been shown to be associated with a higher frequency of attacks [23].

On the other hand, it has been reported that pregnancy, despite the major hormonal alterations it causes, is seldom associated with porphric symptoms and that with appropriate and close management, a good outcome could be achieved [24-27].

At the hormonal level, progesterone variability may partially explain why attacks are more common in women and during the luteal phase of the menstrual cycle [28, 29]. Moreover, oral estrogen intake is linked with a higher incidence of acute attacks in women with AIP [30]. In addition, despite the fact that there is no difference in AIP prevalence between genders, women seem to suffer more often than men. The onset of menses is correlated with a 10% to 20% higher incidence of acute attacks in women with AIP [31, 32]. Furthermore, attacks are more frequent during childbearing years, with only a few cases having been described in women before puberty. Similarly, attacks are limited after menopause [33, 34]. The use of gonadotropin-releasing hormone analogue (GnRH) has been shown to protect women with AIP from cyclical attacks. GnRH use, after an initial period of stimulating gonadotrophin secretion, leads to down-regulation of pituitary function, reduced secretion of gonadotropins and, as a consequence, a drop in the endogenous sex-hormone levels [32, 33, 35, 36].

AIP is characterized by acute attacks of abdominal pain, which is present in 85% to 95% of patients. Abdominal pain is severe, diffuse and unrelenting but typically presents without rebound tenderness or guarding. However, pain is frequently accompanied by nausea/vomiting (43%-88%), constipation (48%-84%), tachycardia (80%) and occasionally by diarrhea (5%-12%). Less often, fever or leukocytosis may present, raising suspicion of acute surgical abdomen. However, despite the severity of symptoms, clinical examination of the abdomen is normal in most cases, probably because there is no peritonism [37]. Pain in the abdomen is believed to be related to autonomic neuropathy, as is pain in the extremities, back, chest, neck or head that present in 50% to 70% of cases. Extremity pain indicates involvement of the sensory nerves, with objective sensory loss being reported in 10% to 40% of patients [38-43].

Peripheral, motor neuropathy manifests early during an acute attack as muscle weakness (42%-68%). This weakness is usually symmetric, affecting the upper extremities more often than lower and involving the proximal muscles of the extremities. Fasciculation is absent and deep tendon reflexes are lost in severe attacks. Weakness may progress to respiratory paralysis (8%-20%). Moreover, seldom, the cranial nerves may be involved resembling Guillain Barre’ syndrome. Mental symptoms occur in 40% to 58% of patients, ranging from minor changes in behavior to agitation, confusion, hallucinations, depression, or even psychosis and schizophrenia [44-46]. Psychiatric symptoms may present as the only manifestation of AIP [47] and this is probably the explanation for the higher prevalence of AIP in patients with psychiatric illness than in the general population [48-50].

Electrolyte disturbances are commonly found in AIP; hypokalemia, hypotension, hypomagnesemia, hypochloremia, azotemia and dehydration may become severe [51]. Seizures may present in up to 15% of patients, due to hyponatremia, which is often the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH) or sodium depletion [52]. AIP is also related to chronic hypertension (36%-55%), despite the fact that hypotension may occur during acute attacks. Renal impairment has also been described as a long- term complication [53]. Furthermore, patients suffering from AIP are at higher risk of developing hepatocellular carcinoma [54-60].
Risk factors of acute attacks

An acute attack of AIP may be precipitated by many factors during surgery and anesthesia, including fasting, dehydration, stress, infection, and drugs. Drugs used in anesthesia, many of which have high lipid solubility, and cytochrome metabolism have been implicated in the development of severe reactions in patients with AIP. In emergency cases, without knowledge of the problem and full biochemical examinations, the situation could well become serious. Knowledge of the situation poses a hard-to-solve puzzle, in selection of the appropriate drugs and operating management. Summaries of anesthetic drugs, known for their safety, have been published; however, there are also numerous conflicting reports [32]. Furthermore, other factors such as stress or infections may precipitate a porphyric crisis. On the other hand, availability of very short-acting anesthetic agents has led to the increased safety of anesthetic techniques. However, it would be fair to say that most analgesic agents may be used safely, despite the fact that some isolated case reports have implicated these drugs in porphyric attacks. Provided that reasonable precautions are adopted and sensible guidelines are followed, anesthesia may be considered safe. Postoperative close monitoring should continue for five days, to delay the onset of a porphyrin crisis [61-74].

Diagnosis - differential diagnosis

Misdiagnosis of AIP unfortunately is very common, probably because of the rarity of the disease. When an acute attack of AIP is suspected, increased urinary porphobilinogen levels are expected. However, due to the low sensitivity (40%-69%) and speciality (28%-53%) of the method, measurement of the 24-hour urinary excretion of porphobilinogen has become the first-line examination. However, further evaluation is needed, in order to differentiate between AIP, variegate porphyria and hereditary coproporphyria. Erythrocyte porphobilinogen deaminase activity is decreased up to 50% in almost 90% of patients. Additionally, urine porphyrin levels are markedly increased, while plasma and fecal porphyrin levels remain normal or slightly elevated [75-81].

Due to its dominant mode of inheritance, it is prudent to screen relatives for acute porphyrins and to offer proper genetic counselling to family members at risk. When possible, diagnosis should be confirmed in childhood to avoid the precipitating factors which may induce acute attacks after puberty. However, given the fact that approximately 50% of patients remain symptom-free throughout their lives, 30-40% experience mild symptoms and that the measuring of porphyrins and porphyrin precursors in these individuals may give variable results, DNA analysis is the only reliable means to screen symptom-free patients. Despite the large number of possible mutations, those reported are usually family specific. Those members who are unaffected experience great psychological relief as it is unnecessary for them to follow the restrictions required to prevent attacks. Moreover, screening of future generations of that particular family branch is not necessary [10, 13, 82].

Treatment of acute attacks of AIP

Hospitalization is required for treatment of acute attacks of AIP. The primary objective is to identify and limit any potential precipitating factors. Careful examination for underlying infections must be performed. Initial treatment comprises high glucose or intravenous hemin intake. Glucose is clearly less effective and is recommended only for attacks with mild pain and without signs of paresis. Hemin acts by repressing hepatic ALA synthase activity, thus reducing the overproduction of ALA and porphobilinogen [83-90]. A response to heme therapy is usually observed within one to four days after the start of infusion, but early initiation of intravenous hemin is associated with an earlier response and improved outcome [91-94]. There are only limited reports supporting the use of hemin during pregnancy, but experience indicates that it can be safely administered in pregnant women [35].

Until clinical improvement is achieved, symptomatic treatment is recommended. One of the main objectives should be that of pain control. However, careful selection of drugs allowed in pregnancy is paramount. Oral contraceptives have been shown to act as precipitating factors [34]. It is recommended that the use of sex hormones in women suffering from AIP is restricted. Notwithstanding, contraception is encouraged when adopting barrier methods.

Prevention of future attacks

Prevention of future attacks requires identification and avoidance of precipitating factors, preferably followed by changes in habits. Prevention comprises adequate carbohydrate and high calorie diets, avoidance of exacerbating drugs, alcohol consumption, smoking, dehydration, psychological stress, sex hormone treatment and sensitivity to treatment of any infection. Moreover, the patient should be forewarned that high estrogen concentrations may provoke attacks during pregnancy. Despite the fact that pregnancy in women suffering from AIP is related to higher rates of morbidity and complications, close management throughout the pregnancy could ensure a good outcome.

References


Pregnancy following calcium ionophore oocyte activation in an oligozoospermia patient with repeated failure of fertilization after ICSI

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Introduction

Intracytoplasmic sperm injection (ICSI) is an extremely useful method of treating patients who have an extremely low sperm count, and it has been reported that the fertilization rate after ICSI is 64% to 71% [1, 2]. Conversely, it has been reported that 3% of all cycles are observed to result in no fertilized oocyte, despite the performance of ICSI [3, 4].

One cause of fertilization failure after ICSI is believed to be oocyte activation failure attributable to the sperm. Correspondingly, it has recently been reported that fertilization can be achieved by using calcium ionophore to activate the oocyte, thereby obtaining favorable results [5-8]. A case of secondary infertility is reported in which fertilization had not been achieved despite the performance of ICSI but wherein fertilization was achieved by using calcium ionophore to activate the oocyte after ICSI.

Case Report

A 40-year-old female and her 47-year-old husband presented at the Niigata Workmen’s Accident Hospital for secondary infertility of two years duration. The patient had previously conceived in intrauterine insemination and delivered a normal mature infant. Her menstrual cycles were regular and her hormonal testing was normal. The semen analyses revealed oligozoospermia (motile sperm: 0.5-1.5 x 10^6/ml). Thereafter the patient elected to undergo ICSI.

The patient underwent ovarian stimulation with 100 mg clomiphene citrate on days 4-8 of her menstrual cycle and 150 IU of HMG injection on day 8, 10. Two mature oocytes were retrieved. Motile sperm with no obvious abnormal morphology were injected into two metaphase II (MII) oocytes using the routine ICSI procedure. However, none of the oocytes became fertilized.

In the second attempt, the patient underwent ovarian stimulation with 100 mg clomiphene citrate on days 4-8 and 150 IU of HMG injection on day 8, day 10 and day 12 of her menstrual cycle. As a result three oocytes were retrieved. Motile sperm were injected into two MII oocytes. However, none of the oocytes became fertilized.

In the third attempt, the patient underwent ovarian stimulation with 100 mg clomiphene citrate on days 4-8 and 150 IU of HMG injection on day 8 and 10 of her menstrual cycle. As a result, three mature oocytes were retrieved. We performed calcium ionophore oocyte activation after obtaining informed consent. Motile sperm were injected into three MII oocytes. After 30 min of the ICSI procedure, three oocytes were exposed to 5 μmol/l of calcium ionophore A23187 (Sigma, St. Louis, MO) in HFF99 (Fuso Pharmaceutical Industries, Ltd., Japan) medium with 10% SSS (Irvine, Santa Ana, CA) for 5 min at 37°C in 5% CO_2/5% O_2. The oocytes were then washed in fresh media and incubated overnight at 37°C in 5% CO_2/5% O_2 in HFF99 medium with 10% SSS. This time, two of three oocytes became normally fertilized (two pronuclei). One oocyte had three pronuclei. One embryo transfer was performed on day 3 of culture. The patient thereafter conceived and delivered a 2,520 g healthy baby without any congenital abnormalities at 36 weeks of gestation.

Discussion

For a case of secondary infertility in which fertilization could not be achieved despite the performance of ICSI, calcium ionophore was used to activate the oocyte after ICSI. Thereby, fertilization was achieved, thus leading to pregnancy and a successful delivery. Recently, it has been reported that in cases in which fertilization could not be achieved via ICSI, oocyte activation has been performed...
using calcium ionophore, and subsequent fertilization has been achieved leading to pregnancy and successful delivery [5-8]. In round-head spermatozoa (globozoospermia) with an abnormal shaped sperm head, fertilization rate after ICSI is low, and there has been the report of a case in which oocyte activation was performed using calcium ionophore [8]. There has also been the report of a case in which fertilization was not achieved via the usual ICSI despite a normal motility rate and shape of the sperm, but oocyte activation using calcium ionophore was performed, thus leading to pregnancy [6]. It is believed that this case is one in which the condition of sperm previously having a fertilizing capacity changes over time thereafter, thus resulting in the loss of oocyte activation capacity. To the extent of our search of the pertinent medical literature, there have not been any reports of cases in which oocyte activation has been performed for such cases, and thereby resulting in a live birth, so the present case constitutes the first such report.

When considering whether the cause of oocyte activation failure after ICSI is attributable to the sperm, it is necessary to examine mainly whether there is any abnormality in the oocyte activation factor within the sperm. Recently, as for the oocyte activation factor within the sperm, phospholipase Cζ (PLCζ) has been reported as a potential candidate, which has been attracting attention [9]. This refers to the fact that fertilization is achieved by oocyte activation due to PLCζ which is brought into the oocyte cytoplasm after ICSI.

In the present case, since the first fetus was conceived via intrauterine insemination and a live birth was achieved, it is believed the sperm had a normal fertilizing capacity. Thereafter, the sperm count decreased, leading to an indication for ICSI, after which it was determined to administer the treatment. The first and second ICSI both constituted ICSI using normal shaped sperm having satisfactory mobility, but no fertilization was observed. It is commonly believed that the cause of fertilization failure may be an abnormality in the quality of the oocyte or an oocyte activation failure attributable to the sperm, but the oocyte that was used in the first and second ICSI had a morphologically favorable condition. Therefore, oocyte activation failure attributable to the sperm might have been the cause of the fertilization failure. One method for proving oocyte activation failure attributable to the sperm is to verify the presence or absence of oocyte activation by performing ICSI for the provided oocyte, but this was not ethically possible. Even though it was not clinically possible to prove oocyte activation failure attributable to the sperm, it was determined that artificial oocyte activation was necessary, and a course of using calcium ionophore to activate the oocyte was taken. After performing ICSI for three mature oocytes and then using calcium ionophore to activate the oocytes, normal fertilization was thus observed in two oocytes. Pregnancy was achieved via implantation, thereafter leading to a successful live birth.

Conclusion

In this study, calcium ionophore was used to activate the oocytes for a case demonstrating secondary infertility of fertilization failure after ICSI and thus a live birth was achieved. The present method is therefore believed to be extremely useful for cases of fertilization failure after ICSI.

References


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Artificial oocyte activation with calcium ionophore allowed fertilization and pregnancy in a couple with long-term unexplained infertility where the female partner had diminished EGG reserve and failure to fertilize oocytes despite intracytoplasmic sperm injection

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Summary

Purpose: To determine if fertilization and embryo development and pregnancy was possible following in vitro fertilization (IVF) in a couple with long-term unexplained infertility where the female partner had diminished egg reserve and where fertilization failure occurred despite conventional oocyte insemination and intracytoplasmic sperm injection (ICSI). Methods: In vitro fertilization was performed using a low-dose follicle stimulating hormone (FSH) stimulation protocol. Prior to ICSI, artificial oocyte activation with calcium ionophore was used. Results: Only one mature oocyte was retrieved but it fertilized and cleaved to a good quality 8-cell embryo on day 3. A pregnancy with fetal viability was achieved but she subsequently miscarried. A second attempt successful. Conclusions: Fertilization and pregnancy is possible even in women with diminished egg reserve with previous failed fertilization with ICSI by performing artificial oocyte activation with calcium ionophore. It is not clear if the sperm lacked oscillin or if the eggs were not responsive to oscillin.

Key words: Artificial oocyte activation; Calcium ionophore; Normal sperm; Diminished egg reserve; Minimal stimulation.

Introduction

Oocyte activation is characterized by a two-step pattern of rises in intracellular calcium (Ca++) concentrations. A first Ca++ rise, referred to as the trigger, originates from the oocyte after sperm-oocyte membrane interaction. This initial Ca++ rise that is released from internal Ca++ stores of the oocyte membrane is dependent on a receptor-mediated interaction between the sperm and the oocyte plasma membrane [1].

With intracytoplasmic sperm injection (ICSI) the sperm-oocyte plasma membrane interaction is eliminated. However, the mechanical injection procedure itself (which can occur by merely the injection without sperm) also causes a massive influx of calcium into the oocyte and is referred to as a pseudotrigger [1].

The second step of oocyte activation is referred to as the oscillator related to the characteristic of a series of shorter calcium transients of high amplitude that begins 30 minutes after the trigger (step one) and continues for three to four hours [1]. The oscillator function is dependent on the release of a sperm associated activating factor. This factor has been named oscillogen or oscillin [2]. This sperm oocyte activating factor can control the frequency of oscillations (thus the name oscillin). It is not species-specific and thus a deficiency of oscillin in human sperm can be detected by failure to activate mouse oocytes [3]. This test is referred to as the mouse oocyte activation test or MOAT. Sperm demembranization is necessary to allow the release of the cytosolic sperm factor responsible for the oscillator function and its sustained activity [4, 5].

ICSI has enabled fertilization of oocytes from extremely low concentrations of viable sperm, sperm coated with a high concentration of antisperm antibodies, and immature testicular sperm even when taken many hours after the death of a man not on life support [6-8]. In 3% or less of cases in women who make an adequate number of follicles there will be complete failure to fertilize the oocytes despite ICSI [9-11].

Fertilization failure despite ICSI can be related to the partial or complete inability of the sperm to activate oocytes [12]. Another reason for fertilization failure despite ICSI is the inability of the oocytes to decondense the sperm [13]. Sometimes the problem is obviously related to the sperm lacking oscillin, e.g., with globozoospermia where the fertilization rate varies from 0-37% [9, 14, 15]. Fertilization has occurred with globozoospermia following ICSI when the eggs were activated artificially by calcium ionophore [15, 16]. A case was described where calcium ionophore allowed activation and fertilization of an oocyte and a successful pregnancy in a couple with fertilization failure despite normozoospermic motile sperm [17].

The case described here reports another situation where there was complete fertilization failure despite normal sperm and ICSI where oocyte activation with calcium ionophore was performed followed by fertilization with ICSI leading to a pregnancy only this time in a woman with diminished egg reserve.
Case Report

A 34-year-old female married for 14 years and having unprotected sex for 12 years presented with primary infertility. She lived in another state and was found to be “approaching menopause” with a serum FSH of 64 mIU/ml. A second serum FSH was 37 mIU/ml with a serum estradiol (E2) of 56 pg/ml. She still had spontaneous menses but had oligomenorrhea. The only interruption to her attempts at fertility was a one and a half respite while she was evaluated and treated for an ocular pseudotumor.

The couple had insurance coverage for in vitro fertilization (IVF) but not for donor egg coverage. The reproductive center that they had consulted presented data from one of the leading IVF centers in the world claiming no live pregnancies despite the transfer of normal appearing embryos in women of any age if the serum FSH was > 15 mIU/ml [18]. They refused to try any treatment other than the use of donor oocytes which the couple could not afford.

The couple was aware of the data from our IVF center that found quite reasonable pregnancy rates with IVF-ET in women whose mean day 3 serum FSH was much higher than 15 mIU/ml as long as a lower dosage of FSH was used for follicular maturation [19]. Though there did not appear to be any problem in the semen analysis or fallopian tubes, because of the length of their infertility and their insurance coverage for IVF-ET we recommended IVF-ET.

The initial semen analysis at our facility showed a normal semen concentration of 32.7 million per ml with 70.6% motility with 18% with rapid linear motion. The hypo-osmotic swelling test was normal at 68% and there were no antisperm antibodies. The one “abnormality” was that the percentage of sperm with normal morphology using strict criteria was only 4% [20]. The couple was advised that for many years some clinicians believed (and some still believe this concept today) that when the sperm morphology was ≤ 4% that neither intercourse, intrauterine insemination or conventional oocyte insemination will result in adequate pregnancy rates [20]. In fact they had concluded the pregnancy rates approached zero [21-24]. However, they were also advised that our own data failed to corroborate these previous studies and in fact found no predictive value of strict morphology ≤ 4% [25-27]. In fact in another study we actually found that there was no greater risk of failed fertilization with conventional oocyte insemination with teratozoospermia sperm compared to ICSI but the former resulted in significantly higher pregnancy rates per transfer [11].

For cycle 1 a protocol was used that used a little more FSH than the usual minimal stimulation used for diminished egg reserve based on a more optimistic baseline blood with a serum E2 of 87.9 pg/ml and a serum FSH of 11 mIU/ml [28]. The peak serum E2 reached 331 pg/ml and two mature oocytes were inseminated by conventional insemination. The couple chose this fertilization option because of the data showing higher pregnancy rates with conventional oocyte insemination and to determine if their long-term infertility failure could be related to failed fertilization [11]. Indeed these oocytes failed to fertilize.

For cycle 2 a lower dose FSH protocol was used and was started on day 5 when the serum E2 was 54.2 pg/ml and the serum FSH was 14.3 mIU/ml. For both cycles the serum FSH was lowered with ethinyl estradiol [30, 31]. Three mature follicles were retrieved but none fertilized despite ICSI. Semen parameters were completely normal.

For her third and final insurance covered cycle we suggested artificial oocyte activation with calcium ionophore. For cycle 3 her day 2 serum E2 was 38.6 and the serum FSH was 12.6 mIU/ml while taking ethinyl estradiol (20 μg) daily. With a minimum stimulation protocol her peak serum E2 reached 200 pg/ml. A single metaphase II egg was retrieved. Artificial oocyte activation was performed using calcium ionophore as previously described [15-17]. An 8-cell embryo on day 3 with 25% fragmentation was transferred and she conceived. She showed fetal viability six weeks from egg retrieval with properly rising serum beta human chorionic gonadotropin levels. However, unfortunately she subsequently had a miscarriage. Knowing now what is needed to achieve a pregnancy the couple tried again using a low-dose FSH protocol because of diminished egg reserve and artificial oocyte activation with calcium ionophore. Two oocytes fertilized and two embryos (a 5-cell and 8-cell) were transferred and she has completed the first trimester.

Discussion

It is clear that women with markedly elevated FSH levels, even over 100 mIU/ml, and even those in apparent menopause, can achieve successful pregnancies [29-35]. Those who believe that an elevated serum FSH results in embryos that do not implant still recognize that there is generally no problem with fertilization [18]. Though it is clear that the probable cause of the couple’s long-term infertility was the inability of the sperm to fertilize the egg, it is not clear whether the problem was a sperm or oocyte factor.

The problem of failed fertilization should not have been related to the first step of fertilization, i.e., the trigger rise of Ca++ that occurs with contact of the sperm with the oocyte membrane since the first cycle using conventional insemination demonstrated no problem with sperm binding. Furthermore, even if for some reason binding of sperm did not cause the trigger, then the defect should have been obviated by the mechanical injection of the oocyte membrane by ICSI (pseudotrigger) in cycle 2.

Most of the data suggests that Ca++ ionophore treatment of oocytes has a reasonable chance of allowing fertilization and normal embryo development and even pregnancies when the sperm are deficient in oscillin. However, there are some data suggesting that Ca++ ionophore treatment can also allow fertilization when the problem with failed fertilization is related to oocyte rather than sperm defects [36].

If calcium ionophore proves less efficient for oocyte vs sperm-related defects leading to failed fertilization there is another technique that has been shown to enable fertilization when the egg does not respond to proper sperm signals [37]. Fertilization and embryo development and pregnancies have been reported using a modified ICSI technique using vigorous aspiration of oocyte cytoplasm when failed fertilization has been related to a defective oocyte factor that is involved in the activation of the oscillator mechanism [37]. Comparative studies in a larger series which would require a cooperative study between many IVF centers could help to determine which technique is more efficacious for sperm or oocyte related defects in the oscillator mechanism of fertilization and whether one technique is safer than the other. When calcium ionophore is used the patient should be advised that there is limited information of its potential toxic effect on oocytes and embryos.
Acknowledgment

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References


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**General Section**

Immediate and perioperative outcomes of polypropylene mesh in pelvic floor repair in a predominantly obese population

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**Summary**

This retrospective study was to identify perioperative and postoperative complications associated with use of polypropylene mesh for pelvic floor repair in a UK district general hospital in a predominantly obese population. The sample size was 27 women with data retrieved from records. Total mesh was used in 37.1%, isolated anterior mesh in 44.4%, and an isolated posterior mesh in 18.5%. There was a high incidence of obese (BMI kg/m² ≥ 30.0) women (66.67%). The highest recorded thus far. A high proportion of the women (44.4%) were also over the age of 65 years with attendant comorbidities. The age range was 45-77 years. Complications included mesh exposure (7.4%), catheterization at discharge (7.4%), bladder injury during dissection (3.7%) and recurrent prolapse (7.4%). In the carefully selected individuals, polypropylene mesh for prolapse repair appears to be a safe technique to correct pelvic organ prolapse. However, long-term follow-up is needed with further research.

**Key words:** Vaginal mesh; Pelvic organ prolapse; Predominant obesity; Immediate and perioperative morbidity.

**Introduction**

The first commercially available ‘system’ for transvaginal delivery of polypropylene mesh into the vesicovaginal and or rectovaginal plane to repair uterine and or vaginal prolapse was approved in 2004 by the Food and Drug Administration in the US. The system has been used in France for some time with data on follow-up being compiled. This system has been shown to be able to provide similar results to abdominal sacral colpopexy while precluding morbidities associated with laparotomy or prolonged laparoscopy. The system used is one of several commercially available kits which through the use of polypropylene mesh, combines apical support with reinforcement of either or both the anterior and posterior vagina. The use of polypropylene mesh has been buttressed by the fact that the scarring and sclerosis produced by classical pelvic reconstructive surgery restores only 50% of the preoperative tissue strength [1-3].

There have been several studies examining the immediate postoperative sequelae. Further studies are compiling data on the long-term sequelae. However this study looked at outcomes in a predominantly obese cohort population.

**Materials and Methods**

This retrospective study was to identify perioperative and postoperative (3 months and 12 months) complications associated with use of polypropylene mesh for prolapse repair in predominantly obese patients in a UK district general hospital. The sample size included a total of 27 women between November 2006 and December 2008 and both practitioners were proficient in performing stress incontinence surgeries.

All patients had preoperative evaluation including history, physical examination and urine culture. Pelvic organ prolapse quantitative examination was a tool used in identifying degree of prolapse. The type of prolapse was identified based on definitions adopted by the International Continence Society [4]. Urodynamic evaluation was performed when indicated by urinary symptoms.

The polypropylene mesh repair procedures were carried out using the manufacturer’s instructions [5]. A course of preoperative vaginal estrogen was offered on a need-to basis. All the women underwent general anaesthesia as this was the local protocol. This was also the case for excisions of persistent eroded mesh. Prophylactic antibiotics were given intraoperatively while a transurethral Foley catheter and gauze packing in the vagina were performed at the end of the procedure. The catheter and packing were left in for a period of 24 hrs. The women were discharged home without catheters on the second or third day. They were reviewed 8-12 weeks and 6 and 12 months later.

The primary outcome was deviation from a normal operative and postoperative course within 8-12 weeks of surgery. Complications seen during surveillance at 6 and 12 months in some of the women have also been included. Complications were based on the Dindo scale of 0-5 based on therapeutic consequences of a complication. Grade I includes minor risk events not requiring therapy other than analgesics, antipyretics, antiemetics and anti diarrheal drugs while grade II includes events which require pharmacological treatment with drugs other than the ones listed for grade I complications. Interventions within grade III included the use of blood transfusions and total parenteral nutrition. This grade is subdivided into grade IIIa and IIIb. Grade IIIb required the need of general anesthesia.

Grade IV included life-threatening complications while grade V complications resulted in death [6].

Data was obtained from the review of patients’ records. Results are presented as mean (range) for continuous variables and as percentages for categorical variables.

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Results

Another focus of this study was to examine if there was a difference in results in overweight and obese patients. The incidence of overweight and obese women in this population was 92.59%. There was a predominant percentage of obesity (BMI ≥ 30) in this group (66.67%).

Most of the subjects were postmenopausal (88.88%) with a good percentage (51.85%) having had no previous hormonal replacement therapy. A good number of the women had previous pelvic organ prolapse repair (37.04%). Most women had grade II prolapse (66.67%). General anesthesia was utilized in all the cases.

Demographic and clinical details are in displayed in Table 1.

Table 1. — Demographic and clinical details of the study population.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>61.78 (45-77)</td>
</tr>
<tr>
<td>Mean body mass index kg/m² (range)</td>
<td>29.8 (22-37)</td>
</tr>
<tr>
<td>Mean hospital stay (range)</td>
<td>3.07 (2 -5)</td>
</tr>
<tr>
<td>Mean estimated blood loss (range)</td>
<td>105.56 (50-250)</td>
</tr>
<tr>
<td>Menopausal status (%)</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>11.11</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>51.85</td>
</tr>
<tr>
<td>Postmenopausal + HRT</td>
<td>37.04</td>
</tr>
<tr>
<td>Preoperative stage of prolapse (%)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>66.67</td>
</tr>
<tr>
<td>Stage III</td>
<td>29.62</td>
</tr>
<tr>
<td>Stage IV</td>
<td>4.71</td>
</tr>
<tr>
<td>Previous hysterectomy</td>
<td>62.96</td>
</tr>
<tr>
<td>Previous surgery for POP</td>
<td>37.04</td>
</tr>
</tbody>
</table>

Mean age was 61 years with average hospital stay about three days and the average BMI being 29.8. Mean operative time was 87.48 minutes with average blood loss being 105.56 ml. The above figures were comparative with other studies examined [7, 8].

Mesh exposure was seen in 7.4% of cases at 12 weeks following a bout of respiratory infection; 7.4% presented with a recurrent prolapse within the 12-week postoperative period. There was also another case of recurrent prolapse following a urinary tract infection. There was resolution of a case of mesh erosion which presented 12 months later with the use of topical estrogen cream.

A case of a promptly repaired bladder injury during dissection was seen. There was no bladder perforation with trocar insertion.

| Complications                  | Total (10) | Anterior (12) | Posterior (5) | Freq (%) | Morbidity grade |
|--------------------------------|------------|---------------|---------------|----------|----------------|----------------|
| UTI                            | 1          | 1             | 0             | 7.4      | II             |
| Intraoperative injury           | 1          | 0             | 0             | 3.7      | I              |
| Recurrent POP                   | 1          | 1             | 0             | 7.4      | IIIb           |
| Rec POP+Resp Infection          | 0          | 1             | 0             | 3.7      | IIIb           |
| Mesh exposure                   | 0          | 1             | 1             | 7.4      | III            |
| Mesh erosion                    | (12 months later) | 0          | 1             | 0        | 3.7            |

There was also no incidence of hematoma or rectal injury. No hemorrhage of more than 250 ml was recorded.

Table 2 reflects type of complication in relation to type of repair done.

Discussion

Polyporeline mesh is the most commonly used synthetic graft material used in prolapse repair surgery. Mesh exposures, erosions, infections and sinus tract formation are the most often encountered complications described [9].

In a predominantly obese population, surgical complications are bound to be on the increase. It was interesting to observe different types of morbidities seen in this subgroup of women. All the complications were found in overweight and obese women. The complications seen in the overweight group included two cases of urinary tract infection, one of intraoperative bladder injury, one of recurrent prolapse and one of mesh erosion. The obese and very obese group had two cases of mesh exposure, one case of recurrent prolapse, and one case of recurrent prolapse following respiratory infection.

The Dindo morbidity scale grades complications based on invasiveness of the successful treatment module. The common complications were recurrent prolapse (7.4%) and urinary tract infection (7.4%).

A significant number of the recurrent prolapses were from the group with a history of recurrent prolapse (37.04%). One had a conservation of cervix following a previous laparoscopic subtotal hysterectomy while the other had conservation of the uterus due to personal requests despite contrary counselling and advice. There was one presentation of a rectocele following an anterior mesh insertion three months later following a bout of respiratory infections.

Reasons for prolapse recurrences are varied and include:

1) Changes in stability of the pelvic floor after surgery. This has been identified by the study done by Clark et al. [10] which revealed a 40% incidence of recurrence postoperatively at another site.

2) A greater likelihood of recurrent prolapse has also been associated with age < 60 yrs and preoperative pelvic organ prolapse quantification stage 3 or 4 [3]. These characteristics were evident in this group of recurrent prolapse.
3) Inherent weak native tissues, the use of which have led to treatment failures [7]. As there was a significant number of repeat procedures for recurrence (37.04%), this may be a contributing factor.

Of the patients, 7.4% went home catheterized as a result of retention from urinary tract infection. This figure was well below the median rate of 10.9% reported after abdominal sacral colpopexy [11].

The visceral injury made during dissection was promptly repaired and a catheter was left in for a period of ten days under antibiotic cover. She was a 77-year-old woman with no previous history of hormone replacement therapy resulting in atrophic vaginal tissues. A cystogram carried out thereafter was normal.

There was no bladder perforation with trocar insertion. The rate of visceral injuries is comparative to a previously published rate of 4.0% during Prolift insertion [12] although it is higher than the 0.2% rate reported for transobturator techniques of midurethral sling placement [13]. There was also no incidence of haematoma or rectal injury. No hemorrhage of more than 250 ml was recorded. These results were better or comparative to other studies [7, 8].

Mesh exposure rate (7.4%) was relatively high in this study as compared to 4% in a post mesh insertion study involving the use of Prolift [7] or 3.7% in an abdominal sacral colpopexy study [14]. However a recent review has shown rates to be between 4.6-10.7% [15]. The overall surgical intervention to correct mesh exposure was 7.4% and this was due to hospital protocol and personal requests. The case of mesh erosion occurred 12 months later in a postmenopausal woman and was possibly due to estrogen deficiency as this erosion resolved months later in a postmenopausal woman and was possibly due to estrogen deficiency as this erosion resolved.

The rates of mesh exposure and erosion could be due to the high mean age in our cohort (61.78 yrs) and the present hospital protocol of intermittent use of preoperative vaginal estrogen on a need-to basis as opposed to a mandatory preoperative course.

Limitations of this study included the relatively small sample size and a retrospective design encouraging bias. This was reduced by data analysis from consecutive consultation notes identified on the computer records. Our findings are particular for women who are overweight or obese with a significant percentage of recurrent prolapse, adding more data regarding safety and complications of mesh pelvic floor repair systems. There appeared to be a high incidence of certain complications. Alterations in practice have been made to reduce these complications, i.e., use of preoperative vaginal estrogen therapy. We hope also to build on our areas of success via an on-going assessment of these women with the aim of following them up to 24 months postoperatively.

Conclusion

In carefully selected individuals, polypropylene mesh for prolapse repair appears to be a safe technique to correct pelvic organ prolapse. However, long-term follow-up is needed. Further research should be directed towards well-conducted and adequately powered randomized controlled trials.

References

Relation between Doppler findings and perinatal outcomes in fetuses with intrauterine growth restriction

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Summary

Purpose of Investigation: To find the relationship between fetal Doppler findings and perinatal outcomes in intrauterine growth restriction. Methods: Eighty-two cases with a prenatal diagnosis of intrauterine growth restriction between November 2008 and July 2009 were included in this prospective study at Ege University School of Medicine. Fetuses were grouped according to Doppler parameters: those with normal Doppler findings (n = 43), and those with impaired arterial (n = 27) and venous systems (n = 12). Results: Out of 82 growth restricted cases, 43 (52.4%) had normal Doppler findings, while 27 (32.9%) displayed impaired arterial parameters and 12 (14.6%) had impaired venous parameters. The mean first minute Apgar scores were 7.57 ± 1.53 for the group with normal Doppler flows, 6.8 ± 2 for the group with an impaired arterial system, and 4 ± 1.9 for the group with an impaired venous system. Two cases from the normal Doppler flow group (n = 42), four cases from the impaired arterial flow group (n = 27), and 11 cases from the impaired venous flow group (n = 11) had fifth minute Apgar scores under 6. Evaluation of the umbilical artery blood gas revealed acidosis in two cases from the normal Doppler flow group (n = 42), three cases from the impaired arterial system group (n = 27), and five cases from the impaired venous system group (n = 11). Conclusion: A Doppler spectrum from normal to venous system impairment correlated with poor fetal outcomes including fetal acidosis, fetal mortality and morbidity, decreased Apgar scores at 1 and 5 min, and neonatal morbidity.

Key words: Fetal Doppler; IUGR, Perinatal morbidity.

Introduction

Normal fetal growth depends on genetic growth potential, along with maternal, fetal, placental and external factors. Defects in one or a combination of these factors affect fetal growth [1].

Intrauterine growth restriction (IUGR) is commonly characterized by birth weight below the 10th percentile. The American College of Obstetricians and Gynecologists (ACOG) describes IUGR as estimated fetal gestational age below the 10th percentile [2]. IUGR stands as one of the significant causes of perinatal mortality and morbidity in modern obstetric practice. Cooperation of an obstetrician and neonatologist in the management of fetuses with IUGR is essential. Mortality and morbidity rates can be decreased with correct diagnosis, suitable care and timely intervention. Timing of birth is very essential in antenatal management as there is no currently available successful intrauterine therapy. Maximum gestational age and minimum risk for intrauterine life should be aimed in timing of birth [3]. Neonatal consequences of IUGR comprise perinatal asphyxia and neonatal adaptive problems, and short- and long-term sequelae. Perinatal mortality rate increases by 10-20 times in infants with IUGR compared to normal fetuses [4].

Presence and severity of fetal hypoxemia and its prena
tal consequences can be correctly determined by Doppler ultrasound (US). Doppler US can noninvasively detect blood flow in uteroplacental circulation. It has been more commonly used in recent years due to its noninvasive and easy to use nature, and the fact that it provides reproducible results. Doppler US provides correct antenatal detection of IUGR, on-time intervention, and decrease in mortality and morbidity rates [5].

The relation between fetal venous and arterial Doppler findings and perinatal outcomes were correlated in a cohort of IUGR fetuses.

Materials and Methods

Eighty-two cases hospitalized in Ege University Faculty of Medicine, Obstetrics and Gynecology Clinic with a prediagnosis of IUGR between November 2008 and July 2009 were included in this study prospectively. The study was conducted in accordance with the guidelines, and approval was given by the Ethical Committee of the Ege University Hospital. Demographic and US data and Doppler parameters of all the patients and fetuses were recorded and prospectively evaluated. Patients were grouped according to Doppler parameters: those with normal Doppler findings (n = 43), and those with impaired arterial (n = 27) and venous systems (n = 12). Fetal or chromosomal anomalies, fetal infections, multiple pregnancies, premature membrane rupture and birth weight above the 10th percentile were criteria for exclusion from the study.

Gestational weeks were determined according to the date of last menstrual period, and confirmed by early US measurements. In patients who were not sure of the date of the last menstrual cycle, gestational weeks were calculated by first trimester crown-rump length (CRL) measurement. CRL was taken as a reference when a difference more than five days was present between the calculation based on the last menstrual date and CRL.

Fetal weight was calculated in all the cases by US measurements of biparietal diameter, head circumference, femur length,
humerus length, and abdominal circumference. Intrauterine growth restriction diagnosis was confirmed when the birth weight was under the 10th percentile. All US examinations and measurements were performed by a single operator with Voluson 730 Expert Ultrasound Color Doppler equipment. A 4-MHz convex probe was used in these procedures. The umbilical artery, bilateral uterine arteries, middle cerebral arteries, umbilical vein and ductus venousus parameters were assessed.

Umbilical artery Doppler measurements were performed at the free segment of the umbilical cord, distant from the fetus and the placenta. Following the observation that the acquired waveforms stayed stable for at least five cardiac cycles, measurements were performed on three different cycles and the results were averaged.

In the fetal middle cerebral artery (MCA) measurements, following detection of the vascular structures of the Willis polygon by color mode, Doppler indexes were measured at 0 degree angle from the MCA closest to the probe.

Absent diastolic flow or reverse flow in the umbilical artery, or an MCA PI less than the 5th percentile was evaluated as a sign of an impaired arterial system. The venous system was considered impaired in case of pulsation in the umbilical vein, and an A wave absence or reversal in ductus venousus.

Birth was performed in at most 24 hours following Doppler US measurement. Right after the infant was born, the cord was clamped before the first respiration, and 2 to 3 cc blood was collected with a heparin-coated needle from the umbilical artery prior to placenta separation. The blood was examined within at most 10 min with a Nova Biomedical blood gas analyzer. Umbilical artery pH values under 7.20 were considered as acidosis.

The clinical parameters compared were maternal age, gestational week, birth weight, Apgar score at 1 and 5 min, umbilical artery blood gas, intrauterine death, neonatal death, and neonatal morbidity.

To evaluate the findings of the study, SPSS 13.0 (Statistical Package for Social Sciences) software was used for statistical analysis. Comparison of the significance of quantitative data between the groups was performed by the variance analysis test, while the chi-square test was used to assess the significance of the differences between the qualitative data obtained. Relations between the parameters were examined by the Pearson correlation test. The results were evaluated in mean ± standard deviation, 95% confidence interval, and p < 0.05 significance level.

Results

Out of 82 IUGR cases, 43 (52.4%) had normal Doppler findings, while 27 (32.9%) displayed impaired arterial parameters and 12 (14.6%) had impaired venous parameters.

Mean age was 29.04 ± 5.49 years in the group with normal Doppler flows, 30.5 ± 5.7 years in the group with impaired arterial system, and 28.5 ± 4.94 in the group with impaired venous system. There was no statistically significant difference between the groups in terms of maternal age.

In the group with normal Doppler flow, mean gestational age was 258.6 ± 19.1 days and mean birth weight was 1968.8 ± 471 g; while mean gestational age was 231.2 ± 17 days and mean birth weight was 1233.7 ± 381 g in the group with an impaired arterial system; and these figures were 222.7 ± 23.7 days and 991.2 ± 564 g, respectively, for the group with an impaired venous system. While there were no statistically significant differences in terms of gestational age between the groups with impaired arterial and venous systems, a statistically significant difference was apparent between the group with normal Doppler flows and the other two groups (p < 0.05). No significant difference was detected in terms of birth weights between the group with an impaired arterial system and that with an impaired venous system, yet a significant difference was found between the groups with impaired arterial and venous systems and the group with normal Doppler flows (p < 0.05).

Mean first minute Apgar scores were 7.57 ± 1.53 for the group with normal Doppler flows, 6.8 ± 2 for the group with an impaired arterial system, and 4 ± 1.94 for the group with an impaired venous system. While there was no statistically significant difference between groups with normal Doppler flows and impaired arterial system in terms of the first minute Apgar scores, the difference detected between the group with an impaired venous system and the other two groups was statistically significant (p < 0.05).

Two cases from the normal Doppler flow group (n = 42), four cases from the impaired arterial flow group (n = 27), and 11 cases from impaired venous flow group (n = 11) had fifth minute Apgar scores under 6. In terms of the fifth minute Apgar scores, there was no statistically significant difference between groups with normal Doppler flows and impaired arterial systems, and the difference detected between the group with impaired venous systems and the other two groups was significant (p < 0.05).

Evaluation of the umbilical artery blood gas revealed acidosis in two cases from the normal Doppler flow group (n = 42), three cases from the impaired arterial system group (n = 27), and five cases from the impaired venous system group (n = 11). While the group with normal Doppler findings and that with an impaired arterial system had no significant difference between them in terms of umbilical artery blood gas values, a significant difference was observed between the group with an impaired venous system and the other two groups (p < 0.05).

Two postnatal death cases occurred in the group with normal Doppler flows (n = 43), while this rate was four for the group with an impaired arterial system (n = 27), and five for the group with an impaired venous system (n = 12). There was one fetal death case in utero in each one of the groups with normal Doppler findings and impaired venous systems. The groups with impaired arterial systems and normal Doppler flow had no statistically significant difference between them in terms of mortality rates, while there was a significant difference between the impaired venous system group and the other two groups (p < 0.05).

There was a significant difference between the three groups in terms of intubation status and respiratory distress syndrome (RDS) (p < 0.05), however there was no significant difference in terms of intraventricular hemorrhage (IVH) (Table 1).
Table 1. — Neonatal morbidity status.

<table>
<thead>
<tr>
<th></th>
<th>Normal Doppler</th>
<th>Abnormal Arterial</th>
<th>Abnormal Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 42)</td>
<td>(n = 27)</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>RDS</td>
<td>4 (%9)</td>
<td>9 (%33)</td>
<td>10 (%91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>IVH</td>
<td>1 (%2)</td>
<td>1 (%3.7)</td>
<td>1 (%9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>3 (%7)</td>
<td>9 (%33)</td>
<td>10 (%91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

RDS: Respiratory distress syndrome; IVH: Intraventricular hemorrhage; n.s: non significant; p < 0.05: statistically significant.

Discussion

Fetuses with IUGR are at higher risk for poor perinatal and long-term consequences compared to the fetuses with normal growth patterns. Perinatal mortality increases 8-fold when fetal weight is under the 10th percentile, and by 20-fold when the fetal weight is under the 3rd percentile [6]. Combined use of fetal biometry, biophysics profile (BPP), NST, and arterial and venous Doppler US provides the best results in the management of these fetuses. When used alone, these tests have a limited value in IUGR management. Timing of birth is very critical in preterm fetuses with IUGR, and gestational age is the factor that contributes the most to poor outcomes [7, 8]. Bilardo et al. [9] found poor perinatal outcomes to be 45% and perinatal mortality rate to be 36% under 30 weeks gestation in a severely premature IUGR group (n = 33).

Birth weight is one of the most significant findings affecting perinatal morbidity and mortality. Risk for poor perinatal consequences increases by 5-30 times for infants born with a birth weight of 1500-2500 g (< 10th percentile) at term compared to infants born at 10th-90th percentile, while this risk is increased by 70-100 times for infants with a birth weight of 1500 g or less (3rd percentile) [10]. In our study, mean birth weight was 991 ± 564 g in the group with an impaired venous system, 1,233 ± 381 g in the impaired arterial system group, and 1,968 ± 471 g in the normal Doppler flow group.

The relation between venous Doppler anomalies and perinatal consequences is very significant for clinical management. A progressive rise in venous Doppler indexes reflects impairment in cardiac function. This impairment indicates progress from fetal hypoxemia to acidosis and intracerebral death if birth does not occur. In case of increase or abnormality in venous system Doppler indexes, sensitivity for fetal acidaemia is 70-90%, and specificity is 70-80% [11]. In our study, we detected acidemia (umbilical artery pH < 7.2) in 45% (5/11) of the group with an impaired venous system, in 11% (3/27) of the group with an impaired arterial system, and in 4.7% (2/42) of the normal Doppler flow group. As a result, Doppler US is useful in the evaluation of fetal oxygenation and acid-base status.

Fetuses with IUGR are also prone to multiorgan failure, RDS, IVH, NEC, bronchopulmonary dysplasia, and hemorrhage disorders [12,13]. In a study which included 300 fetuses with IUGR, cases were separated into 2 groups [14]. Group 1 (n = 137) consisted of fetuses with end-diastolic flow in the umbilical artery, while group two (n = 163) consisted of those with absence of diastolic flow or reverse flow in umbilical artery. Rate of RDS, sepsis, perinatal mortality and morbidity, and need for a neonatal unit was higher in Group 2. Also in a study where 404 pregnant women with IUGR fetuses were examined, 39 (9.7%) of the fetuses developed NEC [15]. NEC incidence has been observed to increase in particular with change in the venous parameters from normal to abnormal in Doppler ultrasound.

Conclusion

IUGR stands as one of the significant causes of perinatal mortality and morbidity in modern obstetric practice. Mortality and morbidity rates can be decreased with a correct diagnosis, suitable care and on-time intervention. Time of birth is very essential in antenatal management, as there is no currently available successful intrauterine therapy. In our study, gestational age at delivery and birth weight decreased, acidosis in umbilical artery blood gas and mortality increased, first and fifth minute apgar scores decreased, and the neonatal morbidity rate was elevated from normal to impaired venous system findings in Doppler.

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Impact of the medicalization of labor on mode of delivery

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Summary

Aims: To evaluate whether routine medical interventions during labor (oxytocin augmentation, induction, amniotomy, epidural analgesia) condition the outcome of delivery independently of each other and of obstetric risk (calculated in an objective manner). Moreover, to evaluate whether there is an ideal window for initiating such interventions. Methods: Prospective, observational study with 1,047 patients enrolled. Results: Medical interventions were high, whether in low-, medium- or high-risk pregnancies. Oxytocin augmentation (odds ratio 4.678) labour induction (odds ratio 1.717) amniotomy (odds ratio 1.403) and obstetric risk (intermediate-risk odds ratio 1.889, high-risk odds ratio 2.008) increase the probability of an operative delivery. Oxytocin augmentation increases both the probability of a Cesarean delivery and vacuum extraction. Epidural analgesia reduces the probability of cesarean delivery and increases the probability of vacuum extraction. The greater the cervical dilation when oxytocin infusion is initiated, the lower the probability of an operative delivery. The more advanced the cervical dilation and the lower the station when amniotomy or epidural analgesia are carried out, the lower the probability of an operative delivery. Obstetric risk and oxytocin augmentation appear to increase the probability of operative delivery in patients who have undergone amniotomy or epidural analgesia. In addition, labor induction in patients who undergo epidural analgesia increases the risk of operative delivery. Conclusions: Medical interventions during labor are high and cause a rise in operative delivery. Therefore, practitioners should defer it as much as possible. The exception is epidural analgesia because it seems to reduce the number of cesarean sections.

Key words: Labor; Oxytocin augmentation; Amniotomy; Epidural analgesia.

Introduction.

It has been reported [1] so far that the term “normal labor” does not have a clearly definable, practical definition and, consequently, in clinical practice it may happen that inappropriate medical interventions could be implemented in some cases in which labor does not seem normal according to a subjective judgement. Such medicalization is not functional to the “normal” progression of delivery [2]. We also believe that physicians may intervene more in high-risk pregnancies, in order to reduce labor time. This may be due to a categorical attribution of obstetric risk resulting in an excessive number of medical interventions, thereby obstructing “normal labor” even in cases where labor could take place without consequences despite the pregnancy being “at risk”.

The goal of this study was to evaluate whether routine medical interventions on labor (oxytocin augmentation, amniotomy, epidural analgesia, induction) condition delivery outcome independently of each other and independently of obstetric risk. In addition, the study evaluates whether there is an ideal window during labor in which to initiate such medical interventions as safely as possible.

Materials and Methods

The study was conducted prospectively on pregnant women admitted to the Operative Unit of the Gynecology and Obstetrics of San Pietro Hospital Fatebenefratelli, Rome between January 2008 and August 2008. This hospital is a tertiary facility in which epidural analgesia is offered “on demand”. The study encompassed 1,047 women with singleton gestations with cephalic presentation, during labor or needing induction of labor (planned cesarean section was excluded). Data regarding labor (cervical dilation and station) in relationship to the initiation of oxytocin augmentation, epidural analgesia, and amniotomy were gathered for each patient. Data concerning labor induction, birth method and all personal and anamnestic data of the parturient were collected after birth by analyzing patient records relative to the admission. On the basis of this information, obstetric risk was determined using a point system reported by Pescetto et al. [3]. This system objectively attributes a score of global risk by considering multiple pregestational and gestational factors (i.e., hereditary diseases, maternal age, social behavior, parity, previous obstetric history, diseases or nutritional disorders during pregnancy, endocrinological disorders, abnormality or diseases of the genital tract, others), to which a point is assigned (0, 5, 10, 15, 20, 30). Such scoring system does not consider all the situations that can be defined as “conferring an obstetric risk” but allows for the introduction of possible missing factors by leaving some fields open. The sum of scores indicates a global risk, subdivided into three categories: low risk (from 0 to 15), intermediate risk (from 20 to 25) and high risk (equal to or over 30). Although this system may be debatable, to our knowledge there is not yet an internationally validated scoring system for evaluating obstetric risk.

Despite the existence of the Pescetto risk scoring instrument [3], in Italy obstetric risk is not usually quantified in clinical practice. Therefore, in this study the clinical decisions were made only on the basis of presence/absence of obstetric risk defined in a subjective manner by the physician caring for the parturient on the basis of his or her own professional expertise. The variable “obstetric risk” was included in the multivariate logistic analysis as an independent variable with three levels of expression (low risk, intermediate risk, high risk). Such variable was used to check if the medical interventions were higher in patients truly at high risk.

Revised manuscript accepted for publication July 19, 2010
Other independent, categorical, variables included oxytocin augmentation, amniotomy, labor induction with prostaglandins, epidural analgesia (interventions that “medicalize” labor) and parity. Continuous independent variables were fetal weight and gestational age. The dependent variable was delivery outcome (overall operative delivery, vaginal operative delivery or cesarean delivery).

To evaluate whether the evolution of labor at the time of each medical intervention influences delivery outcome, a second multivariate logistic analysis was carried out. The independent variables (expressed on scales) were station and cervical dilation at time of each medical intervention, together with the other independent variables demonstrated as conditioning delivery outcome in the previous analysis.

Statistical calculations were carried out using SPSS 16.0 version software (SPSS Inc., Chicago, IL, USA), with a significance of $p \leq 0.05$.

**Results**

Table 1 illustrates the rates of independent and dependent variables (the variables gestational age and fetal weight at birth are described as median values with ranges). Table 2 illustrates the rates of medical interventions in patients with low, intermediate and high risk. All operative vaginal births were vacuum extraction.

Table 3 shows the odds ratio and $p$ values of factors influencing the overall operative delivery, the cesarean section, and the operative vaginal birth. Multiparas were less likely to undergo an overall operative delivery, while oxytocin augmentation, labor induction, amniotomy, obstetric risk increased the probability of an overall operative delivery. Multiparity and epidural analgesia lowered the probability of cesarean delivery, while obstetric risk and oxytocin augmentation increased such probability. Multiparity reduced the probability of operative vaginal birth, while obstetric risk, epidural analgesia, and oxytocin augmentation increased such probability.

Table 4 shows the odds ratio for the variables influencing delivery outcome in patients who underwent oxytocin augmentation, amniotomy, epidural analgesia, and labor induction.

In patients who underwent oxytocin augmentation, multiparity reduced the probability of an overall operative delivery while obstetric risk increased it. The increase in cervical dilation upon administration of oxytocin lowered the probability of an overall operative delivery. Remarkably, it lowered the probability of a cesarean delivery. Additionally, multiparity and epidural analgesia lowered the probability of cesarean delivery. Conversely, epidural analgesia and obstetric risk increased the probability of operative vaginal birth.

In patients who underwent amniotomy, the probability of an overall operative delivery was increased by oxytocin augmentation and obstetric risk, while with an increase in cervical dilation and lowering of station an overall operative delivery became less probable. Oxytocin augmentation and obstetric risk appear to increase the probability of both cesarean delivery and operative vaginal delivery. With increasing in cervical dilation and lowering of station cesarean delivery was less probable, while the lower the station, the lower the probability of an operative vaginal delivery.

In patients who underwent epidural analgesia, multiparity reduced the probability of an overall operative delivery, while labor induction, oxytocin augmentation, and high obstetric risk increased it. Oxytocin augmentation increased the probability of both cesarean delivery and operative vaginal birth. In addition, the greater the dilation and the lower the station, the lower the probability of an overall operative delivery, i.e., a cesarean delivery.

In patients with labor induction, it appears that only multiparity lowered the probability of an operative delivery, while the statistical analysis is not able to recognize the particular weight of other factors on the probability of cesarean delivery or operative vaginal birth due to the small number of patients with labor induction.

It is relevant to state that collinearity is found between intermediate and high obstetric risk, thereby confirming that the risk variable is considered by clinicians merely in a dichotomous and categorical manner (at-risk/not at-risk).
Table 4. — Odds ratio with 95% confidence intervals for the variables influencing delivery outcome in patients who underwent oxytocin augmentation, amniotomy, epidural analgesia, labor induction.

<table>
<thead>
<tr>
<th>Patients with oxytocin augmentation</th>
<th>Overall operative delivery</th>
<th>Cesarean section</th>
<th>Operative vaginal delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiparity</td>
<td>0.504</td>
<td>0.539</td>
<td>/</td>
</tr>
<tr>
<td>C.I. 95% 0.335-0.759</td>
<td>p = 0.001</td>
<td>p = 0.009</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.006</td>
<td></td>
<td>2.135</td>
</tr>
<tr>
<td>C.I. 95% 1.276-3.153</td>
<td>p = 0.003</td>
<td></td>
<td>p = 0.007</td>
</tr>
<tr>
<td>High risk</td>
<td>2.109</td>
<td>1.891</td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 1.379-3.224</td>
<td>p = 0.001</td>
<td></td>
<td>p = 0.019</td>
</tr>
<tr>
<td>Epidural</td>
<td>0.597</td>
<td>1.894</td>
<td></td>
</tr>
<tr>
<td>/ C.I. 95% 0.397-0.899</td>
<td>p = 0.013</td>
<td></td>
<td>p = 0.016</td>
</tr>
<tr>
<td>Dilatation</td>
<td>0.493</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(increasing)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 0.428-0.567</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with amniotomy</th>
<th>Overall operative delivery</th>
<th>Cesarean section</th>
<th>Operative vaginal delivery</th>
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<tr>
<td>Multiparity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 0.956-2.695</td>
<td>p = 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>1.650</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 1.015-2.681</td>
<td>p = 0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxytocin augmentation</td>
<td>3.476</td>
<td>3.128</td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 2.115-5.712</td>
<td>p = 0.004</td>
<td></td>
<td>p = 0.006</td>
</tr>
<tr>
<td>Labor induction</td>
<td>2.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 1.009-4.029</td>
<td>p = 0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilatation</td>
<td>0.388</td>
<td>0.611</td>
<td></td>
</tr>
<tr>
<td>(increasing)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 0.577-0.838</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.021</td>
</tr>
<tr>
<td>Station (lowering)</td>
<td>0.388</td>
<td>0.513</td>
<td></td>
</tr>
<tr>
<td>C.I. 95% 0.247-0.608</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.005</td>
<td>p = 0.017</td>
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<th>Overall operative delivery</th>
<th>Cesarean section</th>
<th>Operative vaginal delivery</th>
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Discussion

The present study is one of the few to evaluate the effects of combined routine obstetric interventions on delivery outcome. In addition, it also appears to be the only one to control both obstetric risk and the timing during labor in which oxytocin augmentation, epidural analgesia or amniotomy were carried out.

Obstetric risk greatly influences delivery outcome. An operative delivery is performed twice as often in parturients labelled as “at-risk”. In addition, these patients seem destined to be submitted to a greater number of medical interventions during labor, resulting in a greater number of operative deliveries. In clinical practice, obstetric risk is not quantified and is determined subjectively. Such policy seems to overestimate the obstetric risk, since the medical interventions are high even in low-risk patients. Therefore, an objective system for assessing risk could be useful for grading the type of interventions, in order to avoid unnecessary medicalization. However, on the basis of the data illustrated in Table 2, it can be noted that the rate of medical interventions is remarkably high. Gould [1] notes that this type of behavior is more likely in large birth centers routinely accustomed to managing pathological pregnancies.

There are other reports about the excessive number of medical interventions in low-risk patients [4, 5] particularly concerning oxytocin administration. The present study highlights a rise in risk of an overall operative delivery of about 4.7. Oxytocin augmentation in clinical practice appears to pose many dangers [6-8]. Concerning the delivery outcome, observational studies report that oxytocin administration seems to reduce labor time in nulliparas and to increase cesarean delivery both in nulliparas and in multiparas [6, 7]. On the contrary, in randomized studies, it is reported that oxytocin augmentation reduces the labor times of nulliparas without causing an increase in the number of cesareans or other unfavorable outcomes [9-12]. We believe that in randomized studies cited, the procedure for oxytocin administration was strictly adhered to. On the contrary, observational studies (among which the present one) do not verify whether oxytocin augmentation follows a precise protocol, with a higher number of operative deliveries. This possibility is indirectly supported by Clark et al. [13]. Said authors have demonstrated that a strict adherence to a check-list for oxytocin augmentation (that takes into consideration, among other factors, the frequency and quality of contractions and electronic fetal monitoring) annuls the dangers associated with the use of this drug. We are not able to assess which kind of protocol was followed during oxytocin augmentation in the present study, however it appears that oxytocin augmentation overall causes an increase in the number of cesarean deliveries when it is administered at onset of cervical dilation, independently of other variables and in particular, independently of station. Because the first phases of cervical dilation do not only depend on the effect of oxytocin, as illustrated in relation to the physiology of labor [14, 15], it may be dangerous to increase uterine contrac-
tions during the latent phase of labor. Moreover, oxytocin augmentation increases the number of operative vaginal births. It may be that administering oxytocin in increasing doses for too long a time could cause uterine inertia and therefore call for vacuum extraction. This fact justifies the data supporting successful spontaneous delivery outcomes when oxytocin augmentation is initiated upon advanced cervical dilation, so that the drug is infused for a shorter amount of time. Therefore we feel it is justified to defer the use of the oxytocin as much as possible rather than administer it from the first stage of labor. This can also be inferred by the results of Daniel-Spiegel et al. [16] which, after labor induction using oxytocin, does not reveal any benefits when it is continued to be used after labor has begun.

It is reported that amniotomy slightly increases the number of cesarean deliveries without clear implications on cervical dilation at the time it is carried out [17]. Some authors [18-20] have reported that amniotomy beyond a 3 cm dilation could prevent dysfunctional labor. Additionally, Barrett et al [20] confirm that amniotomy tends to increase the rate of early deceleration revealed by cardiotocography. Johnson et al. and Sheiner et al. [21, 22] report that routine amniotomy may shorten the first phase of labor only in nulliparas, increasing the overall cesarean deliveries. Cesareans should be due to the anomalies of the cardiotochographic pattern induced by the amniotomy itself [21]. However, the present study suggests that amniotomy may also cause dystocia. In fact, if station is low when amniotomy is carried out, the probability of an operative delivery is reduced. In addition, it does not appear that the procedure particularly increases cesarean births or operative vaginal births, demonstrating that the choice of intervention depends on the evolution of labor.

Some reviews [23-25] have analyzed the effects of epidural analgesia on delivery outcomes, revealing that it does not increase the number of cesareans but does appear to increase the number of operative vaginal births, without there being a clear reason. In fact, the clinical significance of longer labor times due to the epidural is not yet understood [25] but does not appear to confer any neonatal risk [23]. A study by Wong et al. [26] comparing epidural analgesia with systemic analgesia in nulliparas has demonstrated that the former can shorten the time required for cervical dilation, thereby shortening labor time, without increasing the number of cesareans or operative vaginal births. That study suggests therapeutic use of epidural analgesia during labor and the data presented in our own study support this possibility. Epidural analgesia does not appear to cause increased risk of operative deliveries because on one hand it reduces the probability of cesareans and on the other it increases the probability of operative vaginal birth. It is not possible to explain the reason for this effect using the data here presented. However, the decrease in number of cesareans seems to indicate that epidural analgesia facilitates the mechanisms of cervical dilation. This effect appears to increase with increased cervical dilation and station, while it seems annulled in patients induced with prostaglandins or those who receive oxytocin augmentation. A possible explanation could be connected with neurological involvement for cervical dilation [27], which, however, is not decisive if the mechanisms that modify the cervix are not triggered. Such mechanisms are set off by the prostaglandin analogues used for inducing labor.

Concerning labor induction, the data are insufficient to allow for a sufficiently powerful multivariate analysis. It appears to be confirmed that induced parturients can be more susceptible to an operative delivery, as is already known [28, 29].

Some limitations in interpreting the data may appear. In the clinical setting the decisions for managing labor could differ according to a subjective opinion of the obstetric risk and of the need for intervention. For example, some may attempt to prevent dysfunctional labor or to reduce labor time by intervening as soon as possible, while someone else may try to limit any interventions altogether. Additionally, the protocol for oxytocin infusion, epidural analgesia, labor induction were not homogeneous, as it may happen in routine care. Therefore, the indications and the modes of medical intervention vary.

We have controlled the effect of each medical intervention assessing when it was performed, in relationship to station and cervical dilatation. However, we are not able to state which kind of protocol is better for each kind of intervention.

Conclusion

When medical interventions during labor are used excessively, they bring about an excessive number of operative deliveries, both in high-risk pregnancies and above all, in those not at risk. Since we are not able to assess which is the best protocol for each medical intervention, each intervention should be limited or deferred as much as possible to favor the “normal” evolution of labor [1]. The only exception: it is considered very useful to supply “on demand” epidural analgesia in light of the demonstrated reduction of cesarean deliveries.

References

Impact of the medicalization of labor on mode of delivery


Maximizing the benefits of screening mammography for women 40-49 years old

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1Technological Institute of Athens, School of Healthcare Sciences, Faculty of Obstetrics, Athens
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4Aretaieio University Hospital, Gynecology Department, Athens (Greece)

Summary

Background: While women aged 50 and older are broadly considered to benefit from screening mammograms, the evidence of any similar advantages for younger women are still considered insufficient to form any substantial conclusions on the matter. The primary goal of this study was to examine whether or not the mortality rate of younger women is benefited by mammography, and if so, how can this beneficial effect be maximized. Methods: The authors have taken into account all available randomized control trials (RCTs) and have conducted a meta-analysis based on those RCTs to study the effect of mammography on the mortality rate of women younger than age 50. Further interpretation on various aspects of the results has also led to separate meta-analyses, with the RCTs included grouped in accordance to the mean time interval between screening mammograms employed by each study. The findings and conclusions of the comparison were used to calculate the number of mammograms necessary to reduce the absolute death risk, depending on the time interval between screening mammograms. Results: The meta-analysis indicated a reduction in breast-cancer mortality in the intervention group, which reached statistical significance (relative risk (RR) 0.81 [95% CI 0.71-0.93] p < 0.01). Furthermore, when the RCTs included were grouped according to their mean time interval between mammograms, there was a definite increase of statistical significance in favor of those RCTs with shorter interval times (RR 0.76 [95% CI 0.64-0.89] p < 0.01). Conclusions: The significant mortality rate reduction demonstrated by the meta-analytical results is a key indicator of the beneficial effect of mammography on the age group of women younger than 50. Additionally, the increase in the aforesaid significance when combining RCTs with short time intervals between mammograms, as opposed to those RCTs with longer intervals, suggests that the optimal use of mammographic screening lies with the former. This is better demonstrated when taking into account our approach to answering the practical question of “how many screening mammograms will take to save one life?” in correlation with the mean time interval involved.

Key words: Mammography before 50 years old; Screening mammography; Mammography in young women.

Introduction

The unequivocal belief in mammography as a beneficial factor when applied to women aged 50 years and older is the result of several randomized controlled trials which indicate a mortality risk reduction of about 25% [1] in those women who underwent screening procedures. What has been less certain, is whether or not screening mammography is of a similarly advantageous nature on younger age groups, namely on women aged 40-49 years of age. Several randomized controlled trials (RCTs) [1-8] have been conducted to elucidate on the matter, beginning with the HIP trial of Greater New York [4] up to the NBSS Canadian study [7] and the greatly anticipated British Age Trial [8].

The results of most of the trials were consistent with the approach of conducting screening mammography on younger women, albeit, statistically those results did not reach significance – with two possible reasons being either that indeed mammography does not constitute an effective screening method on those specific age groups, or simply because the RCTs themselves were of a limited statistical power to detect any actual difference between the control and study groups. This latter possibility stands as such, primarily because the number of participants was indeed small in relation to the issue at hand, which also poses an issue in accordance with the relatively low incidence of breast cancer in that age group when compared to older age groups [9-11].

The answer to the statistical weakness of several separate studies came in the form of meta-analyses which combined different RCTs, adjusting their different model approach in accordance to the studies’ heterogeneity. At least seven meta-analyses [1, 12-17] have been conducted so far, at least three of which [1, 2, 5, 18, 19] have been revised and updated some years after the initial publication. Only three of those meta-analyses [11, 15, 16] reached a statistical significance regarding the relative mortality risk reduction.

With the majority of studies showing a non-significant trend towards the effectiveness of screening mammograms in younger women, and only a handful demonstrating statistical significance, the question arose: why was mammographic sensitivity in younger age groups lagging behind that of older women? Certain studies [20, 21] indicated that mammographic sensitivity was greatly
affected by the density of breast tissue, which is greater in younger women, whereas rapid tumor growth shared an equally important role in decreased sensitivity when the time-interval between mammograms was lengthened.

With the aforementioned issues in mind, we facilitated the first data of the ten-year follow-up results made available by the British Age Trial. We used these data to conduct our own meta-analysis combining the majority of previous RCTs and we furthermore explored and interpreted different meta-analytical plots in an attempt to shed some light on the importance of interval times between mammograms and the level on which they influence the ultimate effectiveness of mammography on younger women.

Materials & Methods

The results of the analyses of all available RCTs [1, 3-8] were gathered in order to form the statistical pool needed to conduct the meta-analysis. The relative risks (RRs) and confidence intervals (CIs) were used as presented without re-conducting separate analyses of individual data for each RCT and re-evaluated data were used in cases where that approach was applicable [1, 2, 5, 18, 19]. The data were analyzed using MIX v1.7 [22, 23]. All meta-analyses conducted utilized the inverse variance method with a fixed-effects model, although a random-effects model and homogeneity check were also used for cross-check purposes. All RCTs mentioned in this paper were used for the final meta-analysis, excluding the Canadian NBSS Trial. An all-inclusive meta-analysis has nevertheless been conducted to study whether the exclusion of this study significantly altered the outcome, and a sensitivity analysis was also used to study the same matter.

Once the results of the meta-analysis were obtained, the studies included were sorted by the mean interval time they used between screening mammograms. The statistical trend was examined and two new meta-analyses, consisting of those studies with a mean interval time shorter than 24 months and those consisting of studies with a mean interval time longer than 24 months, respectively, were conducted. The relative risk reduction (RRR) was calculated for all groups of studies that were used to examine if and when that reduction was more significant and to draw a comparison where applicable.

Finally, we calculated the absolute death risk reduction for the two groups consisting of studies using different time intervals to answer the practical question of “how many screening mammograms are needed in order to save a life?” and explicate its correlation to the time interval between screening mammograms.

Results

The meta-analysis resulted in statistical significance (RR 0.81 [95% CI 0.71 - 0.93] p = 0.0025) (Figure 1). Although homogeneity among the included samples justified the use of a fixed-effects model (Q = 8.0431, p value = 0.4293), we also conducted a meta-analysis using a random-effects model and the results of each approach were shown to be identical. All studies were included, with the exception of the Canadian NBSS Trial and to ascertain that this study’s exclusion did not affect the statistical significance of the results, we used as reference both a sensitivity analysis plot (Figure 2) as well as another meta-analysis (Figure 3), this time including the NBSS Trial. The results of this all-including meta-analysis were also significant (RR 0.84 [95% CI 0.74 - 0.95] p = 0.0049).

Once statistical significance was ascertained, we moved on to examine possible trends in our results and their respective interpretations. During that procedure, we examined the cumulative forest plot of our meta-analysis with the RCTs arranged by decreasing mean time interval between mammograms. A cumulative plot graphically exhibits the meta-analytical outcome resulting by adding studies up to that point and it was thus demonstrated that with each addition of a study of a shorter mean interval time, the overall RR decreased while the RRR increased (Figure 4). To better examine the importance of time interval between mammograms, we divided the included RCTs in two groups, one consisting of RCTs with a mean time interval between mammograms over 24 months and a second group with studies of a mean time interval less than 24 months. We then conducted a separate meta-analysis for each group (Figure 5) and calculated the relative risk reduction (RRR) for both of these groups to present a viable comparison of the effect of time intervals between screening mammograms. For the group of studies with a mean time interval shorter than 24 months, the RRR was shown to be 24% (RR 0.76 [95% CI 0.64 - 0.89] p = 0.0007) while for the group of studies with mean interval times longer than 24 months, the results were not significant (RR 0.96 [95% CI 0.74-1.25] p = 0.7856).

We then moved on to calculate the RRR for all RCTs included in the meta-analysis and it was found to be 19% (RR 0.81 [95% CI 0.71-0.93] p = 0.0025). We compared this result with that of the meta-analysis consisting only of RCTs with interval times shorter than 24 months and although in both cases the p value was well below 0.01, the significance of the results when considering only the short interval time RCTs, increases 3-fold.

With that in mind, we went ahead to calculate the reduction of absolute death risk (RADR) for both cases. The RADR is equal to the RRR, multiplied by the absolute death risk (ADR). Keen & Keen [24] have estimated that the ADR at age 40 is 0.475% and that risk more than doubles between the starting ages of 45 and 55. We have chosen the modest approach of using the lowest percentage, that of 0.475%. Using the aforementioned formula (RADR = RRR * ADR) we calculated the RADR to be 0.0906% and 0.1155% for all RCTs of the meta-analysis and for the shorter mean time interval RCTs, respectively. Because the ADR acts as a constant, the 22% difference between the two results remains fixed, regardless of the actual value of the ADR.

Discussion

Our aim was to attempt a conclusive analysis of the previous RCTs, facilitated by the relatively new results from the British Age Trial to statistically ascertain
whether or not, screening mammography’s beneficial effects transcends the 50-year-old limit and positively affects younger women as well.

The study selection was based on the up to standard methodology from a statistical and academic point of view. As such, all studies were included with the exception of the NBSS trial which was found lacking the necessary credibility for adding to the statistical conclusions facilitated by the rest of the RCTs. The reasons for this lack of credibility, as have been explicitly described by a number of publications [25-27], include the nature of the selection of the participants for this specific trial, as the NBSS study invited volunteers which were afterwards randomized in study or control groups and thus, a selection bias may have been generated. Additionally, the NBSS study prescreened all participants with a clinical breast examination, something which could have weakened the findings of the trial by distributing women with clinical findings to the control and study groups. This prescreening procedure also leaves room for selection bias within the study, a possibility all the more striking when considering the noteworthy difference of advanced cancer occurrences between the control and the study group: the rate of advanced cancers of the latter was 3.8 times higher compared to that of the control group, a difference that would constitute reason enough to exclude this study from a meta-analysis regardless of the reasons that caused it. Furthermore, a rough 26% of the control
group underwent mammography screening during the study. Criticism has also been addressed towards the quality of the mammography conducted, which may have resulted in false-negative results and unfounded encouragement to the study group as well as to the short-follow up period of the study. For those reasons, we chose not to include the findings of this study in our meta-analysis.

Although the NBSS study was not included, we wanted to make sure that the significant results of our meta-analysis did not occur due to the exclusion of this trial alone. We thus conducted a separate, all-including meta-analysis and a sensitivity analysis. The all-inclusive meta-analysis turned out significant results while the exclusion of the study was adequately supported by the sensitivity analysis as well.

During examination of the cumulative plot of the meta-analysis, it was observed that a tendency of increasing significance occurred simultaneously with a decrease of the mean interval time between screening mammograms. Further examination using two separate meta-analyses, one for short-interval time mammograms and one for long-interval time ones, provided us with statistical evidence that more frequent screening mammograms provide more significant results in terms of mortality reduction. This statistically apparent indication is consistent with previous suggestions [28-33] that due to the differences of mastic density between younger and older women as well as to the more aggressive nature of tumors affecting the former, a more frequent approach of mammographic screening should be implemented.

In particular, while the RRR for the short-interval time mammograms was a promising 24%, the respective result for long-interval time mammograms was not significant statistically. When the RR of the short-interval time mammograms was compared to the RR of all studies included (short and long interval time alike) the significance factor was found to increase 3-fold in favor of the former. This pointed us in a direction of turning numbers to more practical functions, and we attempted to seek an answer to the question of “how many mammograms does it take to save a life?”.

The results were naturally in favor of the short-time interval approach when compared to all time intervals included, with 865 mammograms with a short-time interval between them, as opposed to 1,103 mammograms with a longer intervening time-span. What is noteworthy is that although the actual numbers may vary, the difference between them remains a fixed 22% in favor of the short-interval time mammograms. The idea that fewer mammograms are needed to save a life while at the same time they should be more frequent, may seem hard to grasp initially, but considering a fixed time-span of screening might ease the concept: in a 4-year period of screening, four lives will be respectively saved if an adequate number of women (1,103 in our case) did attend every two years. In our simplified example, this means that out of 3,460 women, four will be saved in four years if annual screening is implemented, while out of 4,412 women, only two will be saved in the same period of time, if implementing biannual screening.

Conclusions

The statistical significance of the meta-analysis, is an explicit indicator of the beneficial results of screening mammography in women younger than 50 years. The RRR of 19% can be considered as a designating factor in the approach of screening mammography where the minimum age for regular screening mammograms is above the 50-year-old “barrier”.

Moreover, the considerable difference between the RRR of those studies comprising short-interval times between mammograms and their long-interval time counterparts, represents the rather obvious advantage of the former in terms of mortality reduction. In a more practical aspect of the results, the obtained values from the meta-analyses of the above-mentioned groups of long-interval and short-interval studies can be used to calculate the number of screening mammograms needed to avert an event of RADR, or, put simply, to save a life. Having the RADR calculated, the number of mammograms needed to save a life when taking into account all studies, long-time and short-time intervals alike, is 1/0.09096% = 1103 while when using the short-interval studies alone, the number of necessary screening mammograms drops to 1/0, 1.155% = 865.

References


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Multidisciplinary approach during menopausal transition and postmenopause in Brazilian women


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Summary

Objective: To identify clinical, physical, life quality and nutritional aspects of Brazilian women during menopausal transition and postmenopausal periods. Methods: 115 women agreed to participate in the study. They were divided into two groups: GI – menopausal transition (n = 48) and GII - postmenopause (n = 67). The Kupperman-Blatt Menopausal Index (IMK) and Women’s Health Questionnaire (WHQ), Food Frequency Questionnaire and functional capacity were used. All patients were examined and underwent clinical and gynecological examination. Results: There was no significant difference in IMK, WHQ and functional capacity in either group. There was a higher caloric intake, especially in sugars, in postmenopause women than in menopausal transition women. Both groups presented reduced parameters in life quality and functional capacity. Conclusion: Our data suggests that there is no significant difference between women in menopausal transition and postmenopause, except in relation to the nutritional parameter. In both groups, the women presented low quality of life and reduced functional capacity.

Key words: Premenopause; Postmenopause; Diet; Comprehensive healthcare.

Introduction

Population ageing occurs in many developed and developing countries. Life expectancy for Brazilian women is 75.6 years [1]. More and more women experience hormonal alterations related to menopausal transition and post-menopause. Not only in developed countries but also in developing ones there is an increasing tendency in life expectancy for women who live with diseases during the ageing years [2]. Health care and adequate treatment are essential to maintain life quality.

Women’s menopausal transition and postmenopausal period is the passage from the reproductive phase (menopause) to senescence that generally occurs between 40 and 65 years [3]. In Brazilian women, natural menopause occurs between 48 and 50 years. It is considered premature menopause when it occurs before 40 years and late menopause after 52 years [4, 5].

Menopausal transition begins with the variation of menstrual cycle duration with high follicle stimulating hormone (FSH) and ends with the last menstruation (menopause). After this phase, postmenopause takes place [3]. Generally, in the first phase, women may present menstrual dysfunction and vasomotor symptoms, while in the second phase the effects of low levels of estrogens may be stronger, resulting in hot flashes, urogenital symptoms and cognitive alterations that may affect a woman’s life [4, 6].

The view of multiprofessional health care teams focused on menopause involves clinical and educational aspects. Activities should be established and integrated, aiming at the success of methodology and development of each project. The knowledge about specific characteristics of each group to be studied is fundamental [7-9].

This study aims at identifying the clinical characteristics, the nutritional habits, the functional capacity and the quality of life of women during transitional menopause and postmenopause.

Materials and Methods

This study is part of the Integral Program of Women Health Care during Climaterium (PIAC). It is a comprehensive health care program and interdisciplinary project that gives orientation to women in the transition to menopause and postmenopause. This project has been approved by the Ethics Committee of the Federal University of São Paulo, São Paulo Medical School (UNIFESP – EPM). Clinical, physical, nutritional and quality of life aspects that may interfere in women’s health during menopause were analyzed. Voluntary patients were examined at the Ambulatory Medical Center for menopausal transition and postmenopause, Discipline of Gynecological Endocrinology, Department of Gynecology, UNIFESP – EPM. The participants’ age varied between 40 and 70 years and they were nominally invited between June and August 2006. After they were informed about the project, 115 women signed a consent form to participate in the study. Exclusion criteria were: the use of any specific hormonal drugs to minimize menopausal symptoms in the previous 12 months to the interview; ingestion of soy and its derivatives or herbal substances; acknowledged or suspicious neoplasia; kidney, thyroid or liver chronic diseases; cerebral vascular disease and myocardial infarction; tabacco use (> 10 cigarettes a day) , hyperprolactinemia; thromboembolic disturbances; diabetes mellitus; systemic arterial hypertension uncontrolled and age below 40. The voluntary patients were divided into two groups: GI - transition to menopause (n = 48); GII – postmenopause (n = 67) with no menstruation for more than a year. The Kuppermann-Blatt Menopausal Index (IMK), Women’s Health Questionnaire (WHQ), the Modified Stanford Health Assessment Questionnaire – simplified, modified and validated version in Brazil (MHAQ-Brazil) and food frequency questionnaire were applied.
in all volunteers in this study. Participants underwent clinical and gynecologic examination. Epidemiologic data was collected such as age, marital status, and economic status (employed or not employed). The IMK was developed in 1953 and it has been used in many studies to evaluate the gravity of menopausal symptoms [10]. The index includes 11 symptoms. Each category is calculated in a four point scale in which zero equals asymptomatic and four, severely symptomatic. Total points for each item evaluates the gravity of menopausal symptoms that may vary from 0 to 51 points, the higher the punctuation the more severe the complaint. The WHQ was the first questionnaire to be included in the International Health Related Quality of Life Outcomes Database [11]. It was validated in Brazil [12] to evaluate health status, because it is easy to understand and to apply. It has 36 items, divided into nine dimensions: depressive mood (six items); somatic symptoms (seven items); anxiety/fears (4 items); vasomotor symptoms (two items); sleep problems (three items); sexual functioning (three items); menstrual problems (four items); cognitive difficulties (three items) and attraction (three items). The scale varies from zero to four points, the higher the score the more pronounced the suffering and dysfunctions. The MHAQ – Brazil [13, 14] allows for the evaluation of measured parameters in therapeutic assay and was used to check functional capacity. It has eight sub-scales which evaluate different aspects of the patient’s daily life. Each one of these sub-scales presents two or three questions related to physical activities. The patient was asked the degree of difficulty he found in realizing a determined activity one week previous to the interview and assign a grade from zero (no difficulty) to three (impossibility to realize the activity). The sub-scale grade is equivalent to the higher grade attributed in one of the two or three questions. The instrument’s final score is obtained by the arithmetical average of the grades of the eight sub-scales and it varied from zero to three. The questionnaire related to food frequency [15] is based on the individual. It registers or describes the patient’s usual food ingestion based on a list of different foods. The quantity and kind of food on the list varied according to the aim of the evaluation. The food frequency questionnaire offers qualitative information on food ingestion. This study established the number of women who ingested specific food during the week previous to the interview. In the statistical analysis data was processed, and estimates were made about the distribution center and of the variability of the results for numerical variables: average, standard deviation and standard error for the average. The unpaired Student’s t-test or chi-square test were use to compare data obtained from the studied groups. The significance level was fixed at 0.05 for both tests; 90% confidence limit was calculated with 40 patients per group.

Results
Clinical characteristics included age, body mass index (BMI), marital status, and economic status (Table 1). The average age of women on transition menopause (48.22 ± 2.30) was lower than that of postmenopause women (55.10 ± 3.4, p < 0.05). There was no statistical difference between the groups as to BMI and marital status. In both groups BMI was above 26. Unemployment rate was significantly higher among postmenopause women. Table 2 indicates IMK, WHQ and MHAQ - Brazil. There was no significant statistical difference between either group. Nutritional characteristics indicated that postmenopause women presented higher daily consumption of carbohydrates, especially of sugars (p < 0.05). The other items considered showed no significant difference (Table 3).

Discussion
This study aimed at identifying clinical, nutritional habits, functional capacity and life quality of women during the menopausal transition and postmenopause. These are important aspects to be considered when planning multiprofessional care for the prevention of diseases and quality of life of women. Our studies suggest that, in
spite of age and hormonal differences in the menopausal transition and postmenopausal women, additional factors were not identified in relation to IMK, functional capacity and WHQ. IMK is an instrument used to evaluate climacteric symptoms that may influence life quality [16, 17].

The most important symptom is vasomotor-related and it might appear in transition menopause and in the first years of postmenopause [18]. It must be emphasized that during menopausal transition hot flashes appear when there is a decrease in estrogen concentration. It is known that during this period estrogen fluctuation occurs and the symptoms may appear or disappear spontaneously [19]. It should be expected that menopausal transition women presented a lower IMK than that of postmenopausal women [16, 20]. Our work did not detect any significant difference between either study group. However, climacteric symptoms have a great impact on women’s quality of life [21] and both groups presented moderate climacteric symptoms. The WHQ evaluation for both groups was not significant. However, depressive mood and somatic symptoms were those mostly mentioned.

Functional capacity evaluated in this study did not present any statistical difference in either group. However, it was noted that the functional capacity of women in both groups was reduced. The studied women are predisposed to limitations in their daily activities which may favor diseases that worsen their quality during the ageing process [16]. The decrease in life quality may be shown in the WHQ and it is in accordance with this study.

Associations between weight gain in relation to age point to postmenopause as a cause [22]. Some other authors consider weight gain similar in postmenopausal compared to transition menopause [23]. We observed no significant differences in relation to BMI in either group. Some studies also did not find any correlation between BMI and climacteric symptoms [24].

An increase was noted in carbohydrate ingestion, especially sugars in postmenopause women which may predispose them to obesity, insulin resistance and diabetes mellitus [25]. The BMI in our study presented overweight that may impair life quality and favor cardiovascular diseases [26, 27] as well as limit functional capacity [28]. The highest sugar ingestion was observed in women in the postmenopause study group which had a great number of unemployed women. The decrease in income may contribute not only to lower protein and vegetable ingestion but also to the increase in daily consumption of carbohydrates.

Conclusion

Both groups presented health conditions, life quality, functional capacity and nutritional habits inadequate for the ageing process. A multidisciplinary approach should alert physicians about patients’ profiles and the focus should be on the prevention of diseases and improvement in healthcare.


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Introduction

Because of the wide variation in clinical presentation and differences in the diagnostic criteria and techniques used for diagnosis, the reported prevalence of Mullerian anomalies has ranged from 0.16% to 10% [1]. It is 2-3% in fertile women, 3% in infertile women, 5-10% in women with recurrent miscarriages and more than 25% in women with late miscarriages and preterm deliveries [2]. Uterine septum is the most common type of Mullerian canal defect, with an incidence of 34.9% [3]. This condition is the result of partial or incomplete failure of the resorption of the uterovaginal septum after fusion of the paramesonephric ducts other they are generally associated with impaired reproductive performance such as recurrent pregnancy loss and preterm births [4, 5]. Prevalence of septa in women with recurrent spontaneous pregnancy loss ranges from 26% to 94% [1]. Hysteroscopic metroplasty seems to be the most effective approach for patients who have obstetric problems in the history [6, 7].

Materials and Methods

This was a retrospective study comprising 30 women who came to us with a desire to conceive, and who were diagnosed with different degrees of septate uterus at the Department of Obstetrics and Gynecology of Ege University Education and Research Hospital during 2003-2008. The mean age was 34 years (range was 23-45 years). In all cases the procedure was performed by resectoscope. Results: The patients had a total 74 pregnancies before metroplasty. Of these, ten (14%) were carried to term, six (8%) ended in preterm delivery, and 58 (78%) ended in spontaneous abortion. At least one year following hysteroscopic metroplasty a total of 20 pregnancies occurred. Of these, 11 (55%) were carried to term, two (10%) ended in preterm delivery, seven (35%) ended in spontaneous abortion. Conclusion: Correction of uterine septum significantly improves the prognosis of the pregnancies in patients with a history of severe obstetric problems. These results are similar to the results reported in the literature. Our data analysis suggests that hysteroscopic metroplasty for uterine septum improves pregnancy outcome of patients who come to us with a desire to conceive.

Results

We achieved sufficient results at the first hysteroscopy in all patients. All of uterine septa were totally resected without complications such as fluid overload syndrome and uterine perforation. The mean period of follow-up was 12 + 36 months after metroplasty.

Patients had a total of 74 pregnancies before metroplasty. Of these, ten (14%) were carried to term, six (8%) ended in preterm delivery, and 58 (78%) ended in spontaneous abortion. At least one year following hysteroscopic metroplasty a total of 20 pregnancies occurred. Of these, 11 (55%) were carried to term, two (10%) ended in preterm delivery, seven (35%) ended in spontaneous abortion (Table 1).

Discussion

There is no study that compares outcomes of treated and nontreated patients in the literature reporting hysteroscopic metroplasty. It may be because performing hysteroscopic metroplasty for uterine septum is a safe and
effective procedure for achieving a normal uterine cavity [7-15]. Any complications that occurred in our study group resemble those reported by other authors [10, 11, 16].

Uterine septa have generally been associated with poor obstetric outcomes. Reasons for complications may be reduced vascularization or altered relationships between the myometrial and endometrial vessels for first trimester abortion and decreased volume of the uterine cavity for second trimester abortion [17]. In many case series, the rate of spontaneous abortion and preterm delivery ranged from 86.3-91% and 6-9.4% in these women, respectively [5, 6, 16]. Improvement of obstetrical prognosis after this procedure has been shown by numerous studies [3, 5-7, 14-16, 18-20].

Also important for visualization is a thin endometrial stripe [18]. In our study, we did not perform insertion of an intrauterine device in order to determine the endometrial thickness. The benefit of this application is controversial at present [6, 16, 23-25]. Moreover, intrauterine adhesions after hysteroscopic metroplasty are a rare finding and usually filmy [4].

Most authors have suggested a postprocedural evaluation of the endometrial cavity for possible septal remnants [3]. A fundal notch smaller than 1 cm does not seem to reduce the reproductive performance [26]. Hysterosalpingogram, ultrasound or second-look hysteroscopy can be used for this purpose [10]. If ultrasound can be applied, it is better to perform it in the secretory phase of the cycle after surgery [21].

The rate of conception in infertile women is much lower, and does not seem to be influenced by metroplasty [10]. Its performance may also be required in infertile patients and in women desiring pregnancy to minimize the risk of future gestational failure [21].

### Table 2. — Reproductive outcomes before and after metroplasty in the selected study groups.

<table>
<thead>
<tr>
<th>Study</th>
<th>Before metroplasty</th>
<th>After metroplasty</th>
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<tbody>
<tr>
<td>Misconceptions (n, %)</td>
<td></td>
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<tr>
<td>Preterm deliveries (n, %)</td>
<td></td>
<td></td>
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<tr>
<td>Miscarriages (n, %)</td>
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**References**

Reproductive outcomes after hysteroscopic metroplasty for uterine septum


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Fertility sparing in young women with ovarian tumors

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Summary

Background: Surveys have shown that fertility sparing in patients with ovarian tumors has proven to be effective. Thus this approach in ovarian tumor cases has been carried out. The purpose of this study was to evaluate the clinical outcome and pregnancies in women who suffered from ovarian tumor and underwent conservative treatment. Materials and Methods: All cases who received conservative treatment and those who had recurrence of the disease during the follow-up period were evaluated at Vali-Asr Hospital from 2000-2004. Results: 60 of 410 patients with ovarian tumor (age range: 13-34) were treated conservatively. Three patients (5%) were infertile. Histology of tumors showed: 26 (43.3%) germ cell tumors, 15 (25%) borderline tumors, ten (16.7%) epithelial tumors and nine (15%) sex cord tumors. The cases were followed for 12-48 months. Seven term pregnancies occurred in six patients. Three in the borderline group, two in the germ cell group, one in the epithelial group and one in the sex-cord group. Nine recurrences were reported among our cases. Two of the patients (serous carcinoma and immature teratoma, both Stage IIc) died during follow-up due to refusal to undergo radical surgery. Conclusion: Fertility preserving surgery in young women with epithelial ovarian tumors, borderline and sex-cord tumors Stage I, grade 1 and 2 is recommended.

Key words: Ovarian tumors; Young women; Desire of fertility; Fertility sparing; Epithelial ovarian tumor; Germ cell tumor; Borderline ovarian tumor.

Introduction

Although ovarian malignancy is predominantly a disease of aging, there is an increasing number of women that survive these malignancies before or during reproductive years. Eighty-nine percent of ovarian tumors occur after the age of 40 and the rest occur before this age [1].

The standard treatment for borderline and malignant ovarian tumors is cytoreductive surgery such as hysterectomy, oophorectomy, partial omentectomy and surgical staging. Surgical staging reveals the need for adjuvant chemotherapy to detect extension of the disease. Cytoreductive surgery causes infertility and, due to this, conservative surgery has been introduced [2, 3].

Conservative surgery consists of unilateral salpingo-oophorectomy, omentectomy, surgical staging, and debulking of metastases in germ cell tumors [4].

The 5-year survival of patients with Stage IA, grade 1, epithelial ovarian tumor who were treated conservatively is 90% [5, 6]. Germ cell tumors represent most (80%) of the pre-adolescent malignant ovarian neoplasms. The mean age at diagnosis is 16 to 20 years and the tumors may occasionally be diagnosed during pregnancy or puerperium [7-10]. Sex cord-stromal tumors (SCSTs) are characterized by 85-100% long-term survival rates for Stage IA tumors, and they have a propensity for late recurrences [11]. Sertoli-Leydig cell tumors account for less than 0.5% of all ovarian tumors, and 75% of these neoplasms are diagnosed in women younger than 40 years of age [11].

In Ayhan et al.’s study, it was noted that diagnosis of ovarian tumors in the premenopausal period has increased by improvement of diagnostic methods and regular gynecologic examination. Ovarian tumors that have been diagnosed in the premenopausal period are mostly in their early stage and lower grade and can be treated by a conservative surgery [4]. Although a variety of studies have tried to document the impact of conservative treatment aimed at preserving ovarian function and reproductive ability, little information is available regarding survivors [5, 12, 13]. Many studies have shown that conservative surgery in patients with germ cell ovarian tumors is successful in outcome and preservation of fertility [8-10].

In a series of borderline tumors (82 patients) with conservative management, fertility and survival have been acceptable after a 25-year follow-up [14].

In another study on 17 patients with Stage II and III borderline ovarian tumors, eight spontaneous pregnancies occurred. After conservative surgery, studies show the effect of conservation surgery on patients with an advanced stage of borderline ovarian tumors [15].

Another study on borderline ovarian tumors shows that there is no significant difference regarding the survival of patients who are treated by conservative surgery or radical surgery, although there are more recurrences in patients with conservative surgery. They were treated by second-look surgery and there was no death reported to have occurred in these groups [16].

Recently, conservative surgery has been conducted on patients with epithelial ovarian tumors in early stage even with adjuvant chemotherapy in Stage IC and grade 3 [17]. In addition, in another study on ten patients with high-
stage and high-grade epithelial ovarian tumors, this modality for treatment has been performed [18].

The aim of the present study was to evaluate the outcome of patients who were treated conservatively for Stage I epithelial ovarian tumors, any stage borderline tumors, malignant ovarian germ cell tumors (MOGCTs), and Stage I sex cord stromal tumors (SCSTs).

Materials and Methods

This was a retrospective study performed on patients with ovarian tumors who had been referred to the Gynecology-Oncology Department of Vali-Asr Hospital, Tehran, Iran in 2000-2004.

Among 410 patients with ovarian tumors who had been referred or were treated by different treatment modalities, 60 who had conservative ovarian surgery were evaluated for pregnancy and recurrence of the disease within 12 to 48 months of follow-up.

The selection criteria were diagnosis of Stage I epithelial ovarian tumors, any stage borderline ovarian tumors MOGCTs, Stage I SCSTs, primary conservative surgical treatment, and age under 40. One patient with a Stage IIIC epithelial ovarian tumor had refused to undergo a radical surgery in another hospital and was referred to our center with recurrence after five months.

Gynecologic pathologists of Vali-Asr Department of Pathology performed history. Histopathology was classified according to the WHO criteria. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system. All the patients underwent surgery as the primary treatment. Conservative surgery comprised tumor excision with preservation of the uninvolved ovarian tissue or unilateral salpingo-oophorectomy (USO). In all cases, surgical staging was performed with peritoneal washings, omentectomy, multiple peritoneal biopsies, retroperitoneal sampling, lymphadenectomy, and debulking of metastasis implants for MOGCTs tumors.

No chemotherapy was given to the patients with Stage IA (G1) epithelial ovarian cancer, with borderline ovarian tumors unless invasive implants were present, with pure dysgerminoma Stage IA, with immature teratoma Stage IA grade 1, or with Stage IA sex cord stromal tumors. Only the patients with Stage I Sertoli-Leydig cell tumors that were poorly differentiated or contained heterologous elements were treated with chemotherapy.

The patients with stage > IA epithelial ovarian tumors received cisplatin in combination with cyclophosphamide or paclitaxel. Those with MOGCTs and Stage IA and grade 2, 3 were treated with BEP regimen (cisplatin, etoposide, bleomycin). This regimen was also administered to the patients with stage > IA SCSTs. The number of cycles depended on surgical staging, the patient’s tolerance to chemotherapy and the objective response of any measurable disease. The different regimens were usually administered for four to six courses. After the primary surgery of chemotherapy in the case of adjuvant treatment, the patients were evaluated at regular intervals of three months in the first year and every six months thereafter. Follow-up examinations consisted of physical and gynecological examination, imaging of the abdomen and pelvis, and measurement of tumor markers.

Clinical data collected were age at diagnosis, desire of pregnancy, date of primary surgery, histology results, stage, grade, adjuvant treatment, second-look procedure, menstrual history, pregnancies and deliveries after treatment, diagnosis of relapse, and tumor status. Information was obtained from medical records and from a questionnaire mailed to all patients who were at least 13 years old at the time of the diagnosis. The project was approved by our Institutional Review Board, and a cover letter included the elements of informed consent, such as provision for confidentiality.

Results

Among 60 patients in this study, ten patients (16.6%) presented epithelial tumors (9 Stage I and 1 Stage IIIC who refused radical surgery), 15 (25%) borderline ovarian tumors (14 Stage I, 1 Stage III with no invasive implants), 26 (43.3%) MOGCTs tumors (13 Stage IA, 1 Stage IB, 1 Stage IC, 1 Stage IIA, 3 Stage IIIA and 6 IIIC), seven unknown stage endodermal sinus tumors (EST), and nine (15%) SCSTs (7 Stage IA, 2 Stage IC).

(Case 1). The youngest patient was 13 and the oldest was 34 years old (mean age 23.2 years). The range of follow-up was 12 to 48 months.

Seven patients with epithelial ovarian tumors (7/10) undergoing conservative surgery received adjuvant chemotherapy (more than Stage IA or more than grade 1). Five received taxol + carboplatin (TC) and the other two received cyclophosphamide + cisplatinum (CP) courses. One of them had a successful pregnancy with a healthy child (she had a history of infertility).

Two cases had recurrence. One was in Stage IC and had recurrence after ten months. The recurrence was treated by omentectomy, appendectomy, and six courses of TC. She is in remission for the time being. The other patient was in Stage IIIC and had recurrence after five months. She was treated by a radical surgery (TAH + BSO + omentectomy) and six courses of TC, but she expired due to progression of the disease.

Eleven (11/15) ovarian borderline tumor patients desired pregnancy (including 2 cases with a history of infertility). The age range of these patients was 16 to 35.

Histologically, ten cases had serous and five cases had mucinous types. Primarily performed surgeries were 14 unilateral salpingo-oophorectomy and one cystectomy + cesarean section. Surgical staging was performed in ten

<table>
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<tr>
<th>Characteristic</th>
<th>EOC</th>
<th>BOT</th>
<th>MOGCT</th>
<th>SCST</th>
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<tr>
<td>No. of patients</td>
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<td>15 (25%)</td>
<td>26 (43.3%)</td>
<td>9 (15.0%)</td>
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patients and the other patients without surgical staging were in Stage I formally at the suggestion of surgeons. Three of these cases had successful pregnancies (1 term + 2 preterm but all of them were healthy). Three cases had recurrence, one after five months and the other two after seven months from the primary treatment. All are in remission for the time being.

Eight (8/26) germ cell tumor patients desired pregnancy (age range; 13-33 years). Thirteen patients had dysgerminoma, four immature teratoma, four embryonal tumors, three mixed germ cell tumors, and two had yolk sac tumors. Primarily performed surgeries included 24 unilateral salpingo-oophorectomies and one bilateral salpingo-oophorectomy with preservation of the uterus.

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<th>Field</th>
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<td>26</td>
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<td>1989-2001</td>
<td>16</td>
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<td>50 mo.</td>
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<td>–</td>
<td>8 (7)</td>
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<td>Donnez et al.</td>
<td>2000-2004</td>
<td>15</td>
<td>Serous (8)</td>
<td>24 yr</td>
<td>30 mo.</td>
<td>1</td>
<td>Ser (Stage IA)</td>
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<td>20.3</td>
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<tr>
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<td>(5 yrs)</td>
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<tr>
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<td>Morice et al.</td>
<td>1982-99</td>
<td>Serous (22)</td>
<td>42 mo.</td>
<td>7</td>
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Dys: dysgerminoma; Muc: mucinous; Chorio: choriocarcinoma; Ser: serous.
Fertility sparing in young women with ovarian tumors

and one case of cystectomy + cesarean section (in yolk sac tumor patients). Surgical staging was performed in 25 (25/26) cases.

Thirteen cases who had dysgerminoma or immature teratoma with stage > IA, grade 3 and EST treated by BEP (bleomycin, etoposide, and cisplatinum). Two pregnancies occurred in a patient. One patient 14 years old, had immature teratoma and died in Stage IIIC after three courses of BEP and one course of VAC (vincristine, actinomycin, cyclophosphamide) without any response to the treatment ten months after diagnosis.

Four (4/9) sex cord tumor patients desired pregnancy. Eight (8/9) patients had granulosa cell tumors and the other one androblastoma.

Primarily performed surgeries in these groups included one salpingo-oophorectomy+cesarean section and eight unilateral salpingo-oophorectomies. Surgical staging was performed in all the cases. Seven were in Stage IA and two in Stage IC. Two cases with Stage IC were treated by BEP chemotherapy, but they had recurrences. The first recurrence occurred after 24 months and was treated by debulking surgery followed by four BEP courses. The second one occurred after five months and was treated by TC chemotherapy. Both of these patients are in remission for the time being.

In summary, conservative surgery and fertility outcomes were evaluated in 60 patients less than 40 years of age, considering the fact that there were only 26 patients (26/60) who desired pregnancy and there was a history of infertility in three patients. Seven pregnancies occurred (in 6 patients) during the follow-up period. Two pregnancies were preterm in patients with borderline ovarian tumors but all of them were healthy. Nine patients had recurrence and seven are in remission after the secondary treatment.

Discussion

This study may emphasize the point that conservative surgery can be performed on premenopausal patients with a selective histological type of ovarian tumors, who desire to preserve fertility, even in a higher stage or grade. However, in epithelial ovarian tumors, it can be done just in early stages (up to Stage IC).

Thus the type of surgery should be decided depending mainly on age of the patient and her desire for fertility preservation. Surgical staging should be performed in all cases to evaluate the extent of the disease, to determine prognosis, and to guide postoperative management. Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is now considered an appropriate surgical treatment for patients with Stage IA, grade 1 epithelial ovarian cancer, any stage borderline ovarian tumors with no invasive implants, SCSTs and MOGCTs, and even an advanced germ cell disease, particularly if the contralateral ovary is normal. Removal of the preserved ovary should be considered after completion of pregnancy (ies) in order to reduce the risk of ovarian tumor recurrence [1].

In a current study on 26 patients with a germ cell ovarian tumor, two pregnancies occurred in eight patients who desired pregnancy during the follow-up. One of these cases had recurrence which is comparable to other studies (Table 2).

In Kanazawa et al.’s study on 31 germ cell tumors (during 15 years), eight pregnancies occurred in six patients [8]. In El-Lamie et al.’s study on 16 patients (over 5 years, with a 30.5 month follow-up), two patients had three pregnancies and there was one case of recurrence [9].

In the study by Zanagnolo et al. on 36 germ cell tumors (with a 10-year follow-up), nine patients had 11 pregnancies with no report of recurrence [10]. In sex cord tumor patients, four desired pregnancy and one pregnancy occurred. These data could show the possibility of conservative surgery on the patients as well.

In 15 patients with borderline tumors in our study, three pregnancies occurred (only 11 were desired pregnancies and there was a history of infertility in 2 of them).

Table 3 shows different studies in which borderline tumors were treated by conservative surgery. In Gotlieb et al.’s study on 39 patients (with 69 months of follow-up), there were 22 pregnancies in 15 patients (there were 3 abortions, 1 early pregnancy, and 1 twin pregnancy) [14].

In Camatte’s study on 17 patients (with 50 months of follow-up), eight pregnancies occurred in seven patients [15]. In Donnez et al.’s study on 16 patients (during 12 years), 12 pregnancies occurred in seven patients [16].

Conservative surgery can be performed on patients with early-stage epithelial tumors, but it is necessary to have adjuvant chemotherapy in high-grade cases. Table 4 compares different studies on epithelial ovarian tumors.

Zanetta et al.’s study (with 30 months of follow-up) on 99 Stage IA epithelial ovarian tumor patients showed 25 pregnancies in 17 patients [17]. Thus conservative therapy can be performed on Stage IA epithelial tumor patients.

In another study by Raspagliesi et al. on ten epithelial tumor patients with a higher grade or stage undergoing conservative surgery (with 70 months of follow-up), three pregnancies occurred and there was no recurrence [18].

In two other studies, one in 2001 and another of multicentral type in 2005, Morice et al showed that conservative surgery should be performed on patients with Stage IA, grade 1 and it can also be considered for grade 2 [19, 20] (Table 4).

The results from our study confirm that management of Stage I (grade 1, grade 2) epithelial ovarian cancer, any stage borderline ovarian tumors with no invasive implants, MOGCTs and SCSTs with fertility-sparing surgery is a safe, practicable treatment option. Of course, further studies are recommended to evaluate this important issue.

References


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Laparoscopic sacral colpopexy for uterine prolapse with prolene mesh

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Summary

Objective: To analyze the clinical effects of laparoscopic sacral colpopexy using prolene mesh for patients with pelvic organ prolapse. Methods: Laparoscopic placement of prolene mesh in the rectovaginal septum and vesicovaginal septum of 42 women with uterine prolapse with bladder and rectum prolapse. One mesh was fixed to the round ligaments and another to the periosteum of the sacral vertebrae. Operation time, blood loss, complication rate and follow-up surgery results were recorded monthly and analyzed according to the POP-Q system. The uterus was preserved in all cases. Results: The mean operating time was 92 ± 12 min and the mean blood loss during surgery was 98 ± 11 ml. Postoperatively, both prolapse and symptoms were highly significantly improved (p < 0.001) according to the pelvic organ prolapse quantification (POP-Q) system. Conclusions: Laparoscopic sacral colpopexy for uterine prolapse using prolene mesh is a minimally invasive and effective new technique that offers a chance for patients who desire to preserve their uterus.

Key words: Uterine prolapse; Laparoscopy; Sacral colpopexy; Mesh.

Introduction

Pelvic organ prolapse (POP) is a common clinical condition that affects the social, occupational, domestic, psychological and sexual lives of women with an estimated prevalence of up to 50% of parous women. Uterine prolapse and vaginal wall bulge are common types of POP. Uterine prolapse occurs when the pelvic floor muscles and ligaments stretch and weaken, providing inadequate support for the uterus [1]. The disorder is among the most demanding and technically challenging problems of female reconstructive surgery. Several surgical options are available to women with the affliction and the results vary widely. Although traditional surgical methods like vaginal hysterectomy and anterior/posterior colporrhaphia have short-term recovery rates, the rate of prolapse recurrence is rising year by year. The levator plication procedure is still an effective procedure, but, postoperatively, 27-50% of women report pain during intercourse [2].

Sacral colpopexy placing synthetic mesh through laparoscopic techniques in the rectovaginal septum and vesicovaginal septum seems to be the more reliable procedure for the the cure of uterine prolapse. In this paper, we describe this novel approach to the surgical management of uterine prolapse. The surgery involved a laparoscopic approach to sacral colpopexy and anterior/posterior colporrhaphia with prolene mesh, which produces excellent results with very few complications. To our knowledge a similar study has not previously been reported in the literature.

Patients and Methods

From October 2006 to November 2009, a total of 42 women with uterine prolapse presented at the Department of Gynaecology II, Renmin Hospital of Wuhan University. The age range at surgery was 35-57 (mean 41.1 ± 9.4) years. Consent was obtained from each patient and we did not take extra blood or tissues from any patient. All medical records were reviewed. Ethical approval was obtained from the Research Ethics Committee of our hospital. All assessments in the study were carried out by a gynaecologist who had not performed the operation.

The stage of prolapse was assessed using the International Continence Society pelvic organ prolapse quantification (ICS POP-Q) [3] system. The patients were selected on the basis of POP-Q stage 2-4. Women with POP-Q stage 1 of prolapse and repeat surgery for recurrent prolapse were excluded.

All patients had a preoperative evaluation which included a detailed history, physical examination, gynaecological examination, routine preoperative examination and thinprep cytologic test (to eliminate cervical lesions). Appropriate antibiotic coverage was given perioperatively. After surgery, total operating time and blood loss during surgery were recorded. The postoperative Foley catheter was removed within 24 hours. Routine physical examination and gynaecological examination were repeated ranging from 2-36 months. Minimum follow-up was two months for all patients. These patients were asked the same questions with respect to possible complaints including tenesmus, dysuria, dyschezia, and dyspareunia. Prolapse recurrence was considered as any symptomatic prolapse or stage at or above 2. The end of follow-up was defined as recurrence of prolapse and any complaint mentioned above.

Comparison between preoperative and postoperative POP-Q scores was conducted with use of the t test (Table 1). Chi-square tests were performed to investigate the influence of tenesmus, dysuria, dyschezia, and dyspareunia (Table 2). A p value less than 0.05 was considered to be significant and less than 0.01 to be highly significant. Prolene mesh (Johnson & Johnson Medical Ltd., Shanghai, China) was used during surgery for all cases.
Operative procedure

According to the degree of prolapse and the area to repair the fascia of the anterior and posterior vaginal wall, respectively, the prolene meshes (10 × 15 cm²), were previously made and designed as a flag- and a T-shaped configuration (Figure 1). The horizontal limb of the T-shaped mesh was 2 cm in width. The patient was placed in the dorsal lithotomy position under general anaesthesia. The abdomen was opened through a hypogastric laparotomy to access the peritoneal cavity.

The operation procedure was as follows (Figure 2). The peritoneum covering the pouch of Douglas was opened between the uterosacral ligaments. After dissection of the rectovaginal septum, the flag-shaped mesh was introduced into the abdomen through puncture cannula in the pelvic peritoneum. The part of the flag was trimmed to proper dimensions of the protrusion of the posterior vaginal wall. The vessel-free area in the retroperitoneum between the right uterosacral ligament and sacral promontory was incised. The incision was longitudinally extended to the medial aspect of the right uterosacral ligament. The strip of the mesh was folded with a turn through 90° at its base and passed through the right uterosacral ligament. After retracting the rectum forward, the presacral fascia was bluntly dissected until the periosteum was reached. A uterine manipulator was inserted into the vagina and the uterus was pushed gently to its normal anatomic position. Using a nonabsorbable suture, the strip was fixed to the periosteum between the second and third sacral vertebrae in the vessel-free area. The residual portion of the strip was removed.

Attention was then turned to the uterovesicorectal reflection. A transverse incision was made in the peritoneum at the uterovesicorectal reflection. The dissection was continued to the deepest part of the cystocele through the vesicovaginal septum. The T-shaped mesh was placed in the vesicovaginal space and flattened without any tension. A hemicycle space was created in the center of the mesh. The free hemicycle edge was fixed to the vaginal wall using a 1/0 nonabsorbable suture. Care was taken not to exit the suture through the vaginal mucosa. The round ligament was held by a grasping forceps and then the puncture cannula was withdrawn. A trocar was introduced extraperitoneally to the attachment of the round ligament and continued subcapsularly to the anterior wound of the broad ligament. After the trocar was removed, another grasping forceps was inserted through the puncture cannula. The ipsilateral horizontal limb of the T-shaped mesh was pulled to the wound in the peritoneum and the free edge of the limb was sutured to the cardinal and broad ligaments. In a similar fashion, the procedure was performed in the contralateral side. Finally, the retroperitoneum was closed using a continuous suture.

After injection of normal saline solution into the posterior vaginal wall, a 3 cm longitudinal incision was made at the site of the anterior wound of the broad ligament. The retropertitoneal space was closed using a continuous suture.

After injection of normal saline solution into the posterior vaginal wall, a 3 cm longitudinal incision was made at the site of the anterior wound of the broad ligament. The retropertitoneal space was closed using a continuous suture.
reached. The free edge of the flag-shaped mesh was pulled down to the lowest position of the posterior vaginal wall and then fixed to the perineal body and bilateral levator ani muscles. The wound in the vaginal wall was closed.

Results

Total operating times ranged from 80 to 104 (average 92 ± 12) min. The mean intraoperative blood loss was 92 ml (range 98 ± 11 ml). No complications occurred during the surgery. Of all cases, there were two with urine difficulty (4.76%) who were released after three continuous urinary catheterisations. Five cases had passing stool difficulty (11.90%), in whom four recovered after symptom treatment, and one recovered one month after surgery. Three cases experienced sexual discomfort (7.14%), in whom two were one month after surgery, and one was three months after surgery. All patients were followed monthly through outpatient department visits and telephone surveys and accurate outcome data of the last follow-up (range 2-36 months) were obtained with the follow-up rate being 97.62%. One patient was lost to follow-up. There was no recurrent prolapse in any of the 41 followed patients. Mesh infection or erosion was not observed. Pre- and postoperative POP-Q scores were assessed, respectively. The index point C, Aa, Ba, Ap, and Bp in all 41 patients was ± 1 cm superior to the hymen, less than grade 2 by the POP level. Five cases had passing stool difficulty (11.90%), in whom four recovered after symptom treatment, and one recovered one month after surgery. Three cases experienced sexual discomfort (7.14%), in whom two were one month after surgery, and one was three months after surgery. All patients were followed monthly through outpatient department visits and telephone surveys and accurate outcome data of the last follow-up (range 2-36 months) were obtained with the follow-up rate being 97.62%. One patient was lost to follow-up. There was no recurrent prolapse in any of the 41 followed patients. Mesh infection or erosion was not observed. Pre- and postoperative POP-Q scores were assessed, respectively. The index point C, Aa, Ba, Ap, and Bp in all 41 patients was ± 1 cm superior to the hymen, less than grade 2 by the POP level. The vaginal index points of preoperative and postoperative follow-up (last follow-up) are shown in Table 1. Calculating the scores gave p values less than 0.0001. There were highly significant differences between the pre- and postoperative POP-Q scores (Table 1). Table 2 shows the preoperative and postoperative pelvic floor function. There were statistically highly significant differences in the number of patients with tenesmus, dysuria and dyspareunia (p < 0.0001), and significant differences with dyschesia (p < 0.01) (Table 2).

Table 1. — POP-Q measurements before surgery and at final follow-up.

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>Aa</th>
<th>Ba</th>
<th>Ap</th>
<th>Bp</th>
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<td>Preoperation</td>
<td>+3.11 ± 3.23</td>
<td>1.12 ± 1.70</td>
<td>+1.37 ± 1.51</td>
<td>-2.43 ± 1.37</td>
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<td>Final follow-up</td>
<td>-7.12 ± 0.61</td>
<td>-2.51 ± 0.43</td>
<td>-2.17 ± 0.55</td>
<td>-2.49 ± 0.85</td>
<td>-2.61 ± 0.17</td>
</tr>
</tbody>
</table>

The Pelvic Organ Prolapse Quantification (POPP): Point C represents the position of the cervix or vaginal cuff. The anterior and posterior points A (Aa, Ap) are located on the midline vaginal wall 3 cm proximal to the hymen (range ± 3 cm). The anterior and posterior points B (Ba, Bp) represent the maximum extent of prolapse of the anterior and posterior vaginal wall (range ± 3 cm to total vaginal length [tvl]); p < 0.01.

Discussion

Uterine prolapse is the herniation of the uterus into or beyond the vagina as a result of failure of the ligamentous and fascial support. A large number of corrective surgical approaches have been described in the literature for uterine prolapse. One concept prevails: if surgery becomes necessary, it allows relief of the symptoms and restores the pelvic organs to their anatomical position. Moreover, the intervention can reduce postoperative complications and incidence of recurrence.

DeLancey et al. [4] described three levels of a support system as follows: level 1, superior suspension of the vagina to the cardinal-uterosacral complex; level 2, lateral attachment of the upper two-thirds of the vagina; and level 3, distal fusion of the vagina into the urogenital diaphragm and perineal body. They noted that uterine prolapse was often associated with defects of the cardinal ligaments, rectovaginal and cervical fascia. Delancey’s three levels of support are now accepted worldwide.

Vaginal hysterectomy with posterior vaginal wall repair has failed to correct the loss of integrity of the cardinal-uterosacral ligament complex. In addition, postoperative scarring can cause vaginal discomfort during penetration. In a retrospective study, Jin et al. [5] found that the recurrence rate was 11.6-31.1% in women who had undergone this procedure. Sacral colpopexy could offer good anatomical and functional results and the reported success rate has been generally as high as 68-100% [6].

A variety of surgical procedures are available for sacral colpopexy. In 1957, Amelie Hugier et al. [7] made a detailed description of open sacral colpopexy in which the vaginal vault was suspended to the anterior perios- teum of the sacrum with unabsorbable material. Scali et al. [8] in 1974 proposed the suspension by the placement of synthetic slings. However, adequate exposure of the rectovaginal septum could not be obtained completely from the vaginal approach. In 1993, Dorsey et al. were the first to describe laparoscopic sacral colpopexy [9]. This minimally invasive surgery implied the placement of prosthetic mesh to restore and confer an adequate reinforcement of the pelvic tissues. Presently, this technique is considered as an excellent option for uterine prolapse [2, 10, 11].

Gynaecologists favour the laparoscopic approach because of its few complications and quick recovery, which are particularly important for patient quality of life. The use of mesh in prolapse repair avoids dependence on the patient’s own weak tissues and maintains vaginal capacity. The dimension of the flag-shaped and T-shaped mesh is individualised and based on the size of the patient defect at the tension-free state. Our results reflect benefits of the laparoscopic approach, including excellent vision, less trauma, less blood loss, less postoperative pain, minimal tissue damage and scarring, no longitudinal incision in the anterior vaginal wall, which can preserve the uterus, decreased discomfort in sexual activity and improvement in quality of life, better than other reports obviously [12].

Table 2. — Summary of the comparison of preoperative and postoperative pelvic floor function.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tenesmus</th>
<th>Dysuria</th>
<th>Dyschesia</th>
<th>Dyspareunia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Cases (%)</td>
<td>Cases (%)</td>
<td>Cases (%)</td>
<td>Cases (%)</td>
</tr>
<tr>
<td>Preoperation</td>
<td>34 (80.95%)</td>
<td>21 (50.00%)</td>
<td>17 (40.48%)</td>
<td>31 (73.81%)</td>
</tr>
<tr>
<td>Postoperation</td>
<td>6 (14.29%)</td>
<td>2 (4.76%)</td>
<td>5 (11.90%)</td>
<td>3 (7.14%)</td>
</tr>
<tr>
<td>χ²</td>
<td>33.939</td>
<td>18.894</td>
<td>7.128</td>
<td>35.230</td>
</tr>
</tbody>
</table>

p < 0.01
Our procedure simultaneously repairs vaginal wall defects of both levels 1 and 2. The pelvic floor is reinforced by fascia repair and ligament reconstruction. During sacral colpopexy, care must be taken not to injure the anterior sacral nerves or the vessels at the lateral border of the sacrum. The round ligaments are sutured with mesh and then combined with uterosacral ligament mesh. This procedure stabilizes the uterus in a neutral position which puts the vaginal vault and uterus in the center part of pelvic cavity, preventing the uterus from pressing on the rectum and the occurrence of cystocele and stress urinary incontinence. The retroperitoneal position of mesh has the potential to decrease the risk of intestinal adhesion and occurrence of a hernia beneath the mesh. Adequate exposure of rectovaginal septum can be made easier by the laparoscopic approach and the mesh can be placed into the interspace of the anterior and posterior vaginal walls for fascial reinforcement.

After surgery, the prolene mesh provokes a fibrotic reaction and scar-tissue formation. Collagen deposition in mesh is sufficient to support the vaginal wall and prevent recurrence [13]. The use of prolene mesh theoretically has a lower risk of wound infection and tissue erosion [14], and these complications were not observed in our series.

The indication for this technique is women presenting with uterine prolapse of stage 2 or more, especially women who desire an active sexual life with a preserved uterus and potential fertility. The contraindications included active infection or cancer. The relative contraindication is severe anterior and posterior vaginal wall prolapse.

This study is limited in that it is a retrospective survey in a small population and further long-term follow-up is required.

In conclusion, laparoscopic sacral colpopexy with prolene mesh can effectively restore optimal vaginal function and anatomy and prevent prolapse recurrence, and preserve the uterus. We therefore believe that this technique produces excellent results.

References


Development of secondary ovarian lesions after hysterectomy without oophorectomy versus unilateral oophorectomy for benign conditions: A retrospective analysis of patients during a nine-year period of observation

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Department of Obstetrics and Gynecology, Ataturk Training and Research Hospital, Izmir (Turkey)

Summary

 Purpose: The effect of retained one or both ovaries on the de novo ovarian pathologies required re-operation after hysterectomy due to benign gynecologic conditions were investigated retrospectively. This study was done to determine the occurrence of disease in retained ovaries after hysterectomy. Methods: A retrospective analysis of patient charts was performed, comparing the patient reports of women who had secondary ovarian lesions those whose previously undergone total abdominal hysterectomy with unilateral oophorectomy or without oophorectomy in our Department during the nine year period of observation (2000-2009). The study included 1242 women with at least one ovary saved after hysterectomy for benign indications. Results: De novo ovarian disease was established in 5.1% of patients of hysterectomy without oophorectomy and in 17.6% of patients of at least one ovary saved after hysterectomy for benign indications (p = 0.005). Ovarian pathology requiring re-operation developed in 3.8% of patients who underwent hysterectomy without oophorectomy and in 5.9% of patients who underwent hysterectomy with unilateral oophorectomy (p = 0.536). Conclusion: Women with unilateral oophorectomy at the time of hysterectomy had more than twice the risk of secondary ovarian lesions, compared with those without oophorectomy at hysterectomy. Determinants, such as age, parity and gravidity must be considered when deciding whether or not to perform oophorectomy at hysterectomy.

Key words: Hysterectomy with unilateral oophorectomy; Hysterectomy without oophorectomy; Secondary ovarian lesions.

Introduction

It is controversial to preserve normal appearing ovaries during gynecological surgery for benign disease in premenopausal women. The incidence of re-operation for de novo developed ovarian pathologies after hysterectomy is suggested to be 3.95%. This risk of re-operation is higher during the first three years. The risk of ovarian pathology is significantly higher among patients in whom only one ovary is saved after hysterectomy [1].

Age, primary histological findings, and degree of peritoneal trauma are the most important factors affecting development of ovarian pathologies after performing vaginal, laparoscopic, and abdominal hysterectomy [2].

In this study, the incidence of developed pathologies required relaparotomy after hysterectomy due to benign gynecologic disease and the consequences of saving one or both ovaries on the de novo developed pathologies were investigated. As a conclusion of our survey, the risk of pathological outcome of retained ovaries is discussed because of benign gynecological disease after hysterectomy.

Materials and Methods

In this retrospective analysis, data obtained from patients who had undergone total abdominal hysterectomy with unilateral oophorectomy or without oophorectomy in the Obstetrics and Gynecology Department of Izmir Ataturk Training and Research Hospital between 01/06/2000 and 01/06/2009 were evaluated. Selection criteria for this study included women who had undergone hysterectomy for benign conditions where at least one ovary was saved. The patients could be contacted by enrolled address and telephone numbers, and were invited to regular examinations annually in the outpatient clinic. The patients who responded to our invitation for evaluation were asked whether or not they had developed any adnexal/ovarian pathological findings and required further gynecologic examination. Ovaries and salpinges were evaluated transvaginally by ultrasound. The patients presenting ovarian pathology were treated by a medical or surgical approach after hysterectomy was registered. The time interval and histopathologic results of developed de novo ovarian pathological lesions after hysterectomy were recorded.

SPSS 15.0 software was used for statistical analysis. Parametric data were tested for their normal distribution and results are presented by using figures with the percentages. Continued variables of the groups of total abdominal hysterectomy without oophorectomy and with unilateral oophorectomy were tested using Mann-Whitney U-tests. Categorical variables of the groups with total abdominal hysterectomy without oophorectomy and with unilateral oophorectomy were tested using Pearson’s and Fisher’s exact tests. Spearman’s correlation and logistic regression analysis were performed. A value of p < 0.005 was considered as significant.
Results

Total abdominal hysterectomy without oophorectomy and with unilateral enrolled oophorectomy was performed on 1,531 patients between 01/06/2000 and 01/06/2009. We reached 12,871 of them by post and telephone calls and 1,242 patients responded to our invitation. There was no presenting pathological finding at the last gynecological and transvaginal ultrasound examinations. After the patients had undergone hysterectomy, an adnexal mass developed in 102 patients, and re-operation was performed on 54 of them. There were no differences between the groups of hysterectomy without oophorectomy and with unilateral oophorectomy (Table 1).

There were also no differences between the groups in terms of infertility, systemic disease, genital disease, breast disease and any familial cancer. Preoperative ovarian diseases were encountered more in the group of hysterectomy with unilateral oophorectomy. The mean-time intervals were 25.50 months in only hysterectomy, while endometrial hyperplasia, endometriosis, and adnexal mass developed respectively in 28.00 months in hysterectomy and with unilateral enrolled oophorectomy.

Mean follow-up time was 38.51 months in the group of hysterectomy and with unilateral oophorectomy patients. Mean follow-up was 52.57 months in the group of patients who underwent hysterectomy with unilateral oophorectomy. During this period, ovarian disease was established in 48 (5.1%) patients of the group with hysterectomy without oophorectomy, and re-operation was performed in 36 (3.8%) of them. Ovarian diseases developed in 54 (17.6%) patients in the group of patients with unilateral oophorectomy. During the other 48 patients. Mean time-interval after hysterectomy and re-operation was 26.33 months for all patients. The mean-time intervals were 25.50 months in only hysterectomy patients, and 28.00 months in hysterectomy with unilateral oophorectomy patients.

There were weak correlations between development of ovarian pathologies after hysterectomies done for indica-
tions of endometrial hyperplasia (rho: –0.243, \( p < 0.001 \)), adnexal mass (rho: –0.179, \( p: 0.010 \)), and unilateral oophorectomy (rho: –0.196, \( p: 0.005 \)). There was also a weak correlation between pathologies requiring re-operation after hysterectomy and indications of an adnexal mass (rho: 0.173, \( p: 0.013 \)).

Discussion

There is no consensus concerning optimal adnexal surgery during abdominal hysterectomy, when continued hormonal function is desired, associated with reduced sequelae in the future.

Oophorectomy was performed for the purpose of preventing ovarian cancer in 78% of hysterectomies of women between age 45 and 64. However, the rate of mortality for ovarian cancer is less than the rate of mortality for cardiovascular disease and hip fracture in these age intervals. Hysterectomy alone has been shown to reduce the risk of developing ovarian cancer by an average of 46% [3]. Prophylactic oophorectomy has been shown to reduce the incidence of ovarian cancer by 8-18% in the literature from developed countries. However, in the countries in which incidence of ovarian cancer is much lower than those in developed countries, prophylactic oophorectomy in women undergoing hysterectomy reduced the ovarian cancer incidence by 0.4-3.2% [4].

Hormonal analysis showed that the functions of the dismissed ovaries were more rapidly lost than the controls of the same age intervals. The results of Chan’s study suggested that hysterectomy with ovarian conservation could preserve a woman’s normal hormonal milieu. The uterus could have a control mechanism on ovulation, and hysterectomy might stimulate early menopause [5].

The changes in the ovaries were investigated in patients who had undergone abdominal hysterectomy with conservation of the ovaries for benign conditions [6]. It was established that hysterectomy affected ovarian blood supply and function. Women with hysterectomy had significant elevated serum FSH level and lower ovarian stromal blood flow as compared with healthy women. There was good correlation between Doppler and endocrine parameters [7-9]. There was an increase in ovarian vascular resistance following hysterectomy. These changes may be responsible for altered ovarian function hysterectomy.

Bukovsky et al. examined ovarian function following abdominal hysterectomy with or without unilateral oophorectomy and they reported that 35% of patients undergoing unilateral oophorectomy demonstrated impaired ovarian function six months after the operation, whereas only one of the patients with both ovaries preserved demonstrated impaired ovarian function. Thus, if the ovaries are to be preserved at hysterectomy, it seems to be more beneficial to preserve both ovaries [9].

In an experimental rat model, histopathologic evaluation of the ovaries after hysterectomy showed that ovaries of the hysterectomized group had significantly fewer primary, preantral, and antral follicles, and significantly more corpora lutea, atretic, and cystic follicles [10].

The results of this experimental rat model suggest that hysterectomy may affect ovarian function. Therefore, when continued ovarian function following abdominal hysterectomy is desired and ovarian cystic pathologies are not encountered, preservation of both ovaries seems to be more beneficial [10].

Holub et al. found that the rate of adnexal pathologies requiring re-operation after abdominal hysterectomy was 5.67%. They suggested that the important factors affecting re-operation rate were age, primary histologic findings, and smaller peritoneal trauma [2].

Plöckinger et al. published a study which included 1,265 women with at least one ovary saved after hysterectomy for benign indications [1]. They found that development of ovarian pathologies requiring re-operation after hysterectomy was suggested to be 3.95% of patients. Of the patient group with prior hysterectomy, 7.63% had some pathologies in the retained ovary. Among patients with hysterectomy only, 3.47% developed ovarian pathologies requiring re-operation. In our study, 4.3% required re-operation. This ratio was found to be 3.8% for patients with both ovaries saved, while 5.9% for patients with one ovary saved after hysterectomy. This difference was not statistically significant. The re-operated patients in Plöckinger’s study had undergone hysterectomy at a younger age, had less parity, and had more nulliparity than the patients who were not re-operated. We did not find any difference in age, parity and gravidity between the patients with and without re-operation. The mean intervals between hysterectomy and re-operation were 29.5 (1-120) months in Plöckinger’s study, and 26.3 (11-49) months in our study. Follow-up time of the groups in our study showed re-operation interval was longer, but not statistically significant. Longer follow-up time may lead to more established pathologies.

A decrease in blood flow and endocrine functions were noted in ovaries preserved after hysterectomy in various studies [10]. Ovarian function loss was earlier in cases in whom one ovary was left than cases in whom both ovaries were left. On the other hand, when one ovary was left, the incidence of developing an ovarian pathology which might require re-operation was more frequent. More studies are needed to determine the factors which affect the development of secondary ovarian lesions when single or both ovaries are left. Simply, after the results of these studies the final decision to perform elective oophorectomy at the time of hysterectomy for benign disease could be established on an individual basis.

Conclusion

Women with unilateral oophorectomy at the time of hysterectomy had more risk of secondary ovarian lesions compared with those without oophorectomy at hysterectomy. Determinants such as age, parity and gravidity must be considered when deciding whether or not to perform oophorectomy at hysterectomy.
References


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Unwanted pregnancy and induced abortion among young women 16-22 years old in Greece: a retrospective study of the risk factors

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Summary
Unwanted pregnancies and the subsequent induced abortions are common problems of our youths in modern Greece. The aim of this study was to recognize the risk factors of the problem in an effort to find the best possible solution out of this social dead end. Method: We interviewed 1,320 young female individuals and analyzed their answers using statistical analysis. Results: Several useful conclusions were reached concerning the forces that are involved in unwanted pregnancy/induced abortions. Discussion: We have tried to underline the strategy to combat the problem. Conclusion: Sexual education and the proper use of contraception remain the essential tools in this effort.

Key words: Unwanted pregnancies; Induced abortions; Risk factors; Contraception; Sexual education.

Introduction
Unwanted pregnancy, defined as a pregnancy occurring accidentally and against the individual’s will and decision, is a public problem with severe health and socioeconomic consequences. Unfortunately, its effects and the subsequent induced abortions are quite enlarged in youths. There is evidence that, compared to women who abort at an older age, women who abort as teens are significantly more likely to report more severe emotional and medical complications related to their abortions; a finding which is supported by the fact that women, who aborted as teens, participate in disproportionately large numbers in post-abortion counseling programs [1]. On the other hand, if an unintended, and most of the times unwanted pregnancy of a young individual ends up in a live birth, the future is rarely optimistic, since such pregnancies are frequently associated with a number of adverse circumstances, like low academic and professional achievements, single parenthood and child abuse [2]. Moreover, giving birth while still a teenager is strongly associated with disadvantages in later life. On average, according to UNICEF, across 13 countries of the European Union, women who gave birth as teenagers are twice as likely to be living in poverty. In other words, reducing teenage births offers an opportunity to reduce the likelihood of poverty and of its perpetuation from one generation to the next [3]. However, most adolescents choose to have an abortion because they have concerns about how a baby would change their lives (e.g., completing their education), they worry about financial problems, or they feel that they are not mature enough to become a parent [4]. Although, according to the official recorded evidence of UNICEF, adolescent birth rates in Greece have fallen more than three times in the last 30 years, we still have one of the highest rates of abortions in Europe [3]; a reality showing at large that more action has to be taken to reduce these numbers and ameliorate the lives of thousands of young people. In our country, there were two remarkable events that took place in the 1980s and contributed to the limitation of unwanted pregnancy: the development of family planning clinics in 1980, which aimed at a higher level of sex education provided in our population, and the legislation of abortion in 1986, for the struggle against unsafe abortions and their complications, like infection, sepsis, perforation of the uterus, subfertility, upcoming psychological problems, troubled relationships and, even worse, maternal death. Despite the efforts that have already been performed by the state, preventive policies are still weak in Greece, making women rely on abortion to control births [5]. These policies must be directly derived from studying the risk factors for the persistence of this situation in youths: Low level of sex education? Low use of safe-reliable methods of contraception? Low level of consultation before or after the abortion by gynecologists? High number of lifetime sexual partners? Self-destructive behaviors (alcohol or drug abuse, smoking, suicidal ideation, etc.)? Others? Furthermore, we have to wonder deeply who is really responsible for this social abnormality; our schools, our families, the media, the doctors, the state or, just the young people themselves?

It is an extremely disheartening fact that there is almost complete lack of evidence in the field of induced abortions in Greece, especially in youths, since the existence of any official records would indeed promote the understanding of the possible risk factors which are involved in the phenomenon, and would underline the best strategy that could be followed towards the elimination of this social scourge. The main reason for this deficiency of
recorded evidence is that induced abortions are often under-reported in national surveys, since they are still considered to be a social taboo and the majority, which are mainly carried out in the private sector (94%), remain unregistered [6]. Of course, the problem is maximized when, in an effort to clarify the correlation between the factors of unwanted pregnancy and its further socioeconomic results, we try to make records of the total percentage of unintended pregnancy among young people, not only those which end up in abortion but also those which are carried out to term. Nevertheless, we have to realize that the matter in question is multidimensional, concerning both its causes and its results, and from this point of view we have to search in many fields in an attempt to detect the factors which enhance the disease, and to point out the several repercussions in our lives. The purpose of this study was to investigate a complex interplay of forces which are supposed to present the risk factors for unwanted pregnancy and induced abortions among women 16-22 years-old within the Greek society and, finally to reach a strategy that could be followed in order to confront this major social problem.

Materials and Methods

Data were gathered from a population-based survey which was conducted among women in the late and post adolescence years (16-22 years-old) who reported that they had already experienced sex. We approached by interviewing them through anonymous questionnaires and studied the experience and opinions of each of 1,320 young women on certain issues concerning sexual health, unwanted pregnancies and induced abortions. Recruitment was performed by approaching the youths in many areas throughout the country – urban or rural –, like high schools and universities (during sexual education programmes), homes and several working places (through invitation letters), giving information about the study. An interview was arranged with each potential participant to administer the questionnaire. The interviews were conducted in a variety of places (at home, in the work place, at schools or in the universities of the interviewees) and sensitive questions, like those on abortion, were answered in a self-completed questionnaire. Finally, we gathered data from 730 pupils in high school, 400 students in several universities and 190 female individuals (either employees or unemployed). Permission to use this sensitive data was obtained from each participant through the Ministry of Health and the Ministry of Education. The questionnaires used were plain and

Table 1. — Questionaire on sexual health.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Question</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education (e)</td>
<td>How many years have you studied?</td>
<td>“&lt; 6 years” (less than 6: rudimentary school, now working or unemployed)? “&gt; 6 e &lt; 9 years” (more than 6 but less than 9: gymnasium or working unemployed)? “&gt; 9 e &lt; 12 years” (more than 9 but less than 12: high school or working unemployed)? “&gt; 12 years e”(more than 12 university or working unemployed)?</td>
</tr>
<tr>
<td>Habits</td>
<td>Have you ever used or been addicted to any kind of substance? (Alcohol? Drugs? Smoking?)</td>
<td>“yes”, “no”</td>
</tr>
<tr>
<td>Medical history</td>
<td>Have you ever been diagnosed to suffer from any psychological conditions? (Official diagnosis of stress, depression, self-destructive behavior, suicidal attempts, suicidal ideation?)</td>
<td>“yes”, “no”</td>
</tr>
<tr>
<td>Age at first intercourse</td>
<td>How old were you at your first coitus?</td>
<td>“&lt; 15”, “15”, “16”, “17”, “18”, “19”, “&gt; 19” years-old</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>How many times have you been pregnant?</td>
<td>“0”, “1”, “&gt; 1”</td>
</tr>
<tr>
<td>Number of children</td>
<td>How many children do you have?</td>
<td>“0”, “1”, “&gt; 1”</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>Did you ever have at least 1 miscarriage in the past?</td>
<td>“yes”, “no”</td>
</tr>
<tr>
<td>Number of induced abortions</td>
<td>Have you ever had an induced abortion?</td>
<td>If “yes”: “1”?, “&gt; 1”?</td>
</tr>
<tr>
<td>Time of abortion(s)</td>
<td>If you have children and you have also undergone abortion(s), could you describe the sequence of these events?</td>
<td>e.g. abortion – birth - abortion</td>
</tr>
<tr>
<td>Quality of information</td>
<td>How well do you feel that you have been informed by the specialist on the field of induced abortion before or after having one? (only for those who had an abortion in the past)</td>
<td>“satisfying”, “not satisfying”</td>
</tr>
<tr>
<td>(consultation) given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>by the specialist before and after the abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sources of sexual education</td>
<td>Pick up the main and the secondary source of your sexual education</td>
<td>“school”, “family”, “friends”, “media”, “doctors”</td>
</tr>
<tr>
<td>Use and type of contraception</td>
<td>What contraceptive methods do you usually use? (pick up to two)</td>
<td>“withdrawal”, “condom”, “IUD”, “pill/OCS”, “abstinence”, “emergency contraception”, “other” (like the rhythm method), “no/none”</td>
</tr>
<tr>
<td>Number of lifetime sexual</td>
<td>How many sexual partners have you had in your life?</td>
<td>“1”, “2”, “&gt; 2”</td>
</tr>
<tr>
<td>partners</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
simple to comprehend and the key questions and measures derived from them are given in Table 1. We obtained information on nationality, age, religion, education, habits, medical history, marital status and number of children, age at first intercourse, number of abortions in the past, sources of sexual education, use and type of contraception, and number of lifetime sexual partners.

Age, nationality, and religion were the information needed to confirm that the interviewees were 16-22 years old, Greeks, and Orthodox Christians. In this way, we prevented any differences in the participants’ opinions to be attributed to nationality or religious influences and consequently, we tried to present the stance and experience of the average young individual with an active sexual life in the Greek society; a reality for which this survey was conducted. Statistical analysis of the data was done with SPSS (Statistical Package for Social Sciences). The chi-square criterion was used to investigate whether distributions of several categorical variables differ from one another (significance level of our study = 0.01, meaning that when p (probability) > 0.01 in certain df – degrees of freedom – (which means that p value in the $\chi^2$ test is < 0.01), the results are statistically significant and the null hypothesis of independence is rejected).

**Results**

The results of the above questionnaire are cited below in Table 2, and the analysis of each potential risk factor follows next.

### Results

The results of the above questionnaire are cited below in Table 2, and the analysis of each potential risk factor follows next.

#### Table 2. — Answers to the sexual health questionnaire.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Number of individuals/interviewees</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education (e)</strong></td>
<td></td>
</tr>
<tr>
<td>’e &lt; 6 years’: 41, “&gt; 6 e &lt; 9 years’: 110, “&gt; 9 e &lt; 12 years’: 752, “&gt; 12 years e’: 417</td>
<td></td>
</tr>
<tr>
<td><strong>Habits</strong></td>
<td></td>
</tr>
<tr>
<td>’yes’ : 468 , ’no’ : 852</td>
<td></td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td>’yes’: 149, ”no”: 1171</td>
<td></td>
</tr>
<tr>
<td><strong>Age at first intercourse</strong></td>
<td></td>
</tr>
<tr>
<td>Mean age: 17.56 years old</td>
<td></td>
</tr>
<tr>
<td><strong>Number of pregnancies</strong></td>
<td></td>
</tr>
<tr>
<td>0”: 804, “1”: 251, “&gt; 1”: 265</td>
<td></td>
</tr>
<tr>
<td><strong>Number of children</strong></td>
<td></td>
</tr>
<tr>
<td>0”: 1175, “1”: 122, “&gt; 1”: 23</td>
<td></td>
</tr>
<tr>
<td><strong>Miscarriage(s)</strong></td>
<td></td>
</tr>
<tr>
<td>”yes”: 90, ”no”: 1230 / “1”: 58, “&gt; 1”: 32</td>
<td></td>
</tr>
<tr>
<td><strong>Number of induced abortions</strong></td>
<td></td>
</tr>
<tr>
<td>”yes”: 435, ”no/none”: 885 / ”&lt; 1”: 338, ”2”: 72, “&gt; 2”: 25</td>
<td></td>
</tr>
<tr>
<td><strong>Time of abortion(s)</strong></td>
<td></td>
</tr>
<tr>
<td>”abortion after birth”: 79, ”abortion before birth”: 28</td>
<td></td>
</tr>
<tr>
<td><strong>Quality of information</strong></td>
<td></td>
</tr>
<tr>
<td>given by the specialist before and after the abortion</td>
<td></td>
</tr>
<tr>
<td>’satisfying’: 151, ”not satisfying”: 284</td>
<td></td>
</tr>
<tr>
<td><strong>Sources of sexual education</strong></td>
<td></td>
</tr>
<tr>
<td>’school’: 217, ”family”: 341, ”friends”: 1134</td>
<td></td>
</tr>
<tr>
<td>’media’: 688, ”doctors”: 260</td>
<td></td>
</tr>
<tr>
<td><strong>Use and type of contraception</strong></td>
<td></td>
</tr>
<tr>
<td>”withdrawal”: 470, ”condom”: 780, ”IUD”: 170, ”pill/OCS”: 109, ”abstinence”: 85, ”emergency contraception”: 792, ”other” (like the method of the rhythm): 65, ”no/none” : 169</td>
<td></td>
</tr>
<tr>
<td><strong>Number of lifetime sexual partners</strong></td>
<td></td>
</tr>
<tr>
<td>”1”: 732, ”2”: 428, ”&gt; 2”: 160</td>
<td></td>
</tr>
</tbody>
</table>

#### Education (e): 41 women (group A) reported education “e < 6 years” (and now working or unemployed), 110 (group B) answered “> 6 years e < 9 years” (and now working or unemployed), 752 (group C) “> 9 years e < 12 years” (high school, working unemployed) and 417 (group D) “> 12 years e” (university, working unemployed). Females, who had had one or more induced abortions (435), are distributed as follows according to their education level: 38 women (92, 68% of group A) in the “e < 6 years” category, 96 (87, 27% of group B) in “> 6 years e < 9 years”, 200 (26, 59% of group C) in “> 9 years e < 12 years” and 101 (24, 22% of group D) in “> 12 years e” category. Using the chi square test, we find $p > 0.01$, a statistically significant relation between the two values (education, abortion) and, to be more precise, there is a negative correlation between the level of education, as a risk factor, and the possibility of induced abortion. In simple words, the less educated someone is, the more likely she is to undergo an abortion.

#### Medical history: 149 young females answered ”yes” to the question and 852 (64.55%) “no”. We noticed that 197 women (42.9% of the “yes” group) that reported having “bad habits” (smoking, alcohol etc.) had undergone one or more induced abortions, while 271 (31.81% of the “no” group) of the second group had had the same experience. Statistical calculations of the data revealed $\chi^2 > 6.635$ (df = 1), $p > 0.01$. “Bad habits” seem to positively affect the incidence of induced abortions.

#### Age at first intercourse: 752 (56.97%) women answered ”yes” to the question. To be more specific, 89 women who reported to have experienced at least one pregnancy before (17.25% of the group of 516 women – see Table 2 “number of pregnancies”), answered that they had had a positive medical history for psychological conditions in the past and they had visited a specialist for this reason at least once in their lifetime. On the other hand, 60 women, out of those who had had no pregnancy in the past (804), gave the same answer as the previous group (7.46% of this population). According to the chi-square test, $\chi^2 > 6.635$ (df = 1), $p > 0.01$, which means that the null hypothesis – that pregnancy in this age group is independent of psychological medical history – is rejected. In other words, we observe that there is a positive relationship between pregnancy rates and psychological conditions in 16-22 year-old women.

#### Children (e): 752 (56.97%) women answered that they had had their first sexual intercourse < 18 years of age and 568 (43.03%) reported age at first coitus > 18 years old. The mean age of first coitus of the sample was 17.56 years old. The statistical study of its distribution among young women, in relation to any potential induced abortions, revealed that the earlier a female had had her

#### Table 3. — Pregnancies categorized by parity, abortions or miscarriages.

<table>
<thead>
<tr>
<th>Number of women reporting</th>
<th>Children “1”</th>
<th>Children “&gt; 1”</th>
<th>Abortion “1”</th>
<th>Abortion “&gt; 2”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy : ”1”</td>
<td>22</td>
<td>-</td>
<td>216</td>
<td>-</td>
</tr>
<tr>
<td>Pregnancy: ”&gt; 1”</td>
<td>100</td>
<td>23</td>
<td>122</td>
<td>72</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>23</td>
<td>338</td>
<td>72</td>
</tr>
<tr>
<td>Miscarriages (at least one)</td>
<td>13</td>
<td>77</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>
first coitus, the more likely she would have undergone an abortion.

Number of pregnancies: 516 women answered that they had experienced at least one pregnancy before and, moreover, 265 individuals out of the above-mentioned group (of these 516 women) reported more than one pregnancy - see Table 3.

Number of children: 122 young females reported having had one child, while another 23 had more than one. Twenty-two women had had just one pregnancy in the past that had ended up in a live birth, 85 reported an abortion before or after their child’s birth, five had had two abortions and had given one live birth, one had had more than two abortions and had given one birth, nine reported one live birth and medical history of miscarriage(s), six had had two children and no abortion or miscarriage in their medical history, 14 had had an abortion before or after two live births, one answered three live births and one abortion in her medical history, one reported two live births and two abortions and finally, one answered two births and history of miscarriage(s) - see Table 4.

Table 4. — Medical history of abortions and miscarriages in relation to parity.

<table>
<thead>
<tr>
<th>No. of children</th>
<th>No abortion/no miscarriage</th>
<th>History of 1 abortion</th>
<th>History of 2 abortions</th>
<th>History of &gt;2 abortions</th>
<th>History of miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children</td>
<td>22</td>
<td>6</td>
<td>85</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

We can clearly conclude that 91 women had had one child and history of abortion (group A), while 16 women, having had the same medical history, answered “more than one child” (group B). Sixty-three women in group A and 16 in group B (all of them) reported that the abortion(s) had taken place after the birth of their child(ren). The chi square test reveals again $p > 0.01$. Number of children is a factor which affects a woman’s decision to abort. The more children a female has, the more likely she is to decide on abortion to control births.

Miscarriage: 90 (6.81% of the population we studied) women (of all groups: with or without any children, with or without having had any abortions) answered positively that they had experienced at least one miscarriage in their life. Fifty-eight females reported just one miscarriage in their medical history, while 32 reported more than one.

Number of abortions: 435 (32.95%) female individuals, either parous or nulliparous, reported having undergone at least one abortion in the past, while 1/6 (72 women) of them (435) reported two and 1/17 (25 women) had experienced more than two abortions. Two hundred and sixteen women answered that they had had only one pregnancy before which had ended up in induced abortion and 122 reported an abortion before or after birth or miscarriage.

Quality of information (consultation) given by the specialist before and after the abortion: 284 women (out of 435 that had had at least one abortion) answered “not satisfying” and 151 “satisfying”; 208/284 (61.54%) of the group of 338 women reporting only 1 abortion had undergone one abortion in the past, 54/284 two (75% of women with 2 abortions) and 22/284 more than two (88% of the women with >2 abortions). Statistical analysis ($\chi^2$ test) showed that the quality of information given by the specialist before and after the abortion plays an important role in the prevention of future induced abortions.

Sexual education: In Greece, like in all the Western world, there are several potential sources of sexual education such as school, family, friends, media and doctors. According to our study, 12.95% (171) of female youths supported “school” as the main source of sexual education, 9.55% (126) chose “family”, 38.79% (512) “friends”, 22.58% (298) “media” and 16.13% (213) “doctors”. As far as the secondary source of sexual education is concerned, 3.48% (46) answered “school”, 16.29% (215) “family”, 47.12% (622) “friends”, 29.55% (390) “media” and 3.56% (47) “doctors” - see Table 5.

We can clearly make out that the main influence on this field is coming from “friends” (1,134 individuals have picked it up either as a main or secondary factor / 85.91%), then from “media” (688/52, 12%), “family” (341/25, 83%), “doctors” (260/19, 697%) and, finally, “school” (217/16, 44%). We noticed that school, family and doctors (their proportion was diminished in the group A category) are more reliable sources of sexual education than friends and media (their proportion was increased in the group A category) in our society, since statistical analysis using the chi square test and evaluation of each proportion have revealed $p > 0.01$; meaning that the null hypothesis (abortions are independent of the quality of sexual education/information) is rejected.

Contraception: The use and type of contraception chosen in the questionnaire were the following: “withdrawal” (470/35.61%), “condom” (780/59.09%), IUD (170/12.88%), “pill/OCs” (109/8.26%), “abstinence” (85/6.44%), “emergency contraception” (792/62%), “other” like the rhythm method (65/4.92%) and “none” (169/12.80%). We noticed that the main preferences in contraception of these young women were “emergency contraception” and “condom”, then “withdrawal”, “IUD”, “pill/OCs”, “abstinence” and in the end, several “other” methods. Of youths, 12 (80%) reported that they had not used any kind of contraception during sexual intercourse - see Table 6.

Statistical analysis of the above data showed that the use and the type of contraception are very important in the prevention of an unwanted pregnancy and the following abortion(s). Traditional methods of contraception like withdrawal, condoms and others appear to be a statistically significant increased proportion in women reporting abortion(s), whereas, in women without abortions, the percentages, which are increased, point to more contemporary methods that are available to the common woman (IUD, pill/OCs, emergency contraception). It is obvious that contemporary methods are more reliable than traditional ones. As far as abstinence is concerned, it is undoubtedly a traditional and efficient way to prevent an unwanted pregnancy.
Unwanted pregnancy and induced abortion among young women 16-22 years old in Greece: a retrospective study of the risk factors

Number of lifetime sexual partners: 732 (55.45%) individuals reported having had one sexual partner until the time of the survey, 428 (32.42%) reported two and 160 (12.12%) more than two lifetime sexual partners - see Table 7.

We noticed that 117 women that had had live births were included in the category of “one lifetime sexual partner”, 23 in the “two lifetime sexual partners” category and five in “more than two lifetime sexual partners”. The chi-square test showed $p > 0.01$ for all the above categories, meaning that parity is related (negatively) to the number of lifetime sexual partners in this age group (the null hypothesis: «number of lifetime sexual partners / parity» is rejected). Moreover, we made out that, of the 435 females who had undergone one or more induced abortions, 169 (23.8% of the subgroup) were coming from the first category, 187 (43.69%) from the second and finally, 79 (49.37%) from the third category. The chi-square test revealed $p > 0.01$, showing that the more lifetime sexual partners someone reports, the more likely she is to have undergone an abortion (the null hypothesis: «number of lifetime sexual partners / possibility of abortion» is rejected).

Discussion

Recently it has been noted that teenagers are sexually active in younger ages and demonstrate lower compliance to contraceptive methods. An unintended, and most of the time unwanted pregnancy brings teenagers to a crisis. The decision to interrupt a pregnancy is today taken frequently. Although the teenage birthrate declined from 9.0% in 1985 to 5.2% in 2003, teenage pregnancy still remains a serious medical and social problem and abortion rates are still extremely high during adolescence [7].

In our study, the prevalence of self-reported abortions was highest among 16-22 year-old women with a low level of education and/or “bad” habits and/or medical history of psychological disturbances and/or high number of lifetime sexual partners and/or earlier age at first intercourse. Additionally, women who were parous (having one or more children), misinformed by specialists on the matter of abortions, without any proper sexual education and using mostly unreliable methods of contraception or no contraception at all were more likely to experience an unwanted pregnancy and a following induced abortion. It seems that this problem reflects more extensive and serious abnormalities in several sectors of our modern society which need to be addressed.

**Education:** The state must take measures to promote the level of youth’s education. Teaching people to think freely, to understand human values, and to act with merit, is the first step to enhance the social balance and to solve many of our contemporary problems, like the scourge of unwanted pregnancies. The more responsible people are in their lives, the more respected the idea of reproduction and birth become. Not only do we have to combat illiteracy, but also it is essential to improve the current way of learning and lead it towards the human principles. This is the deduction from our study in the sector of education – the family, schools and state have to realize that adolescents and young people must be given the chance of high quality education in order to prevent future unwanted pregnancies and induced abortions.

**Bad habits:** In our study there was a significant difference in the abortion rate between females with alcohol abuse or smoking and females without such habits. The family could play an important role through consultation...
on this subject, and so as the state, through laws, and the school, through providing a better education. “Bad” habits, as a sign of personal weakness, can be successfully eliminated, thus helping us to suppress in a more efficient way the abortion rates among our youths.

Medical history: According to our survey unwanted pregnancies and the consequences (induced abortions, undesired births and children, child abuse, etc.) can be limited if we fight several taboos in the area of a psychologist’s consultation. It is necessary for young person to seek and accept a specialist’s advice, when needed, and this should not become a social stigma. In this way, many unwanted pregnancies can be prevented and well being can be established among young women.

Apart from the above-mentioned character of the problem in question, there is another and more practical side which needs to be approached, as cited below:

Sexual education: As the sexual activity rate in adolescence is reportedly increasing worldwide, improving knowledge concerning sexual education in adolescents might contribute to improving reproductive health issues in such age groups [8]. This should be provided mainly by the school, family and doctors. Media and friends can easily mislead and confuse young females. Unfortunately, sex education is still not included in the Greek school curriculum, and only sporadic information is given [5]. Moreover, many parents still believe that there is no need for sexual information at school due to personal taboos. However, the Ministry of Education and several non governmental organizations, such as the Greek Society of Family Planning, organize teaching programmes on Health Education for adolescents [6]. We just have to support this effort in order to reach, via our schools, a satisfying level of sexual education. We should improve the attitudes, beliefs and knowledge of Greek adolescents regarding sexual intercourse, contraception and sexually transmitted diseases through organizing better programmes on sexuality for youths [9]. Also parents can be trained so as to develop an understanding and proper behavior on this topic towards their children. The role of the gynecologists of course is very important and we have to urge youths to have regular visits.

Quality of information (consultation) given by the specialist before and after an abortion: Our study has clearly shown that 65.29% of the women who had had at least one abortion in their medical history, were not satisfied with the quality of consultation by their doctor before and after the abortion. This is in accordance with what the Non-Aligned Women’s Movement in 1992 argued: despite the fact that abortions were legalized in 1986 and covered by insurance funds, some women were being treated in a hostile way by doctors and social workers in the public hospitals [6]. Doctors must be convinced that a woman having an abortion is in a sensitive and vulnerable position, needing information and psychological support before and after the procedure. Younger women have an even more difficult time adjusting to their abortions. One study found that teenage aborters were more likely to report severe nightmares following abortion and to score higher on scales measuring antisocial traits, paranoia, drug abuse and psychotic delusions than older aborters [1]. Considering the above, we understand the necessity of proper information given by the doctor to the patient. Another problem, which can be prevented, is “replacement pregnancies”. Young people tend to repeat pregnancies; a symptom of youths “acting out” unresolved abortion issues and the desire to “replace” the lost pregnancy with another child, which is often aborted because the woman faces the same pressures as she did the first time, and sometimes even more so [1]. To sum up, a high quality of consultation contributes to the decrease of future and repeated unwanted pregnancies and induced abortions in youths.

Use and type of contraception: In Greece poor education on the issue of contraception still remains a major problem among teenagers contributing to the increased prevalence of undesired pregnancies and abortions [10]. Greek society has not fully adopted the modern methods of contraception, and appears to have one of the lowest rates of modern contraceptive use in Europe [5]. Coitus interruptus and condom use are the most commonly used methods in our country, whereas the pill and other reliable contraceptive methods appear to have low use rates. Contraception is the proper way in which sexual behavior is expressed; the personality and level of the general and sexual education of the individual, as well as the maturity of her environment, are reflected thoroughly in the individual’s contraceptive consciousness. Consequently, abortion in our country is a part of the Greek contraceptive culture [11] and from this point of view, it is very important that contraception-related topics be introduced as a part of sexual education, despite several adverse circumstances, like the generation gap between parents and children, the lack of teachers trained in sexual education and discussion and other barriers [12].

Conclusion

The matter of unwanted pregnancies and their following induced abortions among youths 16-22 years-old in Greece is existent and extremely important to be solved to ameliorate the everyday life of thousands of young people. We have to concentrate on the risk factors for the phenomenon and try to find the path away from this scourge. Sexual education and the proper use of contraception remain the essential tools in our effort.

References

Unwanted pregnancy and induced abortion among young women 16-22 years old in Greece: a retrospective study of the risk factors


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Conservative and surgical treatment of abnormal placenta: Report of five cases and review of the literature

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Summary

Abnormal placentation is a serious complication of pregnancy. The disorder is also associated with significant maternal morbidity. Abnormal placentation, comprised of placenta accreta, increta, and percreta, is a leading cause of postpartum hemorrhage and indication for gravid hysterectomy. We present five cases of successful conservative and surgical management of abnormal placentation managed at our institution, together with a review of the literature.

Key words: Abnormal placentation; Cesarean hysterectomy; Hemorrhage.

Introduction

Adherent placenta is one of the major causes of hemorrhage during pregnancy [1]. Adherent placenta is known as abnormal attachment of placental villi through the uterine wall. It has three distinct groups known as placenta accreta, increta and percreta [2]. The etiology is unknown but the incidence of adhesive placenta increases with advanced maternal age, history of previous cesarean section and placenta previa totalis in pregnancy [3]. The major problem with placental adhesive disorder is massive hemorrhage. We report five cases at risk for obstetric hemorrhage because of adherent placenta and placenta previa totalis.

Case Reports

Case 1

A 33-year-old multi gravida was admitted to our department because of vaginal bleeding. She was at 28-29 weeks of gestation. She had had a regular antenatal follow-up with two previous cesarean sections. In her physical examination vaginal bleeding was determined. Obstetric examination at admission showed a 28-29 week uterus without signs of active labor. When she was at 32 weeks of gestation, cesarean section was performed and a 1,800 g live baby was delivered with an Apgar score of 1 and 5 min of 10 and 10, respectively, because of vaginal bleeding and being in active labor. Before cesarean section, magnetic resonance imaging (MRI) was performed. After delivery the placenta was not separated so hysterectomy was performed. Pathological examination revealed placenta percreta.

Case 2

A 28-year-old primigravida was admitted to our department for a planned cesarean section. She was at 35 weeks of gestation. She had had regular antenatal follow-up with no remarkable medical or physical findings. Obstetrical examination included a 35-36 week uterus that was not in active labor with an intact amniotic membrane. When she was at 36 weeks of gestation, elective cesarean section was performed and a 3,000 g live baby was delivered with an Apgar score of 1 and 5 min of 8 and 10, respectively. MRI, which was performed before the cesarean, showed placenta previa totalis. Myometrial and serosal invasion were also noted. In gray scale ultrasonography (US), more than six irregular and large placental lacunae were defined. There were no focal exophytic masses invading the bladder serosa and wall. The hyperechoic serosa-bladder interface was not intact. The subplacental sonolucent area was irregular. A hypervascular serosa-bladder interface was seen. With these findings we supposed the case was placenta percreta. Preoperative exploration was both definitive and diagnostic of pathology. Placenta percreta was suspected before delivery. After delivery hysterectomy was performed. Five units of red blood cells were transfused peroperatively. No postoperative complication was observed. The patient was discharged on the fourth postoperative day with a healthy baby. Pathological examination confirmed the clinical and surgical diagnosis as placenta percreta.

Case 3

A 38-year-old gravida 7, para 4 women was admitted to our department because of vaginal bleeding. She was at 31-32 weeks of gestation. She had had regular antenatal follow-up and a previous cesarean section. In her physical examination vaginal bleeding was determined. Obstetrical examination showed a 28-29 week uterus without signs of active labor. Before cesarean section, MRI placenta previa totalis and increta was reported. Within the operative exploration both myometrial invasion and serosal-bladder adhesions were observed. Bilateral uterine and hypogastric arteries was ligated after delivery and the operation was ended. Three units perioperatively and three units postoperatively red blood cell packages were transfused. In the postoperative period hysterectomy was performed by explorative laparotomy because of unpreventable vaginal bleeding.

Summary

Abnormal placentation is a serious complication of pregnancy. The disorder is also associated with significant maternal morbidity. Abnormal placentation, comprised of placenta accreta, increta, and percreta, is a leading cause of postpartum hemorrhage and indication for gravid hysterectomy. We present five cases of successful conservative and surgical management of abnormal placentation managed at our institution, together with a review of the literature.

Key words: Abnormal placentation; Cesarean hysterectomy; Hemorrhage.
A 34-year-old gravida 2, para 1 pregnant woman was referred to our department because of the diagnosis of placenta previa totalis and placenta percreta. She had had a previous cesarean section and a regular antenatal follow-up. Obstetric examination showed a 38-week uterus that was not in active labor. MRI reported myometrial invasion with the suspicion of bladder wall invasion. An elective cesarean section was performed with a median incision below the umbilicus. Operative exploration was definitive and diagnostic of pathology. Bladder invasion was seen before delivery. An oblique uterine incision was done close to the fundus of the uterus and a 3,000 g live baby was born with 1 and 5 min apgar scores of 8 and 10, respectively. Hysterectomy was not performed because of the tight bladder invasion. The placenta was left in the uterus and the operation was completed. After the surgery methotrexate was given five times with the dose of 100 mg for each treatment. However the placenta did not separate from the uterus after all the medical therapy. Thus second-look laparotomy was done 50 days later and the placenta was separated by sharp curettage.

Case 5

A 28-year-old gravida 2, para 1 pregnant woman was hospitalized in our department because of placenta previa totalis and placenta percreta. She was at 32 weeks of gestation and she was in active labor. Obstetrical examination showed a 32-week uterus and the amniotic membrane was not intact. She had had a previous cesarean section. She had had regular antenatal follow-up in our department and when she was at 28 weeks of gestation MRI was performed. At MRI placenta previa totalis and placenta percreta were shown. There was also a report of bladder invasion at MRI. Gray scale and color Doppler US were also performed and findings revealed the case was placenta percreta with bladder invasion. A medial incision below the umbilicus was performed and in perioperative exploration there was no sign of bladder invasion but myometrial invasion was noted. A 1,800 g live baby was born with 1 and 5 min apgar scores of 8 and 10, respectively. The placenta was not separated and hysterectomy was performed. Three units of red blood cells were transfused. The patient was discharged on the fourth post-operative day without complications.

Discussion

Adherent placenta is an implantation defect characterized by the placental villi growing into the myometrium and serosa [4]. There is an absence or deficiency in Nitabuch’s layer or desidua basalis. It has three distinct subgroups known as placenta accreta, increta and percreta. The incidence of adherent placenta varies from one in 540 to one in 93,000 deliveries [5]. Adherent placenta is one of the major causes of obstetric hemorrhage and its associated with an increasing number of cesarean sections.

The etiology of adherent placenta is unknown. It may be related to damage of the decidua basalis, which allows placental invasion into the myometrium. The barrier function of the decidua is absent and invasive trophoblasts may invade the myometrium. Several conditions are associated with abnormal placenta; placenta previa, a previous cesarean section, multiple pregnancies, a history of dilatation and curettage, a history of manual extraction of the placenta, high parity and advanced maternal age [6]. These may be named risk factors, but they are rarely the sole cause of adherent placenta. In recent studies in women with placenta previa totalis, the adherent placental risk ranges from 2% to 39% with maternal age older than 35 and two or more previous cesarean sections [2]. The rising cesarean section rate may be the cause of an increased rate of placenta percreta in recent years.

In all five cases the patients had placenta previa totalis. In cases 1, 3, 4 and 5 the patients had a history of damaged decidua basalis.

The diagnosis of adherent placenta is difficult, but very important due to the possible fatal and maternal outcomes. It is a significant risk factor for maternal and fetal mortality. Several diagnostic modalities have been introduced in recent years. These include transvaginal and transabdominal US with color Doppler imaging [7-9] and MRI. In gray scale US the subplacental sonolucent zone, regular hyperechoic serosa-bladder zone and lacunale are significant in the diagnosis of adherent placenta [10, 11]. An irregular and thick subplacental sonolucent zone and large, irregular and more than six lacunale with turbulent blood flow can be seen [12, 17]. It has been suggested that the single most important factor affecting outcome is antepartum identification of abnormal placentation [18]. This represents a possibility of accurate planning of labor. It is important for the obstetrician to be aware of the different strategies of management.

In all five cases we performed MRI imaging and two of these cases were also studied by US. In cases 2 and 5 the gray scale and color Doppler US findings indicated placental adhesion disorders, where the placenta was not separated and hysterectomy was performed.

Two main options have been introduced for the management of placenta percreta [19-22]: surgical removal of the uterus and involved tissues, and conservative therapy [23-25]. The latter includes, leaving the placenta in situ with packing, piecemeal blunt dissection with packing, uterine curettage with packing, closing of the uterine defect, localized excision and uterine repair, uterine packing with uterine and even hypogastric artery ligation, and adjuvant chemotherapy [22-25].

Hysterectomy has been the traditional treatment for placenta percreta [4, 20]. This is based on the belief that conservative treatment gives a much higher maternal mortality rate. Conservative management is beneficial in preserving future fertility, and may reduce the need for transfusion [19, 23-25].

We performed a median abdominal incision below the umbilicus and uterine incision close to the uterine fundus in all five cases. In case 4 we could not perform hysterectomy and did conservative therapy. We left the placenta in situ and ligated both the uterine and hypogastric artery bilaterally and continued with methotrexate treatment. However the result was not satisfactory. We performed second-look surgery and separated the placenta with uterine curettage.

The main complication of placenta percreta is severe
bleeding [18]. Other serious complications are rupture of the uterus, coagulation problems, invasion of adjacent organs, uterine inversion secondary to attempted manual removal of the placenta, fistula formation and loss of reproductive organs [11, 14, 17, 18].

The wish to preserve fertility and control bleeding during the operations made it possible to choose a conservative surgical technique.

References


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Abuse Assessment Screen (AAS) questionnaire: 
the Greek validation

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Summary

Aim: Domestic violence is a social problem with increasing dimensions worldwide. The various forms of abuse and especially violence during pregnancy have not been sufficiently studied by the Greek scientific community. The aim of this study was to translate, culturally adapt and validate a special research tool that can be used by health professionals as a diagnostic tool for violence during pregnancy. Methods: The Abuse Assessment Screen (AAS) questionnaire was chosen as a screening tool. The questionnaire was translated into Greek in accordance with the procedure suggested by the ‘Trust Scientific Advisory Committee’, followed by the cultural adaptation of the questionnaire to the Greek reality. Results: Specific psychometric tests were used for the validation of the questionnaire in order to assess the questionnaire’s reliability and validity, and a factor analysis was also carried out. The internal consistency for all the parties who were questioned (n = 262), as expressed by Cronbach’s alpha coefficient for the AAS, was 0.806 which is quite satisfactory and the results of our study suggest that the Greek translation of the AAS has a high correlation index compared to relevant international studies. Conclusions: The AAS questionnaire in the Greek version seems to be a reliable and valid tool for the diagnosis of violence during pregnancy.

Key words: Abuse Assessment Screen questionnaire; Domestic violence; Screening tool; Pregnancy.

Introduction

Violence against women is a complex social phenomenon of a global dimension. At the European level, the official definition of violence [1] against women includes any act of gender-based violence that results in or is likely to result in physical, sexual or psychological harm or suffering to women including threats of such acts, coercion or arbitrary deprivation of liberty whether occurring in public or private life.

Domestic violence is a social and clinical problem with increasing dimensions influencing the lives of many pregnant women and their children [2]. The impact of abuse on a pregnant woman’s health is significant regardless of whether it is associated with violent acts leading to injuries or not [2]. Domestic violence prevalence during pregnancy is estimated at 0.9%–20.1% and domestic violence prevalence in general ranges from 9.7% to 29.7% [3].

The abuse of pregnant women in our country has not been systematically and adequately studied by the scientific community. All attempts made are mainly a revision of studies carried out abroad and do not include empirical data related to the Greek reality [4]. The difficulty in collecting data is mainly due to the lack of adequate data provided by the various structures to which abused women go. Thus, it is difficult to evaluate the degree, nature, seriousness and consequences of the phenomenon [5].

The aim of this study was the translation, cultural adaptation and validation of a special research tool in the framework of studying the issue of abuse against pregnant women, that will become a model diagnostic tool in order to record, assess and evaluate the results with regard to the abuse of pregnant women in our country.

Materials and Methods

Various methods have been recommended in the last two decades for the screening for domestic violence. Nevertheless, few screening tools have been evaluated as diagnostic tools. The Abuse Assessment Screen (AAS) questionnaire [6] (Table 1) is a useful, fast and easy-to-use tool to detect domestic violence during pregnancy and this is why it is widely used in clinical practice [7, 8]. It includes five questions but a shorter version with three questions has also been used [7]. It includes body maps to demonstrate the areas where body injuries have been inflicted.

The questionnaire has been proven to effectively detect abused pregnant women [9], especially in their first regular visit for their pregnancy [10]. In this research, each positive answer to each one of the five questions of the questionnaire was taken as one point. The cutting score was three and a total grading was used to verify the presence of violence during pregnancy or not [11]. Dichotomous variables included in the questionnaire concern questions about physical, psychological or sexual violence during pregnancy and the previous year. The answers to these questions are of the closed type (yes-no) and the psychometric data of the English version of the questionnaire have been documented in various studies [9, 12].

Translation

The translation process into Greek was the one suggested by the Trust Scientific Advisory Committee [13]. The aim was to translate the questionnaire from English into Greek, while
maintaining the basic characteristics of the questionnaire. According to the above-mentioned instructions, the English questionnaire was translated into Greek (forward translation) by two different translators without each one knowing the work of the other. There were no significant differences in the interpretation of the words in the forward translation. The first version of the questionnaire in Greek was the result of the comparison of the two translations. This version was then translated into English (back translation) by a bilingual person (mother-tongue English) with knowledge of the terminology (midwife), but did not know the initial version of the English questionnaire. Following that, a meeting took place with the participation of a third party, an expert in the process, and following a unanimous decision, the first version of the questionnaire in Greek was created (1st reconciliation version). In the end, the English translation (back translation) was sent for comments to a research group of midwives at the University of Salford, studying issues of women’s abuse. These comments were taken into consideration, resulting in the second version (2nd reconciliation version).

Cultural adaptation

Taking into account the way the specific research tool was culturally adapted in similar international studies [6, 14-16], the second version of the questionnaire was used in a random sample of pregnant women for the cultural adaptation in our country, as suggested in the cognitive debriefing process [13]. Thus, the AAS questionnaire was given at the beginning of June 2007 to five random pregnant women who visited the Outpatient Obstetrics Clinics of the two biggest hospitals – maternity hospitals of Athens – in order to be examined. The pregnant women were asked whether each question was understood and if they needed to rephrase it in their own words or preferred a specific word in a question to be changed so that the question could be better understood (cognitive debriefing interview). The questionnaire during the cultural adaptation was in general understood and easy according to the pregnant women’s comments. Their proposals were integrated into the second version of the questionnaire and the final version of the questionnaire’s Greek translation was created. The randomization of the pregnant women’s sample for the cultural adaptation of the questionnaire was carried out on the basis of the simple random sampling which is the simplest form and a flexible and integrated model [17].

Pilot application

Prior to distributing the final questionnaire to the pregnant women, it was distributed on a pilot basis to women selected with the method of simple random sampling during pregnancy. More specifically, the AAS questionnaire was given to ten random pregnant women who visited the Outpatient Obstetrics Clinics of the two biggest hospitals – maternity hospitals of Athens in order to be examined. The women’s sample used for the pilot control had similar characteristics with the characteristics of the people included in the final samples. The aim of the pilot control was to verify:

1) The consistency and whether the questions were understood;
2) The adequacy of the alternative answers to all closed questions;
3) Possible flow problems related to the size of the questionnaire and the time required to fill it in; and
4) The need for changes and clarifications.

In general terms, during the pilot application, no special problems or questions arose and it was characterized by the women as an easily understood questionnaire.

Collection of research material

In the period June-September 2007, following the pilot application, the questionnaire was distributed to 262 pregnant women who visited the Outpatient Obstetrics Clinics of the above-mentioned public hospitals – maternity hospitals of Athens – to be examined. Prior to that, the scientific councils of both hospitals after studying the research protocol approved the questionnaire to be used for a study. Before filling in the questionnaire, all pregnant women were informed orally and in writing by the researcher – midwife for the aim of this study and the possible impacts of the results on the society; all the women signed a consensus form. The SPSS, version 15, statistical programme was used for the statistical analysis of the data.

Results

Application of psychometric tests (questionnaire’s validation)

Specific psychometric tests were performed for the questionnaire’s validation to evaluate the questionnaire’s reliability and validity and a factor analysis was also con-
The internal consistency for all the participants (n = 262) as expressed with Cronbach’s alpha coefficient for the AAS scale was 0.806, which is quite satisfactory. Table 2 shows the change of Cronbach’s alpha coefficient for the internal consistency when a specific variable is abstracted from our factorial model. The variables are five, as many as the questions of the AAS questionnaire.

The exploratory factor analysis was performed with the use of the principal components analysis method with Varimax with Kaiser Normalization (rotation method), looking for the special factors making up the questionnaire. The factorial analysis with the method of principal components was used because we wanted no interaction between the factors so that the groups of variables could be distinguished. In the end, our model showed just one group of variables (Table 3).

The application of the exploratory factor analysis showed that the categories (factors) that may constitute specific characteristics of the questionnaire, as shown in the Screen Plot (Figure 1) are one. More specifically, as shown in Table 3, no latent value of any factor is more than one, so our model is one-dimensional.

The method inter-item correlation matrix was used for the analysis of the examination of the correlation of the various items. The specific analysis showed that all the questions are correlated to a very good degree, as all Cronbach’s alpha values were higher than 0.7 (Table 4).

Discussion

The AAS questionnaire is a useful, fast and easy to use tool to detect domestic violence during pregnancy and this is why it is widely used in clinical practice [8, 12]. It has been found that the questionnaire effectively detects abused pregnant women [9], especially during their first regular visit of their pregnancy [10].

The size of the sample used for the weighing of the questionnaire in the Greek language and the factorial analysis was adequate (KMO measure of sampling adequacy = 0.780). The validation of the questionnaire in Greece showed that the internal consistency, as expressed with Cronbach’s alpha coefficient for all pregnant women that participated (n = 262) was 0.806, which is quite satisfactory. Our factorial model, thus, has a high consistency index. Relevant studies have found that Cronbach’s alpha coefficient for the AAS questionnaire ranges between 0.79-0.89 [9, 18] with 0.88 being the final value which is higher than the one of the Greek edition but the difference is not so great.

The AAS questionnaire in the Greek version seems to be reliable, as it has good internal consistency (Cronbach’s alpha = 0.780), as shown in relevant studies [19]. Furthermore, our results show that the Greek translation of the AAS scale has a high correlation index compared to relevant international studies [20, 21].
Acknowledgment

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Twin pregnancy after *in vitro* fertilization in a woman with a unicornuate uterus

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Summary

A unicornuate uterus is a rare congenital uterovaginal anomaly. A unicornuate uterus is associated with infertility, cervical incompetence, and premature labor. A case of a 32-year-old null gravida female with a unicornuate uterus who had wished to bear a child for five years is reported. After undergoing insemination treatment with the husband’s semen, *in vitro* fertilization was performed and a twin pregnancy occurred. A successful outcome was achieved with the delivery of viable infants following intensive obstetric management.

*Key words:* Unicornuate uterus; *In vitro* fertilization; Twin pregnancy.

Introduction

A unicornuate uterus is a rare congenital anomaly which is observed in only 4.4% of uterine anomalies [1]. This condition is associated with a high rate of primary infertility and poor fetal survival [2]. This study describes the successful outcome of a twin gestation following *in vitro* fertilization in a woman with a unicornuate uterus.

Case Report

The patient was a 32-year-old null gravida female with a 5-year history of primary infertility. She was diagnosed with a unicornuate uterus with a non-communicating right rudimentary horn, and thereafter underwent a resection of the right horn at 23 years of age to treat dysmenorrhea. She first presented at the Niigata Workmen’s Accident Hospital in May 2003. Her menstrual cycles were regular and her hormonal testing was normal. The husband’s sperm test findings were also normal. Magnetic resonance imaging (MRI) of the pelvis showed a small uterine body with a decreased muscular mass (Figure 1). A left ovarian endometrial cyst was also noted on pelvic MRI. Hysterosalpingography showed a banana-shaped uterine cavity (Figure 2). The tubal passage of the left side was normal.

The patient underwent ovarian stimulation with 100 mg clomiphene citrate on days 4-8 of her menstrual cycle and four rounds of intruterine insemination. Thereafter she elected to undergo *in vitro* fertilization. The patient received 900 μg of buserelin acetate (Suprecur; Aventis Pharma Inc.) daily, starting at the midluteal phase of the pretreatment cycle and ending at the time of hCG injection. The patient received 150 IU of hMG (HMG NIKKEN; NIKKEN CHEMICALS CO., LTD., Japan) daily from day 3 of the treatment cycle until the day before the administration of 10,000 IU of hCG (HCG Mochida; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan). HCG was administered when at least two follicles reached a diameter of ≥ 18 mm. Transvaginal follicular aspiration was performed approximately 34 hr after hCG injection. Five oocytes were retrieved. Conventional insemination was performed. Three oocytes were fertilized. Embryo transfer was performed on day 3 of culture. Two good quality embryos were then transferred. A twin pregnancy was identified in the uterus at six weeks’ gestation. A prophylactic Shirodkar cervical cerclage was put in place at 14 weeks’ gestation. The woman was hospitalized for premature labor and a shortened cervical length at 22 weeks’ gestation. Intravenous tocolysis with a β-sympathomimetic agent and bed rest were initiated. Intravenous tocolysis was continued until delivery. A spontaneous rupture of the membrane and labor occurred at 36 1/7 weeks’ gestation. An emergency cesarean section was performed due to the twin gestation. A low transverse cesarean section resulted in the delivery of 2,002 g and 2,164 g infants in cephalic-cephalic presentation. No uterine atony occurred. The subsequent postoperative course was unremarkable.

Discussion

A unicornuate uterus is associated with a poor reproductive outcome [3]. There is a spontaneous abortion rate of 37.1%, a preterm delivery rate of 16.4%, and a live birth rate of 55.1% in patients with this condition [4]. The reproductive success rate depends on variations in the vascular contribution of a uterus, the extent of the reduction of muscular mass of a uterus, and the degree of cervical incompetence [3]. Women presenting with this anomaly should therefore be considered high-risk obstetrical patients.

A decision regarding the number of embryos transferred was necessary in the present case, since there was concern that the patient’s condition would preclude a successful outcome if a twin pregnancy occurred.

To reduce the number of multiple pregnancies, single embryo transfer has become the standard in the Nordic countries using IVF treatment. Sweden at present has 70% single embryo transfer, with 5% twins and a pregnancy rate per transfer remaining constant at 30% [5]. Van Montfoort et al. [6] reported that the ongoing pregnancy rates after an elective single embryo transfer in an unselected group of patients to be significantly lower in
comparison to double embryo transfer (21.4% vs 40.3%). In contrast, the ongoing pregnancy rates in selected groups of patients did not differ between elective single embryo transfer and double embryo transfer. They concluded that the pregnancy rates after single embryo transfer in all patients would therefore decrease two-fold in comparison to double embryo transfer.

Two-embryo transfer was therefore selected in the current patient in order to increase the pregnancy rate and, as a result, a twin gestation occurred. In this case, prophylactic cervical cerclage was performed at 14 weeks’ gestation to prevent preterm delivery. A successful outcome was achieved with the delivery of viable infants following intensive obstetric management. The presence of a unicornuate uterus is therefore not considered to be an absolute contraindication for two-embryo transfer following in vitro fertilization.

Conclusion

A successful outcome was achieved in a patient with a unicornuate uterus and twin gestation. Two-embryo transfer is therefore not considered to be contraindicated in such patients.

References


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Clinical significance of procalcitonin in cervico-vaginal secretions of women with preterm rupture of membranes

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²Department of Biostatistics and Medical Informatics, Faculty of Medicine, Dicle University, Diyarbakir (Turkey)

Summary

Purpose: To compare vaginal fluid procalcitonin (PCT) concentrations in cases of preterm premature rupture of membranes (PPROM) and healthy pregnant women, and to determine whether the PCT concentrations are of value in the diagnosis of PPROM cases and clinical amnionitis. Methods: 50 cases with PPROM and 50 healthy pregnant women were enrolled in the study. In the PPROM group, analysis was conducted on PCT concentrations with reference to serum leucocytosis, serum C-reactive protein level and urine analysis, as well as to presence/absence of clinical amnionitis. Statistical analyses were carried out by using the statistical packages for SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Results: Procalcitonin levels in the PPROM group were significantly higher than in cases of healthy pregnant women (1.17 vs 0.05 ng/ml; p < 0.001). In the PPROM group PCT concentrations between the patients with and without clinical amnionitis were comparable. Also, a significant correlation was observed between PCT and leucocytosis (r = 0.64; p < 0.001) and C-reactive protein (r = 0.90; p < 0.001). Conclusion: These findings suggest that the value of vaginal fluid PCT determinations can be useful for diagnostics of PPROM cases suspected of intrauterine infection.

Key words: Premature rupture of membranes; Procalcitonin; C-reactive protein.

Introduction

Preterm premature rupture of membranes (PPROM) is diagnosed when rupture of amniotic membranes occurs prior to the completion of the 36th week of gestation, and the incidence is reported to be between 6% and 10%, with almost 80% of these cases occurring at term [1, 2]. Preterm PROM is largely a clinical diagnosis. It is typically suggested by a history of watery vaginal discharge and confirmed on sterile speculum examination. The differential diagnosis includes leakage of urine (urinary incontinence); excessive vaginal discharge, such as physiologic discharge or bacterial vaginosis; and cervical mucus (show) as a sign of impending labor [3]. The perinatal complications of PPROM change with gestational age at rupture requiring a gestational age approach to treatment. There is little maternal benefit to conservative management, but there can be significant neonatal benefit, especially in the late second and early third trimester. The benefits of conservative management are mainly in prolonging pregnancy, which has the potential to decrease gestational age-related morbidity associated with preterm birth. This must be balanced with the risks of conservative management, which include cord prolapse, placental abruption, perinatal infection, emergent delivery for a non-reassuring fetal status and fetal death [4]. The number of clinical methods of detecting women suspected of subclinical intrauterine infection is modest and limited. Non-invasive methods of detecting intrauterine infection are desirable. Some mediators may be detected in vaginal or cervical secretions and it seems probable that the concentrations the vaginal compartment, especially after PROM, are representative of their intra-amniotic concentrations [5].

PCT is recognized as a specific marker of generalized bacterial infections [6, 7]. Although there is an increasing awareness of the usefulness of assessing PCT levels in clinical practice, there are only a few published data about PCT being evaluated during term and preterm parturition [8, 9].

The purpose of this study was to evaluate and compare concentrations of PCT in cervico-vaginal secretions in pregnancies complicated by PPROM and healthy pregnant women and to determine clinical significance PCT levels in clinical amnionitis cases.

Methods

This study was performed at Dicle University, School of Medicine, Department of Obstetrics and Gynecology, from September 2008 to September 2009 on 100 pregnant women. Written informed consent was obtained from all patients. The study consisted of 50 pregnant patients and a control group was created consisting of 50 normal pregnant women.

The study group consisted of patients admitted with a diagnosis of PPROM (24-36 weeks gestation). All patients in this group developed spontaneous rupture of membranes. PPROM was diagnosed by traditional methods such as vaginal fluid drainage, vaginal discharge and perineal wetness. Rupture of membranes was diagnosed by sterile speculum examination confirming fluid leakage from the cervical canal or pooling of fluid in the posterior vaginal fornix. All pregnant patients in this group were hospitalized at our clinic and followed-up until delivery. From admission to delivery patients received prophylactic antibiotics (sulbactam-ampiciline 1g 4x1 IV). Steroid therapy (betamethason 12 mg 2x1 IM) was used in cases before 34 gestational weeks. Patients were restricted to bed rest,
Results

The demographic and clinical characteristics of groups are shown in Table 1. There were no significant differences in maternal and gestational age between groups. However, cervical dilatation and effacements were significantly higher in the study group than the control group. Also AFI was significantly lower in the study group.

Serum WBC counts (10.97 vs 13.81k/ul; p < 0.001) and serum CRP level (6.22 vs 25.42 mg/l; p = 0.005) were found to be statistically different between the study and control group, and both of these values were higher in the study group.

Vaginal fluid concentrations of PCT in patients with PPROM were significantly higher than in the control group (1.17 vs 0.05 ng/ml; p < 0.001). Significant correlations were observed between PCT levels with CRP (r=0.90, p < 0.001) and WBC (r=0.64; p < 0.001).

Study group cases were evaluated for clinical amnionitis situations. Fetal tachycardia (> 160/m), maternal fever (> 38°C), maternal tachycardia (> 100/m without any other explanation) or uterine sensitivity were evaluated as clinical amnionitis.

The mean and standard deviation (SD) were calculated for continuous variables. The normality of the variables was analyzed by Kolmogorov-Smirnov test. The chi-square test and student t-test evaluated associations between the categorical and continuous variables. The Student’s t-test evaluated differences between the study and control groups.

Discussion

Rupture of the membranes is thought to result from the effects of physical forces in localized areas of membranes weakened by degradation of structural collagens [10]. The pathogenesis of PPROM resulting in preterm birth remains unknown, but many hypotheses have been suggested. These factors include maternal infection, genetic predisposition, mechanical damage, smoking, nutritional and vitamin deficiencies and plasminogen activation. Intrauterine infection and subsequent inflammation may synergistically weaken the membranes because of the combined effects of microbial, host inflammatory cells, and cytokine-regulated protease production [11]. The first goal of this study was to determine whether vaginal fluid PCT levels in PPROM cases and healthy pregnant women were different or comparable. It was observed that PCT levels in PPROM were significantly higher than in healthy pregnant women, thus adding additional evidence to confirm the hypothesis about the infectious etiology of PPROM.

The current management of patients with PPROM at a gestational age lower than 34 weeks consists of corticosteroid and antibiotic administration, and expectant management until fetal or maternal signs of infection become evident [12]. Optimal expectant management of PPROM requires early detection of chorioamnionitis. To date, no universally sensitive and specific marker for diagnosis of subclinical intrauterine infection has been identified.

Table 1. — Demographic and clinical characteristics of the study and control groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group (n = 50)</th>
<th>Control study (n = 50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>27.38 ± 6.02</td>
<td>27.72 ± 6.60</td>
<td>0.60</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity (mean ± SD)</td>
<td>2.16 ± 2.24</td>
<td>3.36 ± 2.79</td>
<td>0.02</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>30.40 ± 3.18</td>
<td>29.74 ± 4.04</td>
<td>0.36</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation (cm)</td>
<td>25.60 ± 17.39</td>
<td>8.40 ± 5.84</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical effacements (%)</td>
<td>1.61 ± 1.22</td>
<td>0.80 ± 0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFI (cm)</td>
<td>4.86 ± 2.98</td>
<td>12.84 ± 1.73</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (g/l)</td>
<td>10.97</td>
<td>13.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>6.22</td>
<td>25.42</td>
<td>0.005</td>
</tr>
<tr>
<td>Procalcitonin (ng/l)</td>
<td>1.17</td>
<td>0.05</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

p < 0.05 is accepted to be statistically significant. CRP: C-reactive protein. AFI: Amniotic fluid index. WBC: White blood cells.
Clinical significance of procalcitonin in cervico-vaginal secretions of women with preterm rupture of membranes

Torbé et al. [13] found that increased vaginal fluid PCT level is associated with subclinical intraamnionic infection in PPROM cases; likewise in our study high vaginal fluid PCT levels were detected in clinical amnionitis. Rizzo et al. [14] and Jun et al. [15] demonstrated that the measurement of interleukin-6 in cervical secretions of patients with PPROM is a noninvasive and sensitive method to identify the patient at risk for microbial invasion of the amniotic cavity, impending preterm delivery, or neonatal complications. Di Naro et al. [12] found that increased vaginal fluid C-reactive protein concentration is associated with intraamniotic infection and funisitis and that there is a significant correlation between amniotic fluid and vaginal fluid concentrations.

Conclusion

Procalcitonin is a new parameter used in the diagnosis of generalized or systemic infectious diseases. So far, not much is known about its use among pregnant women. In view of the probably infectious etiology of PPROM one of the purposes of this study was to determine whether vaginal fluid concentrations of PCT immediately after PPROM might have any value in the diagnosis of cases with suspected subclinical intrauterine infection.

References


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Placental growth factor: a putative screening test for gestational diabetes mellitus in first trimester

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Summary

Purpose of Investigation: To evaluate placental growth factor as a screening test for gestational diabetes mellitus in the first trimester. Methods: Sixty-seven pregnant women who were admitted to the outpatient clinic of Ege University Obstetrics and Gynecology Department consecutively for first trimester bioanalysis between May 2005 and February 2006 were included in the study. The cohort of patients underwent 50 g or 100 g oral glucose tolerance tests at the 24th week of pregnancy. Placental growth factor levels were analyzed by ELISA (human PGIF, ELIZA kit, Quantikine, R&D systems, USA) from the maternal blood collected at the time of first trimester screening. Results: The study group of 15 patients with gestational diabetes were compared with a control group of 52 pregnant women with normal oral glucose tolerance tests. The level of placental growth factor was mean 35.79 ± 16.79 pg/ml in the study group whereas it was mean 45.12 ± 28.07 pg/ml in the control group. There was no significant difference between either group for placental growth factor maternal serum levels. Conclusion: Maternal placental growth factor serum levels are not useful in predicting gestational diabetes mellitus.

Key words: Placental Growth Factor; Gestational Diabetes; First trimester.

Introduction

Gestational diabetes is defined as the glucose intolerance of variable severity with onset during pregnancy and characterized by defective insulin secretion or insulin resistance. The incidence ranges from 2.2% to 8.8% of all pregnancies and this is the most common medical complication of pregnancy [1, 2]. Several studies have been done to find an optimum screening test as the high concentrations of glucose, especially in the first trimester of pregnancy, may cause several complications such as miscarriages, congenital defects, macrosomia, hypoglycemia, prematurity, cardiomyopathy and respiratory distress. Early diagnosis and optimizing maternal blood glucose levels will decrease the complication rates and fetomaternal morbidity. The 50 g oral glucose tolerance test (OGTT) is now widely accepted all over the world as a screening test between 24-28 weeks of pregnancy; however, a screening test which can be performed in the first trimester may be a better alternative.

Diabetic pregnancy causes abnormal placental growth and fetal development. Placental growth is regulated by several growth factors including placental growth factor (PLGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). PLGF is a member of the VEGF family and the main source of PLGF during pregnancy is the placent al trophoblasts [3]. It is a key molecule in angiogenesis and contributes to the regulation of placental function.

The aim of this study was to investigate PLGF as a screening test for gestational diabetes mellitus in the first trimester.

Material and Methods

The study was conducted in accordance with the guidelines and approval given by the Ethical Committee of the Ege University Hospital. Sixty-seven 11-14-week pregnant women admitted to the outpatient clinic of Ege University Obstetrics and Gynecology Department consecutively for first trimester bioanalysis between May 2005 and February 2006 were included in the study. All selected pregnant women demonstrated intermediate or high-risk factors for diabetes according to the American Diabetes Association [4]. Out of 67 pregnancies three were twin pregnancies, whereas 64 were singleton pregnancies. The study group (n = 15) with gestational diabetes were compared with a control group (n = 52) with normal oral glucose tolerance tests. OGTTs (50 or 100 g) were performed on all pregnant women at the 24th week of pregnancy. The first-hour glucose level above 140 mg/dl in the 50 g OGTT was accepted as abnormal; 100 g-3-hour OGTT was performed after an overnight fast. Gestational diabetes was diagnosed with two or more high glucose levels during fasting, first hour, second hour and third hour glucose levels [5]. Blood samples were collected from the antecubital veins into heparinized vacutainer tubes. After centrifugation at 1000 g for 15 min, serum samples were incubated at –80°C and analyzed in the Biochemistry Department laboratory. PLGF was studied with the ELISA method (human PGIF, ELIZA kit, Quantikine, R&D systems, USA).

Statistical Analysis

Statistical analysis was performed using the SPSS v. 12.0 program. Spearman’s rho test was used for correlation analysis and the Mann-Whitney U test was used to compare groups. The levels were expressed in mean ± standard deviation.

Results

Age of the pregnant women (n = 67) ranged from 22 to 44 years (31 ± 4 years) and mean parity was 0.5 ± 0.7. Maternal levels of PLGF did not correlate with age. The mean birth week and birth weight were 38 ± 1.93 weeks
and 3.296 ± 561 g, respectively. There was also no correlation between birth weight and PIGF levels. The level of placental growth factor was mean 35.79 ± 16.79 pg/ml in the study group whereas it was mean 45.12 ± 28.07 pg/ml in the control group. There was no significant difference between either group for placental growth factor maternal serum levels (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>GDM group (n = 15)</th>
<th>Control group (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>33.30 ± 4.89</td>
<td>29.90 ± 3.81</td>
</tr>
<tr>
<td>Birth week†</td>
<td>37.47 ± 2.13</td>
<td>38.22 ± 1.85</td>
</tr>
<tr>
<td>Birth weight†</td>
<td>32.76 ± 500</td>
<td>33.02 ± 581</td>
</tr>
<tr>
<td>Parity*</td>
<td>0.87 ± 0.83</td>
<td>0.42 ± 0.60</td>
</tr>
<tr>
<td>PIGF levels†</td>
<td>35.79 ± 16.79</td>
<td>45.12 ± 28.07</td>
</tr>
</tbody>
</table>

*Statistically significant difference between both groups (p > 0.05).
†Statistically insignificant difference between both groups (p > 0.05).

Fifty pregnant women underwent cesarean (C) section (74.5%). The major indication for cesarean sections was previous C section (n = 8). Others included macrosomia, fetal distress, placenta previa, prolonged labor, and breech presentation. The most common complication of the newborns was prolonged jaundice (n = 5, 7.4%). Other complications were premature, hypoglycemia, cardiac defects and extremity abnormalities (n = 8, 12%).

According to the correlation analysis, there was no relationship between the apgar scores of the newborns and maternal serum PLGF levels.

Mean weight gain of the pregnant women was 13.59 ± 5.09 kg and out of the 67, seven had excessive weight gain (≥ 20 kg). The weight gain of the pregnant women did not correlate with PLGF levels.

**Discussion**

The placenta has a very critical role for both fetal development and maintenance of pregnancy. Development of the placenta is regulated by several growth factors such as PLGF, VEGF, FGF and abnormal placentation may result in a wide range of pregnancy complications.

PLGF is a homodimeric glycoprotein that is involved in the VEGF family. During pregnancy, it is expressed in trophoblasts and contributes to proliferation, migration and endothelial cell activation [6, 7]. Studies with trisomy 21 fetuses showed higher maternal serum levels of PLGF [8, 9], whereas pregnancies complicated with pre eclampsia and fetal growth restriction showed lower maternal serum levels as these fetuses have defective placentation development and vascularization [10].

Although there are several studies about PLGF, there is limited data about the relationship between PLGF and diabetes. It is now known that pregnancies which are complicated with gestational or pregestational diabetes have higher placental weight and this is accompanied with a delay of placental maturation [11].

Loukovaara et al. [12] compared the umbilical cord PLGF levels of 62 normal pregnant women, 67 pregnant women with type 1 diabetes and 28 pregnant women with gestational diabetes treated with insulin. There was no statistically significant difference between three groups. Cord serum PLGF levels did not correlate with birthweight as it was the same in our study.

Ong et al. [13] evaluated maternal serum PLGF levels of 82 diabetic pregnancies and 400 normal controls. There were four groups in the study including pregnant women with type 1 diabetes, type 2 diabetes, gestational diabetes and healthy pregnant controls. PLGF levels were significantly higher in the type 2 and gestational diabetes group than the control group. On the other hand, there was no statistically significant difference between the type 1 diabetes group and the controls. This was attributed to insulin resistance which is the common pathogenetic mechanism of both type 2 diabetes and gestational diabetes.

Early diagnosis of gestational diabetes is very important as maternal and fetal complications may be decreased due to the early optimization of serum glucose concentration. In this study, we did not find any relationship between maternal serum PLGF levels and gestational diabetes; however more studies with large patient populations are needed for definitive results.

**References**


Haemophilus parainfluenzae infective endocarditis associated with pelvic abscess: an uncommon complication of endometriosis

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Summary
The case of a woman with native mitral valve endocarditis due to Haemophilus parainfluenzae (HPI) associated with a pelvic abscess and endometriosis is reported. Although HPI is an infrequent pathogen involved in endocarditis, association to a gynecological infection has never been reported. Endometriosis could increase this risk.

Key words: Haemophilus parainfluenzae; Infective endocarditis; Endometriosis.

Introduction
Common predisposing factors for salpingitis and gynecologic abscess include sexual behaviour [1], increased age, diabetes and immunocompromised status due to HIV infection or renal transplantation. Endometriosis, which is found in 25-40% of women with infertility and in 2-5% of the general population [2], has been suspected to increase occurrence of gynecologic abscess [3]. Although Haemophilus influenzae (HI) is a common respiratory tract pathogen in humans but, rarely isolated from fallopian tubes, few reports have described HI salpingitis and tubo-ovarian abscesses [4-7] and only two Haemophilus parainfluenzae (HPI) genital infections have been reported [5, 6]. HI and HPI are also recognised as rare causative agents of pathogens implicated in bacterial infective endocarditis (IE) [8].

We report an unusual case of Haemophilus parainfluenzae endocarditis IE associated with a gynecologic abscess in a patient with endometriosis.

Case Report
A 33-year-old woman, gravida 0, para 0, suffering from severe endometriosis (Stage IV) and ovarian cysts was known to have a heart murmur, never explored. In March 2008, she presented suddenly with a flu-like syndrome and was prescribed ibuprofen and paracetamol. Laboratory investigations were normal. Four days later, the patient was still febrile (38.6°C) and complained of pelvic pain. Blood samples revealed a thrombopenia (28 g/l). White blood cell count was 23.0 g/l with a predominance of polymorphonuclear leukocytes and the C-reactive protein level was 437 mg/dl. At hospital admission, her temperature was 39.1°C, while her blood pressure and pulse rate were normal. A mitral insufficiency murmur was audible. No sign of heart failure, palpable spleen or peripheral cutaneous lesions were observed. Dental examination and radiography were normal. There was localised mild tenderness in the lower abdominal quadrant. Vaginal examination resulted in severe pain. Ultrasound exam revealed a right tubo-ovarian abscess (62 x 43 mm). Abdomino-pelvic computed tomography (CT) showed that the lesion was non homogeneous, with enhancement after contrast administration (56 x 45 mm) and was associated with a peripheral abscess in the Douglas pouch (63 x 54 mm). Sternal puncture confirmed the peripheral thrombopenia. Amoxicillin-clavulanate (1 g x 3 per day), ofloxacine (200 mg x 2 per day) and gentamycin (150 mg per day) were started after bacteriological samples (blood, urine and vaginal cultures). Twenty-four hours later, 3/3 blood cultures became positive with small gram-negative rods. Urinalysis was negative. Microbiological identification confirmed a multi sensible HPI. Transthoracic and transeosophageal echocardiography were performed and confirmed the diagnosis of endocarditis, with vegetation on the mitral valve and a mitral prolapse. Left ventricular function was normal, but mitral regurgitation was evaluated Stage III. Antibiotherapy was switched to amoxicillin (12 g per day) plus gentamycin. Antinuclear factors, rheumatoid factor, complement and antiphospholipid antibodies were negative. No immunosuppression or sexually transmitted diseases were diagnosed (B and C hepatitis, TPHA VDRL and HIV serologies were negative). Because of persistent abdominal pain, laparoscopy was done ten days after initiation of antibiotherapy. Examination of the pelvic cavity revealed the presence of moderate adhesions of the ileum, and a right abscess in the Douglas pouch. The ovaries were normal and an abscess had developed on an underlying pseudo-cyst of endometriosis. Drainage of the cavity was performed. Culture and 16S ribosomal RNA gene sequencing of perioperative sampling were negative, probably because of previous antibiotherapy. Biopsy was performed in the Douglas pouch and histological analysis showed typical lesions of endometriosis, with inflammatory reaction and altered polymorphonuclear leukocytes. After 24 hours, fever disappeared, abdominal pains and inflammatory syndrome decreased and further outcome was favourable. Control blood cultures were negative. After three weeks of amoxicillin, results of MIC allowed switching to ceftriaxone 2 g a day IM, for three weeks to simplify the treatment. Control of
Haemophilus parainfluenzae infective endocarditis associated with pelvic abscess: an uncommon complication of endometriosis

Discussion

This patient had an IE due to HPI (positive blood cultures and echocardiographic findings). Haemophilus spp are a rare responsible pathogen of IE (3%) [8]. Darras-Joly et al. reported 42 cases of Haemophilus spp endocarditis [9]: HPI was the main pathogen (26/42), like in Vasquez et al’s study. In this study, the mean age was 27 years, 60% of patients had no identifiable predisposing illness [10]. Although surgery is often necessary, HPI endocarditis has a favourable outcome prognosis [9].

In previous reports, origin of the micro-organism was unknown in 70-80% of cases and no case of gynaecologic infection was noted. In our case, a pelvic abscess was present. The lack of isolation of HPI from this site may be explained by the fact that samples were performed ten days after the onset of antibiotic therapy. The role of HPI in genital infections has been described. HI is a small gram-negative rod that commonly inhabits the upper respiratory tract. HI biotypes II and III are found to predominate among strains from the respiratory tract and biotypes II and IV among strains from the genital tract. HPI, biotype II, is most frequent in both sites [11]. It has rarely been isolated in tuboovarian abscesses, salpingitis, endometritis and other obstetrical infections. In Vasquez et al’s. study [6], Haemophilus spp was isolated from 2.8% of 5,572 genital specimens; of whom HPI was detected in 64.5% and HI in 29% of cases. Their pathogenic role is evoked when it is isolated as the single pathogen in infections as urethritis in men or Bartholin’s abscess in women [6]. To explain urogenital infection with HPI, few hypotheses have been suggested: role of orogenital sexual contact or colonization by a reservoir in the colon. Genital infections with bacteremia caused by Haemophilus spp have been described [7], suggesting a possible risk of endocarditis in case of underlying valve disease. In our case, the origin of infection was probably gynaecologic.

Since it is of outstanding to describe HPI endocarditis from genital infection, it is a hypothesis that endocarditis may have favoured this rare complication. Occurrence of tuboovarian abscess seems to increase in women with endometriosis [12], particularly in women with Stage III and IV, at the age between 20 and 29 and those older than 40 [3]. It has been suggested that endocarditis could be responsible for impairment of local immunity (particularly cystic wall and ovarian epithelium) and that the presence of old blood in an endometrioma may provide a culture medium for bacteria to grow slowly after transvaginal inoculation and facilitate the spread of infection. Thus, infected endometriosis could be a risk factor for endocarditis, like any other infected site (dental, digestive...), particularly in case of underlying heart disease. The most probable mechanism is a bacteremia but we can wonder if migration of cells (like catamenial pneumothorax) could be incriminated.

In conclusion, we report an unusual case of HPI infective endocarditis probably related to endometriosis with pelvic abscess. Evolution was favourable with adapted antibiotherapy and surgery treatment. The patient remained asymptomatic for 15 months. The present case report suggests that in women with Haemophilus spp endocarditis, it may be of interest to detect pelvic inflammatory disease or endometriosis if no origin of infection (particularly dental) is identified. Gynaecologic tract infection is probably an underestimated cause of endocarditis, particularly in young women. It highlights the importance of considering the potential role of endometriosis in these settings. Prospective larger cohorts of patients with endometriosis would be necessary to define incidence and types of infective complications. Practitioners should consider Haemophilus species as a potential pathogen in extra respiratory or oto-rhino-laryngologic infections.

References


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A rare case of congenital pulmonary lymphangiectasia, hydrothorax and ascites in a male embryo aborted at 20 weeks of gestation

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Summary
A case of a male embryo aborted at the 20th week of gestation with extensive ascites, hydrothorax, pulmonary lymphangiectasia and pulmonary hypoplasia is presented together with the pathological findings, the etiology, differential diagnosis, course and therapy of this pathologic entity. Also a short review of the literature is discussed.

Key words: Hydrothorax; Pleural effusion; Ascites; Lymphatics.

Introduction
Congenital pulmonary lymphangiectasia is a rare condition, characterized by extensively dilated pulmonary lymphatics in the bronchovascular connective tissue along the interlobular septa and in the pleura [1, 2]. This disease is usually fatal within a few hours or days of life. Its etiology is heterogenous [3-5]. It may present as part of syndromes such as Noonan, Turner or Down, but most cases are sporadic [5]. The incidence of congenital pulmonary lymphangiectasia is one in 10,000 gestations, with a 2:1 male/female ratio [1, 2].

Case Report
A 33-year-old primigravida visited our hospital at 20 weeks of an uneventful gestation for a routine check-up. The ultrasound of the second trimester revealed bilateral pleural effusion especially in the left thoracic cavity and ascites. The first semester check-up showed that the patient was CMV (+), toxoplasma (-), coxsackie (-), rubella (±) and Prader-Willi syndrome (-). No fetal defects were mentioned in the previous ultrasound.

The patient underwent a therapeutic abortion after giving an informed consent. The aborted embryo was male and weighed 381 g; its length from head-foot was 25.5 cm and from head-hips 15.5 cm. The foot sole length was 3.3 cm. The head, thoracic and abdominal circumference were 19 cm, 16.5 cm, and 16 cm, respectively.

On gross examination, extensive abdominal distension was observed. The face (ears, nose, mouth) was normal and the eyes were closed. The extremities were normal and the external genitalia were male. The thoracic and the peritoneal cavity were full of pellucid, serous fluid and the viscera were congestive, normal in position and size. The brain weighed 43 g. The brain ventricles were full of cerebrospinal fluid and the meninges were congestive. The thoracic cavity was dilated and full of serous fluid. The lungs showed extensive, hemorrhagic infiltration especially the left lung. The heart revealed an atrial septal defect and patent ductus arteriosus, whereas the aorta and the pulmonary artery were normal. The peritoneal cavity was also dilated and full of serous fluid. The viscera were congestive and fetal weight was within normal limits for the fetal age.

Microscopic examination of the lungs revealed many cystic spaces filled with fluid, lined by endothelium and distributed under the pleura, in the interlobar spaces and round vessels (Figures 1, 2). Hydrothorax, ascites and visceral congestion were also present.

The placenta was discoid measuring 10.5 x 10.5 x 3 cm and weighing 208 g with an eccentric outgrowth of the umbilical cord. The coloboma of the umbilical cord had three vessels. Its diameter was 1.2 cm and length 10.5 cm. Furthermore, focal, dispersive, white lesions measuring 0.2 cm were found in the placenta.

Microscopic examination showed:
- a) intensive vascular congestion and elevated vascularization of the chorionic villi;
- b) dilatation and congestion of the lung vessels;
- c) old and recent focal placenta infracts;
- d) lesions of placentitis;
- e) lesions of chorioamnionitis.

Discussion
Congenital pulmonary lymphangiectasia is a rather fatal disease. There are three forms of the disorder [3]:
- a) isolated congenital pulmonary lymphangiectasia (poor prognosis) [4];
- b) congenital pulmonary lymphangiectasia associated with pulmonary venous obstruction;
- c) congenital pulmonary lymphangiectasia associated with a generalized defect in lymphatic development.

Certain genes are implicated in such a pathology e.g., FOXC2 transcription factor on chromosome 16q24.3, VEGFR3 mutation in the endothelial growth factor receptor 3, and integrin alpha-9-beta-1 receptor for extra-cellular matrix protein [5].

The pleural effusion is usually chylos and occurs in the right pleural space (our case occurred in the left pleural space) [1]. In a retrospective study of eight
A rare case of congenital pulmonary lymphangiectasia, hydrothorax and ascites in a male embryo aborted at 20 weeks of gestation

aborted fetuses (7 males, 1 female), the fetuses weighed 463.4 g (range 177-681 g) [4]. Our case was a male embryo weighing 381 g. Six were aborted between 19 and 24 weeks of gestation for multiple malformations or anencephaly and two were spontaneously aborted [4]. Our case underwent a therapeutic abortion at 20 weeks of gestation. The main characteristics are the dilatation of subpleural and septal lymphatic space and the positive D2-40 immunostaining of lymphatic endothelium [1].

The differential diagnosis includes chromosomal, cardiac and infectious parameters. The diagnosis is confirmed by the postnatal lung biopsy. The prognosis depends on the severity of the symptoms. The infants usually die due to respiratory distress shortly after birth [6]. A subgroup of children with congenital pulmonary lymphangiectasia – if treated aggressively – may have a good prognosis for long-term survival [7]. Prenatal counseling should be proposed to the parents.

References


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Introduction

Radioactive iodine (131I) has been used effectively in the diagnosis and treatment of thyroid diseases. It is mostly used in differentiated thyroid cancer (DTC) [1, 2], where it has been proven to prevent relapses and treat metastases. DTC has a female predominance and more than 50% of cases occur in the reproductive years. It seems that certain reproductive and hormonal factors that occur during pregnancy and during the first years after giving birth may predispose to the development of the thyroid cancer. The prognosis for DTC is good [3, 4], and treatment with 131I prolongs life, even when distant metastases occur [5, 6]. Since radiation is delivered to the whole body, including the ovaries, it is a reasonable concern as to whether there is a possibility of mutagenic effect on germ cells. The relevance of the mutagenic effects of radiation as assessed by untoward pregnancy outcomes, such as miscarriages, congenital abnormalities and malignancies in offspring, remains to be clarified in humans. One extensive study of Japanese atomic bomb survivors and two large studies of patients who had been exposed to abdominal radiation during childhood and adolescence did not detect any statistically significant effects of radiation on pregnancy outcome [7-9]. Despite that, the relevance of the mutagenic effects of radiation on the fertility and well-being of the offspring is still debated and discussed in cases of high-dose 131I treatment for DTC because large and conclusive data have not yet arisen. Hence, further research in this field is urgently needed so that a significant body of data can be collected. It is interesting that a recent study reported increased risk of leukemia in offspring whose fathers were exposed to radiation preconceptionally [10].

The radiation dose delivered to the ovary is approximately 0.14 cGy after administration of 37 MBq (1 mCi) 131I in normal subjects [11]. Thyroid cancer patients receive diagnostic doses of I131 ranging from 1-5 mCi and therapeutic doses ranging from 30 to 150 mCi or more. In many cases functioning metastases are in close proximity to the ovary having as a consequence greater doses of radiation delivered to them. Furthermore, many patients during radiotherapy exhibit hypothyroidism due to insufficient thyroid hormone replacement therapy. This condition decreases renal iodine clearance, resulting in prolonged gonadal exposure [12].

Case Report

We report the case of a 33-year-old woman who complained of local pain in the glandular thyroid location. She also complained of weight loss during the previous few months. Ultrasound and scintigraphy examinations revealed a mass of 2.5 cm in the thyroid gland and fine needle aspiration (FNA) was suggested. The results of the FNA were suggestive of a differentiated papillary carcinoma. Thyroid hormone levels at that time were as follows: TSH: 2.1 mU/l, T4: 7.3 μg/dl, T3: 110 ng/dl, CEA: 3.5 ng/ml, calcitonin:18 pg/ml.

The patient underwent a chest and abdominal computed tomography (CT) scan and a body scintigram, but neither metastases nor nodules were found. Also, the capsule of the thyroid gland did not seem infiltrated. According to the TNM classification it was a T2N0M0 tumor. The woman underwent a total thyroidectomy and pathological examination confirmed FNA findings and preoperative classification, adding that it was a grade 3 papillary carcinoma.

The case was discussed in the oncologic council and it was concluded that thyroid hormone replacement therapy should be
prescribed and that surgery should be followed by percutaneous radiotherapy.

The woman underwent the radiotherapy three weeks after the surgery. The dose was 80 mCi (= 2960 MBq) of 131I. Afterwards thyroid hormone replacement therapy was started. TSH values were evaluated to confirm the expected TSH suppression, since TSH seems to reflect the growth of tumor cells of the thyroid. TSH values were lower than normal range.

Three months after surgery the following parameters were checked: lung parenchyma (chest X-ray), thyroid hormone levels, TRH test, erythrocyte count and TKE, and there were no indications of metastases. Six and 12 months after surgery this checkup was repeated without any remarkable findings.

One year after finishing her therapy the patient became pregnant. She had a normal and uncomplicated pregnancy and at the 38th week of gestation she delivered vaginally a healthy female neonate weighing 3100 g. The appgar score was 9 at the 1st and 10 at the 5th minute. During the pregnancy the woman did not undergo any radioactive examination. After delivery follow-up of the above-named parameters was continued every six months. The child at the age of five years is healthy with no signs of malignancy or other disease associated with radioactive therapy.

Discussion

The most important limitation in any study trying to clarify the effect of radiotherapy with 131I on pregnancy outcome is to eliminate all other cofactors that could influence mother or the infant. Age at conception, socioeconomic class, alcohol intake, and smoking, as well as adequacy and fluctuation of thyroid hormone replacement and radiation dose to the ovaries are biases difficult to overcome. The physical half-life of 131I is 8.04 days [13], and the median effective half-life is at least 14 hours [14], with substantial variations. Consequently, washout of 131I of the whole body takes place in a few days. Nevertheless, most guidelines recommend avoiding pregnancy for four [15] to six [16] or even 12 months after radioactive iodine (RAI) treatment or scanning [17, 18]. Despite instructions to patients unexpected pregnancies may occur. If radiotherapy followed conception with an interval of less than ten weeks it is essential to estimate the dose to the fetal thyroid and whole body and counsel the couple regarding their options. The tendency to adopt the recommendation for avoiding pregnancy up to one year after radiotherapy is based on two facts. The first one is that a greater miscarriage rate [18] and some untoward pregnancy outcomes such as birth defects [19], Edward’s syndrome [20], and aplastic anemia [20] have been described to occur in pregnancies conceived within the first post-RAI year. The second one is that during that annual interval complete remission of the disease can be confirmed and the thyroid hormonal status controlled [18]. Therapeutic abortion has been a quite common approach for accidental RAI administration in the first trimester of pregnancy [21]. Knowledge of the timing of fetal thyroid development and the potential effect on the fetal thyroid and whole body irradiation on a developing embryo can guide management. The fetal thyroid begins to develop and differentiate into follicles at ten weeks of gestation. Consequently, if maternal RAI is administered after the 10th week of gestation it is quite possible that fetal hypothyroidism will appear [22]. To avoid such inadvertent events, patients should be strongly counseled to avoid pregnancy before radiotherapy, while determining the date of the woman’s last menstrual period and contraception practice, and providing pregnancy testing within 48 hours before RAI administration are good procedural safeguards [23]. Since, DTC is considered a malignancy with a very good prognosis and slow growth rate, guidelines recommend delaying thyroid surgery and any RAI investigations until after delivery [15]. Some authors support the concept that hCG binds to the TSH receptor, stimulating the growth of benign and malignant thyroid tissue. Endogenous estrogen binding activity in neoplastic thyroid cells is described by some researchers. Diethylstilbestrol also was shown to have a relationship to thyroid neoplasia in C57BL/6 mice. Pregnancy termination or thyroidectomy during pregnancy is considered a rare approach, and mostly employed when diagnosis is made in the first trimester. The most commonly adopted approach is to keep the pregnancy, deferring thyroidectomy to either the second trimester or even until after delivery. The most important prognostic factors seem to be maternal age at the time of diagnosis. Tumor size, grading and other pathologic findings are of less importance. Thyroid cancer during pregnancy is reported to be associated with increased fetal loss, especially if more extensive surgery, including neck lymph node dissection is performed. Although most of the studies have failed to reveal any statistically significant effect of radiation such as 131I on fertility [24-26], ovarian [27] or testicular function [28], childhood cancers [29], congenital malformations [30], chromosomal abnormalities [31], or, some studies have demonstrated a greater frequency of chromosomal aberrations in the peripheral lymphocytes of patients treated with 131I [10, 32] or suggested an association between ionizing radiation of the father and an increased risk of congenital abnormalities [33] and leukemia [10]. Women previously irradiated for Wilms’ tumor or other cancers with abdominal doses of 20 to 30 Gy are reported to have an increased rate of miscarriages, but this increase was attributed mostly to somatic damage to the abdominopelvic organs [34]. Recently controversial reports have been published showing an apparent increase in the number of leukemias in young people, whose fathers worked at the Sellafield nuclear reprocessing plant in Northwest England and were occupationally exposed to radiation [10], raising new concerns about these effects at low doses. It is quite interesting that the most profound reproductive effect of the Chernobyl accident was a sharp increase in elective terminations of pregnancy in Europe, which most of the time was unjustified after negligible exposure [32]. Therefore, the importance of clarifying the effect of 131I on pregnancy outcome is important not only for the management of patients with DTC, but also for assessment of the impact of ionizing radiation on human health in general.
Conclusion

Although the number of children born to mothers exposed to radioiodine is relatively small, there is no reason for patients exposed to radioiodine to avoid pregnancy. Radioiodine treatment of differentiated thyroid cancer does not affect female fertility nor is it associated with any genetic risk to the offspring. A washout period of one year is a reasonable approach. During pregnancy, thyroid function needs to be closely monitored and given these precautions RAI is a safe treatment method in young women.

As reported in our case a normal uncomplicated pregnancy can follow an operative and complementary treatment of thyroid cancer. Non differentiated thyroid carcinomas, as in our report, can be treated by total thyroidectomy followed by percutaneous radiotherapy, and the dose of thyroid hormone replacement therapy has to be very high in order to develop TSH suppression, since TSH seems to have a growth effect on the thyroid tumor cells. Our report is in accordance with the recent medical literature, stating that a one-year interval between radiotherapy with 131I for DTC and pregnancy is a safe option.

References


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Sequential methotrexate treatment with and estrogen and progestin in a retained adhesive placenta

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Introduction
The incidence of placental adhesive disorders has drastically increased in recent years, due to the increasing cesarean rates in most countries [1]. Though hysterectomy is the definite and recommended treatment, conservative management may be considered in patients desiring future pregnancy [2, 3]. We present a successful case of conservative treatment with methotrexate and estrogen-progestin.

Case Report
A 33-year-old woman, gravida 1, para 1, at 38 weeks and one day of pregnancy had a cesarean delivery due to previous history of myomectomy. On ultrasound placental retention was noted thus curettage was attempted two weeks postpartum but it induced moderate fresh bleeding. A contrast-enhanced computed tomography scan depicted the multiple vessels within the intrauterine mass and the absence of deep myometrial invasion. The patient received four doses of 50 mg of methotrexate intramuscularly every other day, alternating with four doses of 15 mg of folic acid. An attempt to evacuate the necrotic tissue along with withdrawal bleeding was successful after three courses of sequential conjugated estrogen (0.25 mg)-progestin (5 mg) therapy. Subsequent ultrasonographic examination documented an empty uterine cavity.

Discussion
Methotrexate affects placental tissue by decreasing vascularity leading to necrosis [1]. The sensitivity of chorionic tissue to methotrexate is well documented by its use in gestational trophoblastic neoplasia, abnormal pregnancy, and medical termination of pregnancy [1]. There are some reports of successful use of methotrexate in cases of placenta accreta or placenta increta [2, 3]. This report adds another and justifies its use in selected cases. The patient in this report received estrogen and progestin derivatives to effectively protect the endometrium, induce regular withdrawal bleeding and hasten expelling retained necrotic placenta. Combined sequential estrogen replacement regimens with progestin given very rarely fail to protect the endometrium, rather than surgical curettage [4]. The use of estrogen and progestogen and of methotrexate in combination may be simple and potentially effective for placenta accreta and placenta increta. Though experience in the management of placental adhesive disorders with this protocol is limited and should be strictly supervised, it should be taken into consideration if the patient desires future fertility.
References


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Figure 1. — Retained adhesive placenta. a; sagittal T2-weighted MRI showing a placental mass embedded in the uterine posterior wall with minimum myometrial involvement (arrow), in accord with placenta accreta. b; horizontal contrast-enhanced CT showing the highlighted area of increased vascularity that does not cross the uterine wall (arrow).
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