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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/EXCEPTRA MEDICA.

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In vitro fertilization is expensive: when should a couple be advised to stop trying with their own gametes and seek other options? Review of three cases

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Summary

Purpose: To describe refractory infertility cases that preserved many failed in vitro fertilization (IVF) cycles to achieve the goal of delivering a baby. Methods: Case reports with a description of the various approaches and change in strategy that finally led to success. Results: Factors causing repeated failures in these cases included adverse effects of the controlled ovarian hyperstimulation regimen on the uterine environment, failure to realize that the sperm from a male with a low hypo-osmotic swelling test cannot cause embryo implantation failure unless intracytoplasmic sperm injection is performed, and the discovery that sperm abnormalities rather than exclusively oocyte problems can lead to embryo fragmentation. Conclusions: It is imperative that infertility specialists individualize cases – especially ones that have failed several cycles – and stop using the same process that has repeatedly failed. They should stop and think if there are some less common but important factors they may have overlooked. Merely recommending donor oocytes without exploring other options is inappropriate.

Key words: Refractory infertility; In vitro fertilization; Hypo-osmotic swelling test; Controlled ovarian hyperstimulation; Embryo fragmentation.

Introduction

In vitro fertilization (IVF) is expensive and frequently is not covered by insurance carriers. Even when it is covered there is usually some limit to the number of cycles that are paid for or a certain limit to the amount of money that is given.

There are some patients who are willing to spend huge amounts of money and time to achieve a pregnancy with their own gametes even when the likelihood of success with donor eggs, donor embryos, or even in some instances donor sperm, would be potentially far greater.

We present several cases of couples who persevered many failed cycles to achieve their goal or who were willing to spend money for IVF even though they were advised that the chance of conception with their own gametes was very slight.

Case 1

A 38-year-old woman presented with a 10-year history of infertility [1]. She advised us of her past medical history which was as follows: She had a history of oligomenorrhea and was considered anovulatory with a diagnosis of polycystic ovarian syndrome. She had tubal patency established by hysterosalpingogram and laparoscopy. No endometriosis or adhesions were noted. The semen analysis was normal as were postcoital tests. She failed to conceive despite six years of ovulation induction with clomiphene citrate in a minority of cycles and gonadotropins in the majority of cycles. Egg release was confirmed by sonography in many cycles and the luteal phase was supplemented with extra progesterone taken vaginally. Endometrial biopsies while taking follicle maturing drugs and progesterone supplementation were considered in-phase. Many intrauterine insensations were performed over the 6-year treatment period but she did not conceive.

At this time the couple decided it was time to try IVF. They flew from the Middle East to the United States to one of the world’s leading IVF centers. Unfortunately the woman failed to conceive following two cycles of controlled ovarian hyperstimulation (COH), egg retrieval and fresh embryo transfer. She similarly failed to conceive following two fresh embryo transfers at a world renown IVF center in England. She returned to her middle eastern country where she had IVF-ET performed by a successful IVF center that was willing to grant her request of transferring 12 embryos at a time. Unfortunately she still failed to conceive following six more IVF cycles with 12 fresh embryos transferred each time. Thus she failed to conceive despite 92 fresh embryos being transferred over ten IVF-ET cycles.
Though donor eggs had been suggested, this was not possible for religious reasons. Thus she presented at our IVF center hoping for a different approach. As mentioned she had ten years of primary infertility when she consulted with me. I advised her that sometimes the drugs used for controlled ovarian hyperstimulation (COH) may create an adverse environment that can prevent embryos from implanting [2, 3]. Based on the detection of a protein called progesterone-induced blocking factor (which requires trophoblast invasion for expression) at an earlier time in the luteal phase than normal which has been associated with a very low pregnancy rates, we considered that COH may allow, in some instances, premature trophoblast invasion [4, 5].

Thus our suggestion was to do IVF-ET again but to freeze all embryos at the 2 pronuclear stage and then in a subsequent cycle transfer frozen-thawed embryos. Out of 38 metaphase II oocytes 28 fertilized using conventional insemination and 27 were frozen at the 2 pronuclear stage.

One month was skipped. She was then started on a graduated regimen of oral estradiol followed by progesterone supplementation. Eight embryos were thawed and the best five were transferred (two 7-cell and one 6-cell with ≤ 25% fragmentation and a 5-cell and 2-cell embryo were also transferred). She conceived and successfully delivered a viable full term child [1].

Comment

IVF is expensive and thus many would argue that this woman should have been told to quit. She had had 92 embryos transferred over ten IVF cycles! If she had had three embryos transferred each time, she would have had the equivalent of 31 failed IVF cycles! This couple represents a prime example of people who should be counseled as to when enough is enough and even if donor eggs are not allowed from a religious standpoint, adoption or maybe a donor embryo should be considered.

Nevertheless, the couple’s point of view was that doctors are not infallible and maybe another doctor could have a different idea that might lead to success. Indeed, my group has found that the COH regimen itself may cause implantation problems [2-4]. It was surprising that with all the embryos she had made in the past that no one had ever performed frozen embryo transfer. Thus we purposely froze all embryos.

It could be argued that one successful case might have just been fortuitous and that there is no proof that the COH regimen actually caused the problem. The patient was advised that because of the great distance from the Middle East to the United States, that instead of coming here for another frozen embryo transfer right away, when she was ready for a second child, she should ask the doctors to prescribe metformin to see if she could actually be made to ovulate spontaneously. She was also advised that sometimes following a pregnancy women with polycystic ovarian syndrome may spontaneously ovulate for a while. In either case, she was advised to use progesterone supplementation in the luteal phase [5, 6].

She reconsulted us at age 40 to have another frozen embryo transfer. Though she did not take metformin she admitted to having had nine regular menstrual cycles since her delivery but without a pregnancy. However, she forgot to request progesterone support in the luteal phase.

Her consult was calculated to be about three days after ovulation so too late to thaw the embryos and do a frozen embryo transfer since they had been frozen at the 2 pronuclear stage and thus synchronization on a natural cycle could not be achieved. Since she had had intercourse at mid-cycle, she was prescribed 200 mg progesterone vaginal suppositories. She conceived in this natural cycle without embryo transfer and again delivered a full-term healthy baby [7].

This second pregnancy in this same woman provides additional support for the concept that in some women the drugs used to stimulate multiple follicles can have an adverse effect on subsequent implantation [8].

The suggestion had been made to her previously by other physicians to use either donor eggs or a gestational carrier. Since her problem was the COH regimen, both of these options would have worked but would not have provided the ideal objective that she wanted. Furthermore, the expense for a gestational carrier, which would have been the only option based on her religious beliefs, would have been markedly more expensive.

It is not clear why despite all the embryos that were formed from three different IVF centers that no one provided the option of frozen embryo transfer but kept attempting fresh embryo transfer on stimulated cycles.

Case 2

A 34-year-old woman with three years of unexplained infertility and failure to conceive despite eight cycles of COH and intrauterine insemination had failed to conceive following seven cycles of IVF-ET with fresh embryo transfers each time, and in addition four frozen embryo transfers.

She came to us for a second opinion already in the midst of COH for IVF cycle number eight. Her plan was to continue with the IVF center that had performed all of her previous embryo transfers but she would change to our facility for number 9 if she was not successful.

The semen analysis according to the previous IVF center was normal and therefore all oocytes were fertilized by conventional insemination. I suggested that the husband repeat the semen analysis and perform a test not previously performed, i.e., the hypooosmotic swelling (HOS) test.

Though the couple had been advised that the sperm was perfectly normal, especially since they fertilized a high percentage of the oocytes which led to embryos with normal morphology for transfer, I explained that a low HOS test detects an interesting abnormality. In this circumstance, there is normal fertilization but extremely low implantation rates [9, 10].

Though a repeat of standard semen parameters including antisperm antibodies was indeed normal, the HOS test was clearly subnormal with only 42% of sperm showing tail swelling. I advised the couple that this abnormality might be related to the transfer of a toxic factor from the sperm to the zona pellucida by the supernumerary sperm that attach, and that the zona pellucida is incorporated in the embryo membrane [11]. HOS defects are associated with a functional defect in the sperm membrane and the hypothesis is that the toxic factor thus causes a functional defect in the embryo membrane which interferes with its attachment to the endometrium [11].
In vitro fertilization is expensive: when should a couple be advised to stop trying with their own gametes and seek other options?

Therefore, it was suggested that she continue with the IVF center that had performed the previous seven IVF cycles since they started the present COH regimen, but to just advise them to do intracytoplasmic sperm injection (ICSI) since this bypasses exposure of the zona pellucida to the toxic factor. Intracytoplasmic sperm injection seems to fully correct an embryo implantation defect related to the HOS defect [12].

The reproductive endocrinologist initially refused to perform ICSI stating that his beliefs were that the HOS test is a meaningless test. The patient sought my advice and I told her that we would be willing to do her egg retrieval and inseminate the oocytes by the ICSI process. However, I suggested that the couple give the other IVF center one more chance and to inform them that unless they performed ICSI that the IVF would be performed at our center. Reluctantly, the other IVF center agreed to perform ICSI. The woman conceived in that eighth IVF cycle and had a full-term delivery.

Comment

In vitro fertilization is expensive but a donor egg is even more money. Nonetheless even that expense does not compare to the cost of a gestational carrier. The usual assumption by most reproductive centers is that failure to conceive despite transferring normal embryos is either an oocyte problem or a uterine problem.

The mind set of most IVF centers is that the job of the sperm is to fertilize the egg so if normal embryos are formed then the problem is not related to a sperm defect. This is not true as evidenced by implantation defects caused by conventional fertilization with sperm with low HOS test scores as illustrated by this case.

Certainly it is the responsibility of the IVF center to explore possible remediable factors that could explain persistent failure to conceive despite transferring normal embryos. Manuscripts in major reproductive journals have appeared for over 20 years and are still being published about the implantation problems associated with the HOS sperm defect. To be fair to the couple, the aforementioned IVF center should have performed due diligence to determine if they could be missing some key factor to explain the patient’s repeated failures.

However, when given the opinion from another IVF center that this could be the reason for the problem, the reproductive endocrinologist did not call me to inquire about the source of my knowledge or the basis of my opinion, or to review recent literature but merely expressed his opinion that he did not believe in the test. He has never published any data refuting the importance of this test. It was not that he was trying something new for cycle 8 but was merely planning to proceed in the same manner that had failed seven times before!

In the last three years, since the eighth IVF cycle for this patient, I have had the occasion to evaluate several patients who have been to the IVF center that performed the eight IVF cycles on this patient, and to this date, the semen analysis that they perform does not include this simple inexpensive HOS test. In fact most IVF centers, for reasons not clear to me, do not perform this test.

Case 3

A 35-year-old woman with four years of primary infertility presented for IVF and ICSI. The reason for the desire for IVF with ICSI was because of a male factor problem related to antisperm antibodies (82% IgG and 77% IgA) using the direct immunobead assay and a low HOS test (47%). Typically IVF with ICSI corrects both defects and allows normal pregnancy rates following embryo transfer [12-14]. However this woman kept making highly fragmented embryos and failed to conceive following 12 IVF-ET cycles at our institution and following four at two other IVF centers [15].

Antisperm antibodies typically impair fertility by preventing the sperm from progressing in the cervical mucus and by inhibiting attachment of the sperm to the zona pellucida [16]. A subnormal HOS score leads to implantation defects [9, 10]. There are no data showing that these defects lead to embryo fragmentation.

Though highly fragmented embryos do not necessarily lead to implantation failure, we considered that this could be the cause of her refractory infertility despite IVF-ET [17, 18]. We tried various nuances to see if we could achieve a pregnancy in this couple and fresh embryo transfer, and lymphocyte immunotherapy [7, 19-21].

We advised the couple that in their case the most likely cause of the refractory infertility was related to the embryo fragmentation problem. Theoretically the problem could be related to an oocyte or sperm factor or both. At our institution we have for many years used oocytes from infertile donors as the source of oocytes from recipients [22]. In fact, we have demonstrated that these eggs are just as likely to form embryos that lead to successful pregnancies in recipients as eggs from paid donors [23].

To help determine if the problem was a sperm or oocyte issue we asked the woman if she would be willing to be a shared oocyte donor. Most of the time recipients will choose a donor who has a tubal factor or definite male factor but it was unlikely that anyone would select this woman because of so many failures to conceive despite the transfer of many embryos plus the fragmentation issue (all these details would be made available to the potential recipients). For research purposes we offered free IVF to any recipient who would select this patient’s eggs.

This infertile donor who had failed to conceive despite 16 previous fresh embryo transfers and many frozen embryo transfers had 49 oocytes retrieved following COH [15]. The donor fertilized 17 of the 24 oocytes and all 17 were cryopreserved at the 2 pronuclear stage because of fear of developing ovarian hyperstimulation syndrome [24]. There were 13 of these 17 embryos transferred over three frozen ET cycles (4 were discarded for cleavage arrest). All 17 embryos had > 25% fragmentation and none of the transfers resulted in a pregnancy.

The recipient received 25 oocytes which were fertilized using conventional insemination and 13 fertilized. Three embryos were transferred on the donor retrieval cycle with ≤ 25% fragmentation but she did not conceive. Subsequently five frozen embryos were thawed and three were transferred and two discarded because of cleavage arrest. She conceived triplets and all three were successfully delivered at 35 weeks. Two of three embryos transferred had ≤ 25% fragmentation.

Because of having triplets, the couple decided when they were one year old to donate the remaining eight embryos to our donor embryo pool [25]. The new donor embryo recipient thawed all eight embryos and only one had > 25% fragmentation (but < 50%). Three embryos were transferred, two were discarded for failure to cleave, and three were refrozen. She failed to conceive on that
cycle but subsequently transferred the three remaining embryos and all three implanted. There was enlargement of the yolk sac on one of the three gestations which was suspicious for a chromosome abnormality. Chorionic villus sampling of the gestation was performed and chromosome analysis revealed trisomy 21. Multifetal selective reduction was subsequently performed and she delivered viable twins at 37 weeks.

These data have clearly shown that at least in this case the problem of embryo fragmentation was related to a male factor problem. Furthermore, at least in this case, the fragmentation was associated with implantation failure [15].

Though the option of changing gametes was presented to this couple many times after they had had several failures, the success of the recipients with different sperm convinced them to try donor sperm. They failed to conceive after two cycles of intrauterine insemination with donor sperm so they proceeded to IVF with donor sperm.

Though they proceeded with IVF with donor sperm they chose to freeze all embryos to allow them to try another retrieval IVF cycle with the husband’s sperm. However the mature eggs failed to fertilize so they decided to thaw some of the embryos created by donor sperm which were frozen at the 2 pronuclear stage. They transferred four embryos – two 8-cell embryos with < 25% fragmentation, a 6-cell embryo with < 25% fragmentation, and a 7-cell with 25-50% fragmentation. The patient conceived and subsequently delivered a full-term healthy baby.

Discussion

A 45-year-old infertile woman with a high day 3 serum FSH level sought infertility help. She was told that her prognosis was extremely poor and that she should consider donor oocytes. However, donor gametes were not an option due to personal reasons. She and her husband were diagnosed with a luteal phase defect and mild male factor problem, and treated with intrauterine insemination and progesterone supplementation in the luteal phase. The patient conceived at age 46 on her 14th treatment cycle and had a successful delivery [26].

In the aforementioned patient her insurance covered all the IUI cycles and she did not have to undergo any risky, invasive or painful procedures. Thus she had nothing to lose by continuing treatment. However, IVF requires daily injections, risk of ovarian hyperstimulation, very frequent monitoring and great expense.

Neverthelesss, with perseverance all the couples achieved successful pregnancies with IVF-ET. Lessons to be learned by couples from these anecdotes, are to be patient up to a certain number of cycles because “bad luck” can only explain a few failed cycles. If the treating physician has no new plan, the couple should challenge the treating physician to consider possible reasons for failure and treatment options. If patients covet their own gametes they should not allow the “quick fix” suggestion that maybe the eggs are not good and thus they should consider donor eggs or adoption. Indeed, in case 1, where the drugs used for COH caused the problem, the use of donor eggs would have worked because of the lack of use of COH drugs, but success could be achieved with the preferred “self” gamete by merely doing frozen embryo transfer. The patient’s decision to try other IVF centers if a couple of cycles in a given center were not successful, hoping that the new center might approach the problems with new insight leading to success makes sense. However, she should have considered getting an opinion from another IVF center before going through so many failed cycles in the third IVF cycle with so many embryos transferred. Case 2 showed a loyalty to one given IVF center that defies logic.

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From the physicians’ standpoint, these anecdotal cases illustrate the importance of avoiding complacency. With the risk and great expense of the procedure, it behooves the treating physician to spend some time in considering reasons for the failures and not merely try the same thing that failed over and over. For case 1, one cannot fault the first two IVF centers since chance alone could explain even three failed embryo transfers. Though I still think that the second IVF center should have considered trying something different before proceeding with cycle 4, e.g., frozen embryo transfer. Nevertheless, why they never tried the less invasive and far less expensive frozen embryo transfer defies logic. However one must seriously question why the third IVF center did not do anything differently not only for cycle 5, but was willing to proceed with no logical change in the procedure for five additional IVF cycles. Not only did she fail cycle number 5 but she failed with the transfer of 12 embryos. Yet they continued to transfer 12 embryos for five additional IVF cycles without making any changes!

In my opinion in one circumstance, e.g., case 1, the third treating physician should have insisted that the couple get another opinion from another IVF center to get a fresh view and he should have guided them to a facility that specialized in finding and correcting reasons for repeated failures. The referring center could offer their help in considering the proposed new solution to advise the couple as to whether it would seem reasonable and whether the referring IVF center could carry out the suggested change or would the couple be more advised to continue with the new center. The reluctance of the physician in case 2 to proceed with ICSI with the low HOS test is an example of the arrogance of some physicians and the need for patients to get second opinions earlier.

The couple in case 3 was very happy that they had a baby with donor sperm. However they were not ready psychologically to use other gametes until they were completely convinced that this was the only way. Nonetheless case 3 illustrates that it “takes two to tango” and one cannot always assume that if embryos do not implant the problem must reside with the woman’s ovaries or uterus. The couple was constantly advised of the low likelihood of success with their own gametes and/or uterus after many failures and the gametes were more suspect because of fragmented embryos. Nevertheless, I tried various new approaches, and when the couple tried another IVF center, it was following my suggestion. Nevertheless, when they failed, I was very willing to take them back.

I believe that the chance to help a given couple with their dream supersedes the business objectives of some IVF centers. With published statistics on pregnancy rates by the Center for Disease Control, some IVF centers would
In vitro fertilization is expensive: when should a couple be advised to stop trying with their own gametes and seek other options?

stop offering more IVF attempts not necessarily for the benefit of the couple, but rather not to sacrifice their published pregnancy rates which could detract from future business from other couples who may seek an IVF center with a high success rate.

Case 3 also illustrates the importance of the treating physician to do due diligence and not guess at whether to use donor eggs or a gestation carrier for repeated failures but to consider some method to determine the real source of the problem. The expense this couple had trying with their own gametes was considerable but it would have been "adding insult to injury" if they wasted even more money on very expensive donor oocyte cycles before finally proceeding to donor sperm.

References


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Ovulation induction and pregnancy in a woman with premature menopause following gonadotropin suppression with the gonadotropin releasing hormone antagonist, cetrorelix - a case report

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Summary

Objective: To determine if ovulation and pregnancy could be achieved in a case of amenorrhea, estrogen deficiency, and markedly elevated serum follicle stimulating hormone (FSH) through reduction of the serum FSH by a gonadotropin releasing hormone antagonist. Methods: A 37-year-old woman with hypergonadotropic secondary amenorrhea related to two courses of chemotherapy with alkylating agents and abdominal radiation therapy (Hodgkin’s disease and breast cancer) was treated with cetrorelix in an attempt to induce ovulation by lowering elevated serum FSH and hopefully restore sensitivity of the few remaining follicles by restoring down-regulated FSH receptors. She was monitored with serum estradiol (E2), FSH, luteinizing hormone (LH), progesterone (P) levels and sonography. Results: As the serum FSH dropped the serum E2 rose and peaked at 200 pg/ml after ten days of cetrotide. She conceived in that cycle. A viable ongoing pregnancy with appropriate ultrasound findings was demonstrated 40 days from conception. Conclusion: This is the first case description of successful ovulation and pregnancy following induction of ovulation with the GnRH antagonist cetrorelix. The possibility exists that the ovulation was spontaneous but it seems unlikely. It has been estimated that the chance of spontaneous ovulation and pregnancy in cases of premature ovarian failure is 1:9,200.

Key words: Premature menopause; Gonadotropin releasing; Hormone antagonist; Pregnancy; Ovulation induction.

Introduction

Spontaneous ovulation and conception in women with premature menopause without any treatment is extremely rare [1]. In fact one case was described of a 33-year-old woman with hypergonadotropic amenorrhea and gonadotropin resistance who spontaneously ovulated and successfully delivered despite a serum follicle stimulating hormone (FSH) level of 124 mIU/ml and a previous laparoscopy demonstrating bilateral streaked gonads [2]. Despite the fact that spontaneous ovulation has occurred, most reported pregnancies that have not been intentional have been while the woman was taking replacement estrogen or even oral contraceptives [2-5].

Ovulation induction and pregnancies have been achieved in hypergonadotropic amenorrhea in a more controlled manner by the use of ethinyl estradiol (20-50 μg daily) with or without a small boost of gonadotropins [6]. This regimen was not random but was purposely used to lower the elevated serum FSH in an attempt to restore down-regulated FSH receptors in the few remaining follicles. The theory is that there are still viable follicles present, albeit a paucity of them, that are resistant to both endogenous and exogenous gonadotropins [7, 8]. Lowering the high serum FSH with a pharmacologic dosage of estrogen works more efficiently than mere replacement dosages of estrogen. Moreover by using ethinyl estradiol follicular recruitment can be determined by observing the serum estradiol (E2) levels because ethinyl estradiol is not measured by the ELISA assay or radioimmunoassay for serum E2 [7].

Aiman and Smentek estimated that the likelihood of spontaneous ovulation with or without estrogen replacement therapy was 1:9,200 [9]. In 91 women with ovarian failure there were 61 ovulations in 311 cycles using this technique (29% ovulation rate) with 19 of 91 (20%) achieving pregnancies [6]. This was far higher than the expected rate of 1:9,200.

Though the theoretical reason for using ethinyl estradiol was to lower the elevated FSH levels and hopefully restore receptors, the possibility exists that the estrogen works in some other way, e.g., a direct effect on the follicle. However a 43-year-old woman with amenorrhea and estrogen deficiency with a serum FSH of 45 mIU/ml tried to achieve a pregnancy with the ethinyl estradiol method [10]. She actually ovulated 12 of the 18 times that she used this technique; however she became refractory to the therapy and failed to ovulate in her last three trials. She was put on leuprolide acetate, a gonadotropin-releasing hormone agonist, and she ovulated on the tenth...
day of treatment without any gonadotropins [10]. She did not conceive this cycle or in the two other cycles (out of 5) where she ovulated with leuprolide alone, nor in three additional cycles with leuprolide acetate and human menopausal gonadotropins. However she was 45 years old when she started the leuprolide treatment.

In the summary of 100 consecutive cases of attempted ovulation induction in women in menopause, 91 used ethinyl estradiol but there were nine using leuprolide acetate for various reasons, mostly because of side-effects from the estrogen or trying something different in women failing to ovulate with ethinyl estradiol. There were seven ovulations in 43 cycles (16.3) in three of nine women so treated. However, there were no pregnancies [6].

Theoretically, if the theory of reducing the elevated serum FSH to restore receptors is valid, then lowering the FSH with a GnRH antagonist may also accomplish ovulation. The following case is not only the first case described of ovulation induction in a woman with premature menopause using a GnRH agonist but it is also the first ongoing pregnancy completing the first trimester.

Case Report

A 37-year-old woman presented with secondary infertility. She conceived at age 30 and successfully delivered a full term baby by cesarean section. At age 19 she was diagnosed with Hodgkin’s disease. She was treated with radiation therapy using the mantle technique and inverted y without an oophoropexy. She was also treated with chemotherapy (MOPP).

At age 35 she had been diagnosed with breast cancer and had a right mastectomy. In addition she received chemotherapy including alkylating agents, e.g., cyclophosphamide.

Her menstrual periods had ceased following the diagnosis of breast cancer at age 35. She was told after subsequent testing of her serum follicle stimulating hormone (FSH) and estradiol (E2) that she was in premature ovarian failure related to her history of radiation therapy and chemotherapy.

In her treatment cycle her baseline serum E2 was < 7 pg/ml, luteinizing hormone (LH) 16.3 mIU/ml and FSH 50.0 mIU/ml. Four days later those same values were E2 < 7 pg/ml, LH 20.5 mIU/ml and FSH 55.8. Another three days later the serum E2 was < 7 pg/ml, LH 25.3 mIU/ml and FSH 67.2 mIU/ml.

The woman was aware of our studies of inducing ovulation with successful pregnancies in women with ovarian failure using ethinyl estradiol to decrease the elevated FSH and theoretically restore down-regulated FSH receptors. However, because of the history of breast cancer she was reluctant to take a pharmacologic dosage of estrogen, especially since she could be given this treatment for many months.

She was advised that we had also induced ovulation by lowering serum FSH with leuprolide acetate but had not had any successful pregnancies. She was told that we could possibly accomplish the same feat even quicker using a gonadotropin releasing hormone (GnRH) antagonist but this had never been tried before. Since there had been no pregnancies recorded with the GnRH agonists she elected to try the GnRH antagonist.

The woman began 250 μg of cetrorelix subcutaneously daily. Three days later the serum E2 was 8 pg/ml and the serum FSH was 31.1 mIU/ml. After eight days the serum E2 rose to 11 pg/ml and the serum FSH was reduced to 28.6 mIU/ml. After 11 days of therapy the serum E2 rose to 53 pg/ml and the serum FSH decreased to 21.9. On day 13 of therapy the E2 rose to 111 pg/ml and the serum FSH decreased to 13.5 mIU/ml. The next day the serum E2 climbed to 163 pg/ml, the LH 9.1 mIU/ml and the serum FSH 12.6 mIU/ml. An ultrasound showed a follicle with an average diameter of 13 mm on the left ovary on that day; the next day (treatment day 11) the serum E2 rose to 290 pg/ml, the serum P 0.2 ng/ml, LH 14.8 mIU/ml and the FSH 16.0 mIU/ml, the follicle was 15 mm in average diameter. On treatment day 17 the serum E2 dropped to 161, the serum P rose to 0.8 ng/ml, the LH surged to 52 mIU/ml and the serum FSH increased to 44.2 mIU/ml. The endometrial thickness at this time was 10 mm and the echo pattern was triple line using vaginal sonography.

Three days following the day of marked LH surge with decreasing serum E2, an ultrasound revealed collapse and luteinization of the follicle. The woman was started on progesterone vaginal suppositories 200 mg twice daily.

She conceived on that cycle and her first serum beta human chorionic gonadotropin (bCG) level was 58 mIU/ml. The serum P was 18.4 ng/ml and the serum E2 was 78 pg/ml. The serum beta hCG levels appropriately doubled every two days and the ultrasound 40 days from conception showed a viable single gestation with appropriate-for-date, crown rump length and sac size and normal heart rate. There was no subchorionic hematoma noted and the decidual reaction was appropriate. The yolk sac was not enlarged. Unfortunately she had an early second trimester miscarriage.

Discussion

Since the publication in 1990 of the 100 cases of attempted induction ovulation in women in ovarian failure with either ethinyl estradiol (n = 91) or leuprolide acetate (n = 9), there have been several anecdotal reports involving extreme cases and pregnancies in women with hypergonadotropic amenorrhea and estrogen deficiency using ethinyl estradiol but none with leuprolide acetate or other GnRH agonists. These included a 25-year-old woman with a serum FSH of 164 mIU/ml [11], a 45-year-old with a serum FSH of 43 mIU/ml [12], a 42-year-old woman with tubal factor who required in vitro fertilization-embryo transfer (IVF-ET) with a maximum serum FSH of 37.5 mIU/ml whose only follicular drug was ethinyl estradiol [13], and a 40-year-old woman who conceived and delivered a full-term baby following exclusive estrogen therapy who had a serum FSH of 123 mIU/ml (she claims that in another state it had been as high as 180 mIU/ml) but most amazingly she had failed to conceive in another IVF center despite four previous embryo transfers using donor oocytes (12 embryos transferred total) [14].

Thus this is the first case of proven ovulation induction and pregnancy achieved by lowering elevated serum FSH levels without the use of ethinyl estradiol. This case thus supports the concept that follicles remain in the ovaries of women in apparent ovarian failure. However they are resistant to both endogenous and exogenous gonadotropins. However, by lowering the elevated serum FSH down-regulated FSH receptors will be restored, thus improving sensitivity to FSH. Successful pregnancies indicate that at least some of these follicles contain normal eggs.

This case also demonstrates that it is not necessary to reduce the serum FSH to the normal range to improve
sensitivity of the follicle to FSH. Thus one should watch carefully for a rise in serum E2 generated by endogenous FSH rather than giving a longer course of GnRH antagonists, wait for the FSH to be suppressed, then add exogenous gonadotropins.

Since no pregnancies have been recorded following ovulation induction with GnRH agonists despite ovulation induction, GnRH antagonists should probably be the treatment of choice for women with premature ovarian failure who want to achieve a pregnancy with their own egg but where estrogen is contraindicated.

References

Pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women of more advanced reproductive age with elevated serum follicle stimulating hormone (FSH) levels

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5Division of Reproductive Endocrinology & Infertility, Camden NJ (USA)

Summary

Purpose: To present data on the chances of pregnancy following in vitro fertilization embryo transfer, according to day 3 serum FSH and age groups in women aged 36. Materials and Methods: Data were analyzed according to three age groups (36-39, 40-42, ≥ 43) and five serum FSH ranges (< 10, 11-12, 13-14, 15-16, ≥ 17). Results: No live pregnancies were found in women aged ≥ 40 with serum FSH ≥ 15 mIU/ml but they were seen in women aged 36-39. Live deliveries were seen in women even ≥ 43 with serum FSH 13-14 mIU/ml. Conclusions: The higher the serum FSH and the greater the age, the lower the chances of successful conception. However, reasonable pregnancy rates are found in women aged ≥ 36 with serum FSH ≥ 15 mIU/ml and a live delivered pregnancy rate of about 10% can occur even in women aged ≥ 43 with mild FSH elevations [11-14].

Key words: Advanced reproductive age; Diminished egg reserve; In vitro fertilization; Serum FSH.

Introduction

The prognosis for achieving a successful pregnancy following IVF-ET is related to certain variables. Lower chances of conception and higher rates of miscarriage are found with advanced age.

Elevated day 3 FSH is also a negative factor both in the quantity of eggs retrieved, and it is also considered to be associated with poor quality eggs. There are even some reports that state that live pregnancies following IVF-ET are not possible if the day 3 serum FSH is increased [1-3].

The present study evaluated the effect of day 3 FSH and age in women aged 36 undergoing IVF-ET. More specifically, the study was aimed to determine the effect of the degree of age advancement and degree of increased serum FSH on pregnancy and implantation rates. The main objective was not to compare these groups to each other but more to determine if there is an age/FSH combination where live pregnancy is highly unlikely.

Materials & Methods

A retrospective review of all IVF-ET cycles in women aged ≥ age 36 over a 6-year time period was performed. For this study to allow adequate comparisons only women with ≥ 2 embryos transferred were included.

The data were analyzed according to FSH range (mIU/ml): < 10, 11-12, 13-14, 15-16, ≥ 17. The data were also analyzed according to age ranges: 36-39, 40-42, ≥ 43.

Results

The clinical and delivery pregnancy rates in women aged 36-39 and implantation rates according to day 3 serum FSH levels are shown in Table 1. Clinical pregnancy rates were significantly higher for women aged 36-39 with day 3 serum FSH ≤ 10 mIU/ml vs all those > 10 mIU/ml (38.3% vs 23.2%, p < .05).

The live delivery rate per transfer was also significantly higher in women aged 36-39 with FSH < 10 vs ≥ 10 mIU/ml (31.6% vs 18.6%, p < .05) (Table 1). The implantation rates were also significantly higher for women aged 36-39 with serum FSH ≤ 10 vs > 10 mIU/ml (17.8% vs 10.1%, p < .05).

The clinical and live delivery rates in women aged 40-42 according to day 3 serum FSH are shown in Table 2. There were no significant differences in clinical pregnancy rates per transfer in women aged 40-42 with serum

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FSH \leq 10 vs FSH 11-14 mIU/ml (31.6% vs 28.5%, p = NS). There were no significant differences in live delivery rates in women aged 40-42 with serum FSH \leq 10 vs FSH 11-14 mIU/ml (24.1% vs 21.4%).

The clinical and live delivery rates according to day 3 serum FSH in women aged > 43 are shown in Table 3. Clinical and live delivered pregnancies were less common in women aged \geq 43 but the rates were similar in women with FSH < 10 vs 11-14 mIU/ml.

In contrast to women aged 36-39 there were no live pregnancies in 17 transfers in women > age 40 (including women \geq 43) when the serum FSH was \geq 15.

Table 1. — Pregnancy and implantation rates in women aged 36-39 according to day 3 serum FSH range.

<table>
<thead>
<tr>
<th>FSH range mIU/ml</th>
<th>No. of transfers</th>
<th>% of clm pregnancies transferred</th>
<th>% ongoing delivered/implanted</th>
<th>% embryos implanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>\leq 10</td>
<td>373</td>
<td>38.3</td>
<td>31.6</td>
<td>17.8</td>
</tr>
<tr>
<td>11-12</td>
<td>23</td>
<td>26.5</td>
<td>17.6</td>
<td>9.2</td>
</tr>
<tr>
<td>13-14</td>
<td>7</td>
<td>25.6</td>
<td>28.6</td>
<td>10.5</td>
</tr>
<tr>
<td>15-16</td>
<td>5</td>
<td>20.0</td>
<td>20.0</td>
<td>10.0</td>
</tr>
<tr>
<td>\geq 17</td>
<td>8</td>
<td>12.5</td>
<td>12.5</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Table 2. — Pregnancy and implantation rates in women aged 40-42 according to day 3 serum FSH range.

<table>
<thead>
<tr>
<th>FSH range mIU/ml</th>
<th>No. of transfers</th>
<th>% of clm pregnancies transferred</th>
<th>% ongoing delivered/implanted</th>
<th>% embryos implanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>\leq 10</td>
<td>253</td>
<td>31.6</td>
<td>24.1</td>
<td>12.7</td>
</tr>
<tr>
<td>11-12</td>
<td>15</td>
<td>40</td>
<td>26.7</td>
<td>14.0</td>
</tr>
<tr>
<td>13-14</td>
<td>13</td>
<td>15.4</td>
<td>15.4</td>
<td>5.7</td>
</tr>
<tr>
<td>15-16</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\geq 17</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Table 3. — Pregnancy and implantation rates in women aged \geq 43 according to day 3 serum FSH range.

<table>
<thead>
<tr>
<th>FSH range mIU/ml</th>
<th>No. of transfers</th>
<th>% of clm pregnancies transferred</th>
<th>% ongoing delivered/implanted</th>
<th>% embryos implanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>\leq 10</td>
<td>139</td>
<td>15.1</td>
<td>10.8</td>
<td>4.7</td>
</tr>
<tr>
<td>11-12</td>
<td>14</td>
<td>14.3</td>
<td>7.1</td>
<td>5.0</td>
</tr>
<tr>
<td>13-14</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>3.4</td>
</tr>
<tr>
<td>15-16</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\geq 17</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusion

Although there were no live pregnancies in this study following IVF-ET in women aged \geq 40 with serum FSH \geq 15 mIU/ml, there have been studies published of live deliveries with and without IVF in women with FSH \geq 15.

A successful pregnancy in a 42-year-old woman with blocked fallopian tubes with imminent ovarian failure following ovulation induction with ethinyl estradiol without gonadotropins and with IVF-ET was reported [4]. The patient conceived on her second treatment cycle and serum FSH was 61 mIU/ml. Another woman in apparent ovarian failure aged 45 also conceived by lowering the high serum FSH (43 mIU/ml) with ethinyl estradiol on her second treatment cycle with intrauterine insemination for severe oligoasthenozoospermia [5]. Both of these women had healthy live babies.

There was also another 45-year-old who successfully delivered with a serum FSH of 16.1 mIU/ml [6]. Although she was ovulating, ethinyl estradiol was used to lengthen the follicular phase [7]. Another woman with a serum FSH of 23.6 actually conceived at age 46 and had a healthy baby [8]. In her case it took 14 cycles of IUI for mild male factor. All these cases were treated with progesterone supplementation in the luteal phase.

Two other cases of pregnancy at age \geq 40 with a serum FSH > 15 mIU/ml are worth mentioning even though they were only 40 years old. One woman seemed to be in menopause (amenorrhea and estrogen deficient and unresponsive to gonadotropins) with a serum FSH of 124 mIU/ml [9]. She was made to ovulate in seven consecutive cycles by using ethinyl estradiol to lower serum FSH and restore down-regulated FSH receptors in the granulosa-theca cells and she conceived on her seventh cycle. She delivered a healthy baby by cesarean section, and her right ovary was described as a streaked gonad and the left ovary as markedly hypoplastic with an average diameter of 12-18 mm [9].

Another woman in apparent menopause with serum FSH of 123 mIU/ml was made to ovulate two consecutive times with ethinyl estradiol but she failed to conceive [10]. The same treatment regimen failed to make her ovulate in cycle 3. She decided to enter a donor oocyte program but since she lived 3000 miles away, she decided to have donor oocytes closer to her residence. Unfortunately she failed to conceive despite four transfers of fresh embryos derived from donor oocytes. She decided to try the donor oocyte program at our facility. Interestingly, in preparation for donor oocytes we placed her back on estrogen. She ovulated again and was treated with progesterone suppositories in the luteal phase. Miraculously, she conceived in this cycle with her own eggs and had a healthy baby [10]. She informed us that while undergoing the donor oocyte program her serum FSH once attained a level of 180 mIU/ml [10].

Though these rare pregnancies have been reported in women \geq 45 with elevated day 3 serum FSH it is unusual to achieve a pregnancy in women aged \geq 45. In our IVF program the live delivery rate per transfer in women aged \geq 45 including women with normal serum FSH and even those who respond well is 0.5%. Yet extremely poor responders who only had one embryo to transfer aged \leq 39 were reported to have a clinical and delivery rate per transfer of 3.8% and 3.8% with a 4-cell embryo transferred on day 3, 9.5% and 9.5% with 5-cells, 37.9% and 31.0% with 6-cells, 40.0% and 35.0% with 7-cells and 42.4% and 36.4% with 8-cells [11]. Six to 8-cell embryo transfers occurred 65% of the time [11].

These data on single embryo transfers show that when very little gonadotropin stimulation is used a respectable pregnancy rate can be achieved in younger (\leq 39) women with such marked diminished egg reserve that only a single embryo could be transferred. Their paucity of eggs makes them comparable to women age 49-50 from a
quantitative aspect. However, based on their pregnancy rates (clinical pregnancy rate of 27.8% and live deliveries of 22.4% per transfer) they behave more like their chronological peers from an egg quality standpoint.

Thus these data suggest a different etiology causing lower egg reserve in younger women with high FSH. We favor the hypothesis that some factor (possibly a product of mitochondrial DNA) is responsible for the recruitment of the monthly cohort of follicles and the best eggs are recruited. Therefore in advanced reproductive age the best follicles are already gone.

However, in the majority of younger women with decreased egg reserve, the mechanism of low egg reserve is not due to an acceleration of the normal process of atresia but is related to damage to portions of the ovary. Nonetheless the remaining undamaged section of ovary has the same proportion of good healthy eggs as its chronological peers with normal FSH, just less of them.

As mentioned, one theory is that a mitochondrial DNA factor is responsible for the monthly recruitment of the cohort of follicles. The hypothesis continues that this same factor is needed to prevent apoptosis of the cells of the embryos that occur after the blastocyst stage. Thus a woman of more advanced reproductive age is less likely to release an egg with this apoptosis releasing factor since the theory is that the follicles with more of this factor present will be selected chronologically before the others. Therefore the theory favors the marked reduction in oocytes present in some younger women and is not related to an accelerated rate of atresia, but instead, to a destructive process leaving the same proportion of "normal" eggs as their age peers with this apoptosis inhibiting factor still present.

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Difficulty of embryo-transfer (ET) and pregnancy rate based on the uterocervical angle

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Summary

When the angle formed by the uterine body and cervical axes (uterocervical angle) was less than 115°, a catheter for embryo transfer could not be smoothly inserted into the uterine body, and so a hard catheter was used, which significantly reduced the pregnancy rate and implantation rate. When the uterocervical angle measured before embryo transfer by ultrasonography is less than 115°, careful preparation, such as catheter selection for embryo transfer and the setting of a longer operation time, is necessary.

Key words: Uterocervical angle; Embryo transfer; Pregnancy rate; Implantation rate.

Introduction

The success rate of IVF-ET is dependent on the quality of the sperm and ova of the couple and therapeutic techniques [1]. For the latter, stimulation of the ovary, ovum pickup, culture, and embryo transfer (ET) are necessary. ET is the last stage of all IVF-ET procedures, and its technology has progressed. Ultrasound-guided ET [2-8] is currently the main method because the pregnancy rate is higher than that obtained by blind ET [2]. It has been reported that ultrasound-guided ET on days 3 and 4 increased the pregnancy rate compared to that on day 5 [7], and catheters used for ET were related to the pregnancy rate, showing the importance of catheter selection [9,11]. Furthermore, performing a mock ET as a trial shortened the operation time of real ET and increased the pregnancy rate [12]. Various modifications have been made for ET as described above, but failure of these actions wastes the long-term IVF-ET treatment. Thus, ET should be very carefully performed. A catheter for ET cannot be easily inserted into the uterus in some cases in which ET is difficult and the pregnancy rate may be low. As we repeatedly performed ET, it was clarified that the angle formed by the uterine body and cervical axes was small in cases with difficulty in ET catheter insertion. Catheter insertion for ET was easier as the angle formed by the uterine body and cervical axis was close to 180° (linear), and soft catheters could be used, which may have increased the pregnancy rate. When the angle was small (close to 0°), catheter insertion was difficult, and a hard catheter was necessary, or a catheter was inserted after the angle was expanded by traction of the ectocervical region using Martin forceps in some cases. The pregnancy rate may decrease as this angle decreases, but the clinically problematic angle has not yet been identified.

In this study, we retrospectively investigated the angle, smaller than that whereby catheter insertion for ET becomes difficult, and the pregnancy rate is reduced. Measurement of this angle and careful preparation before ET are clinically significant.

Materials and Methods

Patients

The subjects included 102 patients (162 cycles) who underwent in vitro fertilization/fresh or frozen ET between September 2005 and December 2006. The mean patient age was 35.7 (25-45) years, and the mean frequency of assisted reproductive technology (ART) was 1.4. The mean BMI of the patients was 20.9 (17.4-33.3), the mean endometrial thickness at the time of ET was 12.2 (6.3-23.2) mm, and the distance between the catheter tip for ET and the fundus of the uterus was 5.8 (0.0-17.2) mm.

Ovarian stimulation protocol

For ovarian stimulation, the long protocol was mainly used. FSH (300 units) was intramuscularly injected for two days from day 3, followed by intramuscular injection of 150 units of hMG for several days, and ova were collected 35 hours after hCG injection. The luteal phase was supported by IM injection of 125 mg of progesterone (3 times every other day).

Measurement of the uterocervical angle

Measurement of the uterocervical angle was performed using transvaginal ultrasound sonography immediately before embryo transfer. A transvaginal ultrasound scan was then performed and a mid-plane longitudinal section obtained. The uterine body and cervical axes were traced. The uterocervical angle was measured on the ultrasonogram using a protractor.

The uterocervical angle is the angle between a line joining the external cervical os and internal cervical os, and a line joining the internal cervical os and uterine fundus (Figure 1).

Culture

For the culture medium, universal IVF medium (Medicult) or 10% SSS-HTF (Irvine Scientific) was used until confirmation of fertilization, and Blast Assist System 1 (Medicult), 10% SSS-...
early cleavage medium, or complete early cleavage medium (Irvine Scientific) was used for two days after confirmation of fertilization. For freezing/thawing in the pronucleus phase, vitrification kits VT101 or VT102 (Kitazato Supply) were used. Embryos were cultured at 37°C in 5% CO₂, 5% O₂, and 90% N₂.

**Embryo transfer procedure**

One to three embryos were transferred two or three days after ova pickup. ET catheter insertion into the uterus was tested in the follicular phase of the previous cycle before ET. For the ET catheter, a soft (Kitazato Supply, Tokyo, Japan) was used first, and a hard style-attached Flespout catheter (Kitazato Supply) was used when the insertion was difficult. When insertion remained difficult, a hard Wallace embryo replacement catheter (code no. mantle: 1816NST, tube: 1816, Smith Medical) was used. The catheter for the actual ET was selected based on this trial. In actual ET, the intravaginal region was washed with physiological saline after urination, and the mantle was inserted into the uterus. With transvaginal ultrasonic guiding, an ET catheter was inserted into the uterus, and embryos were transplanted by placing the catheter tip 10 mm from the uterine fundus.

In all cases, the catheter was then checked under a dissecting microscope for retained embryos. If these were found, they were reloaded and transferred again. The patients were asked to remain in bed for two hours after the procedure.

**Judgment of clinical pregnancy**

Clinical pregnancy was judged positive when urinary hCG was positive at two weeks after ET, and the gestational sac was observed by transvaginal ultrasonography at three weeks after ET. The pregnancy rate for ET cycles was investigated.

**Data analysis**

Statistical analysis was performed using the Microsoft software package. The Student’s t-test, multiple mean comparison and chi-square test were used with p < 0.05 being considered as significant.

---

**Results**

**Patient profile**

In Table 1 the profiles of the three patient groups are reported. No statistically significant differences were found among the three study groups. The groups were homogeneous for patient age, number of previous ETs, estradiol level, number of oocytes retrieved, fertilization rate, number of good embryos, and number of transferred embryos.

**Table 1. — Patient profile.**

<table>
<thead>
<tr>
<th>Uterocervical angle (°)</th>
<th>0-114</th>
<th>115-129</th>
<th>130-</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>42</td>
<td>44</td>
<td>76</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.1 ± 5.4</td>
<td>35.6 ± 5.1</td>
<td>35.5 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>No. of previous ETs</td>
<td>1.4 ± 0.5</td>
<td>1.5 ± 0.8</td>
<td>1.4 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol level (pg/ml)</td>
<td>2646 ± 3011</td>
<td>2261 ± 1356</td>
<td>2385 ± 1616</td>
<td>NS</td>
</tr>
<tr>
<td>No. of oocytes retrieved</td>
<td>8.5 ± 7.2</td>
<td>8.2 ± 5.1</td>
<td>9.6 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fertilization rate</td>
<td>58.1 ± 23.0</td>
<td>60.0 ± 23.2</td>
<td>56.4 ± 25.4</td>
<td>NS</td>
</tr>
<tr>
<td>No. of G1, G2</td>
<td>0.9 ± 1.0</td>
<td>0.9 ± 0.8</td>
<td>0.9 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>No. of G1, G2, G3</td>
<td>1.9 ± 1.1</td>
<td>1.7 ± 0.9</td>
<td>1.9 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>No. of transferred embryos</td>
<td>2.4 ± 0.7</td>
<td>2.5 ± 0.7</td>
<td>2.3 ± 0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD. NS: not significant.

**Resistance due to the uterocervical angle in embryo transfer**

Catheter insertion into the uterus for ET was not smooth in 43.2% (70/162) of all patients, and a longer time was necessary because of resistance to insertion. Regarding the uterocervical angle, insertion was difficult in 76.2% (32/42) of cases with an absolute angle value smaller than 115°, 31.8% (14/44) of cases with an angle between 115° and 129°, and 30.3% (23/76) of cases with an angle larger than 130°, respectively (Figure 2). The number of cases with insertion resistance was significantly increased in cases with an angle smaller than 115° compared to that in cases with larger angles (p < 0.01).

**Catheter selection for ET based on the uterocervical angle**

The hard catheter (Wallace embryo replacement catheter (Wallace)) was more frequently used in cases with a small absolute angle (Figure 3). The angle was smaller than 100° in 77.8% (7/9) of cases in which Wallace was used, but the Wallace was not used in cases with a 115° or larger angle. The pregnancy rates obtained using the three types of catheters for ET used at our hospital (Flespout catheter: code nos. FRC-3G-1 and FRC-3ST-1, Wallace: code nos. mantle: 1816NST, tube: 1816) were 27.0% (31/115), 26.3% (10/38), and 22.2% (2/9), respectively, showing no significant differences.

**Frequency of use of single-hook forceps for embryo transfer in relation to the uterocervical angle**

The number of cases in which the Martin forceps were used for ET was investigated in relation to the angle (Figure 4). Martin forceps were used in 19.0% (8/42) of cases with an absolute angle value smaller than 115°, and
2.3% (1/44), and 7.9% (6/76) of cases with an angle between 115° and 129°, and larger than 130°, respectively. The frequency of Martin forceps usage was significantly higher in cases with an angle smaller than 115° than in cases with an angle between 115° and 129° (p < 0.05). The pregnancy rates in cases with and without the use of the Martin forceps were 26.7% (4/15) and 26.5% (39/147), respectively, showing no significant differences.

### Relationship between the uterocervical angle and clinical pregnancy rate

The overall pregnancy rate to embryo transfer cycles was 26.5% (43/162). The uterocervical angle and pregnancy rate are shown in Figure 5. The pregnancy rates were 16.7% (7/42), 31.8% (14/44), and 28.9% (22/76) in cases with an absolute angle smaller than 115°, between 115° and 129°, and larger than 130°, respectively. The pregnancy rate was significantly lower in cases with an absolute angle smaller than 115° than in cases with an angle between 115° and 129° and larger than 130° (p < 0.05 and p < 0.05).

### Relationship between the uterocervical angle and implantation rate

The overall implantation rate to embryo transfer cycles was 13.4% (52/388). The uterocervical angle and implantation rate are shown in Figure 6. The implantation rates

---

**Figure 2.** — Rates of cases with resistance to catheter insertion in ET in the uterocervical angle groups are presented. **p < 0.01.

**Figure 3.** — Catheters for embryo transfer used for various uterocervical angles. Black and dark gray bars represent Flespout retrocatheters, and the light gray bar represents the Wallace embryo replacement catheter.

**Figure 4.** — Rates of Martin forceps usage in embryo transfer in relation to the uterocervical angle. The rate of cases in which Martin forceps were used in ET in each angle group is presented. *p < 0.05.
Difficulty of embryo-transfer (ET) and pregnancy rate based on the uterocervical angle

were 6.9% (7/102), 16.7% (18/108), and 15.2% (27/178) in cases with an absolute angle smaller than 115°, between 115° and 129°, and larger than 130°, respectively. The implantation rate was significantly lower in cases with an absolute angle smaller than 115° than in cases with an angle between 115° and 129° and larger than 130° (p < 0.05 and p < 0.05).

Pregnancy rate in relation to differences between ante- and retroflexion of the uterus

Differences in the pregnancy rate between ante- and retroflexion of the uterus were investigated. The pregnancy rates in cases with ante- and retroflexion of the uterus were 32.2% (38/118) and 11.4% (5/44), respectively. Both the number of pregnancies and pregnancy rate were significantly lower in cases with retroflexion (p < 0.05 and p < 0.05) (Figure 7).

The pregnancy rate was investigated in relation to the angle in ante- and retroflexion of the uterus. The rate decreased with a reduction in the angle in both ante- and retroflexion of the uterus, and the decrease was more marked in retroflexion (not significant) (Figure 8A/B).

Discussion

The uterocervical angle changed depending on the degree of urinary bladder filling. Sallam et al. measured the uterocervical angle with the urinary bladder filled immediately before ET by transabdominal ultrasonography.
We froze the sagittal view of transvaginal ultrasonography immediately after urination, not with a full urinary bladder and measured the uterocervical angle by tracing the uterine body and cervical axes on the image. ET was also performed immediately after the measurement of the uterocervical angle with transvaginal ultrasound guidance. As a rule, we performed transvaginal ultrasound-guided ET after urination because the resolution of transvaginal ultrasonography was better than that of transabdominal ultrasonography in not only retroflexion but also anteflexion of the uterus, allowing reliable ET at 10 mm from the fundus of the uterine body. When the angle of anteflexion is sharp, filling of the urinary bladder increases the uterocervical angle, making catheter insertion easier. Thus, transabdominal ultrasound-guided ET after filling the urinary bladder is also useful [13]. However, when the angle of retroflexion of the uterus is sharp, there is no stimulation-free method to increase the angle.

We retrospectively investigated the angle formed by the uterine body and cervical axis, which is involved in the clinical success of ET, expecting an increase in the success rate of ET by careful preparation for ET in cases with a clinically problematic small angle.

On investigation of the pregnancy rate in relation to the angle formed by the uterine body and cervical axis (uterocervical angle), the pregnancy rate was significantly lower in cases with an angle smaller than 115° than in cases with 115° or larger, suggesting that ET is difficult in cases with an angle smaller than 115°. Sallam et al. reported that the pregnancy rate significantly decreased when the angle was larger than 60° (smaller than 120° in our study), compared to that with 0 degrees [13], which is consistent with our findings.

Regarding the difference in the pregnancy rate between cases with ante- and retroflexion of the uterus, the rate was significantly lower in cases with retroflexion. ET was more difficult in retroflexion than in anteflexion, suggesting that the difference in uterine morphology between anteflexion and retroflexion affects the pregnancy rate.

The pregnancy rate was investigated in relation to the uterocervical angle in ante- and retroflexion of the uterus. The pregnancy rate decreased as the angle reduced in both ante- and retroflexion, and the decrease was more marked in retroflexion.

When the uterocervical angle was less than 115°, the ET catheter could not be smoothly inserted, and a hard catheter was used, or the ectocervical region was pulled using Martin forceps.

Accordingly, when the angle measured by ultrasonography before ET is less than 115°, careful preparation, such as selection of the ET catheter, use of the Martin forceps, and setting a longer operation time, is necessary before the execution. Sallam et al. modified the catheter
to adjust it to the cervical angle, and obtained good outcomes [13].

The pregnancy rates obtained using the three types of ET catheters with different degrees of hardness were 27.0% (31/115), 26.3% (10/38), and 22.2% (2/9), respectively, showing no significant differences. The pregnancy rates in cases with and without the use of single-hook forceps were 26.7% (4/15) and 26.5% (39/147), respectively, showing no significant differences. The catheter was changed, or single-hook forceps were used in cases with difficulty in ET, and these actions did not reduce the pregnancy rate, i.e., no significant difference was noted in the rate between cases with and without difficulty in ET [14, 15]. These findings indicate that adequate performance of ET avoids reduction of the pregnancy rate.

However, the pregnancy rate decreased when the angle was less than 115°, although an appropriate catheter was selected, and preparation for embryo transfer was carefully set, suggesting that the usefulness of catheter selection and use of single-hook forceps was limited when the angle was less than 115°, and ET into the uterine body was not reliable. For cases of repeated ET failure with a small uterocervical angle for which a hard catheter has been used, transcervical ET into the uterine body should be avoided, and consideration of zygote intrafallopian transfer (ZIFT) a transvaginal transmyometrial embryo transfer (Towako method), in which embryos are transferred to the endometrium by transvaginal puncture of the myometrial layer under ultrasound guidance, but not using a catheter [16], is necessary.

Conclusions

When the angle formed by the uterine body and cervical axes was less than 115°, a catheter for ET could not be smoothly inserted, and a hard catheter was used. The pregnancy rate and implantation rate by ET was significantly lower when the angle was less than 115°. When the angle is less than 115° on ultrasonography before ET, careful preparation, such as catheter selection and setting a longer operation time, is necessary before ET execution.

References


**General Section**

**Attitudes towards contraception in three different populations**

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¹Department of Obstetrics and Gynecology, Democritus University of Thrace, Alexandroupolis (Greece)
²Obstetrics and Gynecology Clinic, Aschaffenburg (Germany)

**Summary**

**Objective:** To investigate contraceptive behavior of women belonging to three different ethnic and/or socioeconomic populations as well as to evaluate the main sources of information concerning contraception in each population. **Methods:** 150 Muslim women living in Germany (group A), 120 Muslim women living in Thrace, Greece (group B) and 140 Christian Orthodox women living in Thrace, Greece were enrolled in the study. Attitudes concerning contraceptive practices were assessed by means of a questionnaire. Demographic and socioeconomic characteristics of each group were compared with the method of contraception used. Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Turkey’s test, chi-square test and multiple logistic regression analysis. **Results:** The contraceptive pill (41.7%), the condom (35.1%), periodic abstinence (24.4%) and interrupted coitus were the most common methods of contraception. The gynecologist (23.4%), the family consultant (12.0%) and the sexual partner (10.2%) were the most usual sources of information. The use of contraceptive pills was more frequent among Muslims from Germany and Christians from Greece (p < 0.001), while the use of condoms was more frequent among Christians from Greece (p = 0.019). The use of IUDs was more frequent among Muslims from Germany and Greece (p = 0.039). **Conclusions:** Our study results reveal that there are behavioral differences between race/ethnic groups and minorities regarding contraceptive practices, probably due to different cultural, socioeconomic and educational factors.

**Key words:** Contraceptive behavior; Different populations; Demographic characteristics; Socioeconomic status; Religion.

**Introduction**

Worldwide, an immense amount of time, energy and money is being spent on the prevention of unwanted pregnancies. Since use of contraception is crucial in this endeavor, various studies have looked at the determinants of effective contraceptive behavior [1-5]. From these studies it is clear that contraceptive practice is influenced by a number of determinants. Some of them can be located at the individual level, such as demographic characteristics, psychological factors, attitude towards sexual activity, sexual experience, knowledge and attitudes towards contraception. Some determinants are located at the interpersonal level, such as communication and interaction skills. But other determinants of effective contraceptive behavior are situated outside the two persons involved, in society at large. The organization of contraceptive health care and sex education in a country, the quality of the information and care given by family planning professionals, the influence of mass media: all these variables influence individual contraceptive choices and decisions. Effective contraceptive behavior is not an individual achievement, just as ineffective contraceptive behavior should not be dismissed as an individual failure [1].

Consistent use of effective birth-control methods is the primary strategy for preventing unintended pregnancies. However, population-based information about contraceptive use patterns are limited in the international literature. Information about contraceptive use in sub populations can be used to guide the development of state programs and policies regarding unintended pregnancy and the spread of sexually transmitted infections, as well as to further refine state efforts to improve contraceptive use in groups with special demographic, social, educational, economic, and religious characteristics.

The aim of the present study was to investigate contraceptive behavior of women belonging to three different ethnic and/or socioeconomic populations. We also intended to draw conclusions on social and economic parameters influencing female attitude towards contraception as well as to evaluate the main sources of information concerning contraception in each population.

**Method**

To investigate the differences in attitudes towards contraception, representatives of three female subgroups were studied: 150 Muslim women living in Germany (group A), 120 Muslim women living in Thrace, Greece (group B) and 140 Christian Orthodox women living in Thrace, Greece. All respondents were of reproductive age (from 16 to 41 years) and each group was reasonably representative of the corresponding reproductive-aged female population in terms of education, marital status and professional life. Attitudes concerning contraceptive practices were assessed by means of a questionnaire. All women included in the study were very cooperative in answering the questions. Each question was explained to the participants, who subsequently completed the questionnaire in private and finally sent it back by post. Women gave detailed answers regarding their age, place of residence, religion, economic, social, marital and professional status, as well as the main source of information offered to them about contraception. The above-mentioned characteristics of each group were compared with the method of contraception used. Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Turkey’s test, chi-square test and multiple logistic regression analysis.
Results

The three groups were compared in terms of age ($p = 0.904$) and residence ($p = 0.499$) but not in terms of social status ($p < 0.001$), permanent partner ($p = 0.012$) and occupation ($p < 0.001$) (Table 1). The contraceptive pill (41.7%), condom (35.1%), periodic abstinence (24.4%) and interrupted coitus were the most common methods of contraception (Table 2). The gynecologist (23.4%), family consultant (12.0%) and sexual partner (10.2%) were the most usual sources of information (Table 3).

Table 1. — Epidemiologic data of the study populations.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of women (%)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muslims/Germany</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>Muslims/Thrace</td>
<td>29.3</td>
<td></td>
</tr>
<tr>
<td>Christian Orthodox</td>
<td>34.1</td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>63.4</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>34.1</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>65.9</td>
<td></td>
</tr>
<tr>
<td>Way of living</td>
<td></td>
<td>0.499</td>
</tr>
<tr>
<td>Urban</td>
<td>40.7</td>
<td></td>
</tr>
<tr>
<td>Semi-urban</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.904</td>
</tr>
<tr>
<td>$\leq$ 20</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 36</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Social status$^*$</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Married</td>
<td>31.7</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widow</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Unmarried with partner</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>Permanent partner$^{**}$</td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>No</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67.8</td>
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<tr>
<td>Occupation$^{***}$</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>Student</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>21.7</td>
<td></td>
</tr>
<tr>
<td>Part-time employment</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>Full-time employment</td>
<td>20.2</td>
<td></td>
</tr>
</tbody>
</table>

* Low percentage of married and unmarried Muslim women in Germany. High percentage of unmarried Muslims with a partner in Germany. Low percentage of divorced Muslims in Thrace.

** High percentage of permanent partner in Muslims/Thrace.

*** Low percentage of students and high percentage of homemakers in Muslims/Thrace.

Table 2. — Method of contraception in the study population.

<table>
<thead>
<tr>
<th>Contraception method</th>
<th>No. of women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>41.7</td>
</tr>
<tr>
<td>Condoms</td>
<td>35.1</td>
</tr>
<tr>
<td>Periodic abstinence</td>
<td>24.4</td>
</tr>
<tr>
<td>Interrupted coitus</td>
<td>21.5</td>
</tr>
<tr>
<td>Injectable contraception</td>
<td>1.0</td>
</tr>
<tr>
<td>IUD</td>
<td>3.9</td>
</tr>
<tr>
<td>Spermicides</td>
<td>2.9</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>2.2</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>–</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0.2</td>
</tr>
<tr>
<td>None</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* Low percentage of married and unmarried Muslim women in Germany. High percentage of unmarried Muslims with a partner in Germany. Low percentage of divorced Muslims in Thrace.

** High percentage of permanent partner in Muslims/Thrace.

*** Low percentage of students and high percentage of homemakers in Muslims/Thrace.

Table 3. — Source of information regarding contraception.

<table>
<thead>
<tr>
<th>Source of information</th>
<th>No. of women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents</td>
<td>7.8</td>
</tr>
<tr>
<td>Partner</td>
<td>10.2</td>
</tr>
<tr>
<td>Insurance doctor</td>
<td>7.3</td>
</tr>
<tr>
<td>Gynecologist</td>
<td>23.4</td>
</tr>
<tr>
<td>Doctor of Family Planning Services</td>
<td>12.0</td>
</tr>
<tr>
<td>Female group</td>
<td>7.3</td>
</tr>
<tr>
<td>Friends</td>
<td>6.8</td>
</tr>
<tr>
<td>School</td>
<td>7.3</td>
</tr>
<tr>
<td>Books</td>
<td>7.1</td>
</tr>
<tr>
<td>Newspapers</td>
<td>1.7</td>
</tr>
<tr>
<td>Magazines</td>
<td>1.7</td>
</tr>
<tr>
<td>Brochure</td>
<td>3.7</td>
</tr>
<tr>
<td>Radio</td>
<td>2.0</td>
</tr>
<tr>
<td>Television</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Table 4. — Use of oral contraceptives according to women’s characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of women using OCs (%)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muslims/Germany</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Muslims/Thrace</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Christian Orthodox</td>
<td>54.3</td>
<td></td>
</tr>
<tr>
<td>Residence place</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Greece</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Christian</td>
<td>54.3</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>34.8</td>
<td></td>
</tr>
<tr>
<td>Way of living</td>
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<td>0.511</td>
</tr>
<tr>
<td>Urban</td>
<td>41.3</td>
<td></td>
</tr>
<tr>
<td>Semi-Urban</td>
<td>39.0</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>46.8</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.410</td>
</tr>
<tr>
<td>$\leq$ 20</td>
<td>37.8</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>47.2</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>44.4</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 36</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>Social status$^*$</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Married</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widow</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td>Unmarried with partner</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Permanent partner$^{**}$</td>
<td></td>
<td>0.954</td>
</tr>
<tr>
<td>No</td>
<td>41.7</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41.4</td>
<td></td>
</tr>
<tr>
<td>Occupation$^{***}$</td>
<td></td>
<td>0.698</td>
</tr>
<tr>
<td>Student</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>47.2</td>
<td></td>
</tr>
<tr>
<td>Part-time employment</td>
<td>42.4</td>
<td></td>
</tr>
<tr>
<td>Full-time employment</td>
<td>41.0</td>
<td></td>
</tr>
</tbody>
</table>

* Low percentage of married and unmarried Muslim women in Germany. High percentage of unmarried Muslims with a partner in Germany. Low percentage of divorced Muslims in Thrace.

** High percentage of permanent partner in Muslims/Thrace.

*** Low percentage of students and high percentage of homemakers in Muslims/Thrace.
Use of contraceptive pills was more frequent among Muslims from Germany and Christians from Greece \((p < 0.001)\) as well as among unmarried women with a partner \((p = 0.021)\) (Table 4), while the use of condoms was more frequent among Christians from Greece \((p = 0.019)\) and women living in rural areas \((p = 0.038)\) and less frequent among unmarried women with a partner \((p = 0.022)\) (Table 5).

Muslims from Thrace were more likely to practice periodic abstinence (Table 6) and interrupted coitus (both \(p < 0.001\)) (Table 7). Interrupted coitus was also frequent among unemployed women \((p = 0.009)\) (Table 7). Use of IUDs was more frequent among Muslims from Germany or Greece \((p = 0.039)\) (Table 8), while spermicides were more frequent among women younger than 25 years \((p = 0.028)\), unmarried women with or without a partner \((p = 0.012)\) and students \((p = 0.012)\) (Table 9).

### Table 5. — Use of condoms according to women’s characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Use of condom (%)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muslims/Germany</td>
<td>31.3</td>
<td>0.019</td>
</tr>
<tr>
<td>Muslims/Thrace</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>Christian Orthodox</td>
<td>44.3</td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>37.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Germany</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td>0.972</td>
</tr>
<tr>
<td>Christian</td>
<td>44.3</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td>Way of living</td>
<td></td>
<td>0.634</td>
</tr>
<tr>
<td>Urban</td>
<td>38.3</td>
<td></td>
</tr>
<tr>
<td>Semi-Urban</td>
<td>37.8</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.392</td>
</tr>
<tr>
<td>(\leq 20)</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>30.2</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>(\geq 36)</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>Social status*</td>
<td></td>
<td>0.202</td>
</tr>
<tr>
<td>Married</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widow</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Unmarried with partner</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Permanent partner**</td>
<td></td>
<td>0.237</td>
</tr>
<tr>
<td>No</td>
<td>28.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Occupation***</td>
<td></td>
<td>0.516</td>
</tr>
<tr>
<td>Student</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Part-time employment</td>
<td>26.1</td>
<td></td>
</tr>
<tr>
<td>Full-time employment</td>
<td>22.9</td>
<td></td>
</tr>
</tbody>
</table>

* Low percentage of married and unmarried Muslim women in Germany. High percentage of unmarried Muslim with a partner in Germany. Low percentage of divorced Muslims in Thrace.

** High percentage of permanent partners in Muslims/Thrace.

*** Low percentage of students and high percentage of homemakers in Muslims/Thrace.

### Table 6. — Use of periodic abstinence according to women’s characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Use of periodic abstinence (%)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muslims/Germany</td>
<td>12.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Muslims/Thrace</td>
<td>39.2</td>
<td></td>
</tr>
<tr>
<td>Christian Orthodox</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Greece</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td>0.972</td>
</tr>
<tr>
<td>Christian</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>Way of living</td>
<td></td>
<td>0.634</td>
</tr>
<tr>
<td>Urban</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>Semi-Urban</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>25.3</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.368</td>
</tr>
<tr>
<td>(\geq 20)</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>27.4</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>(\geq 36)</td>
<td>44.4</td>
<td></td>
</tr>
<tr>
<td>Social status*</td>
<td></td>
<td>0.202</td>
</tr>
<tr>
<td>Married</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widow</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Unmarried with partner</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Permanent partner**</td>
<td></td>
<td>0.237</td>
</tr>
<tr>
<td>No</td>
<td>28.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Occupation***</td>
<td></td>
<td>0.516</td>
</tr>
<tr>
<td>Student</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Part-time employment</td>
<td>26.1</td>
<td></td>
</tr>
<tr>
<td>Full-time employment</td>
<td>22.9</td>
<td></td>
</tr>
</tbody>
</table>

* Low percentage of married and unmarried Muslim women in Germany. High percentage of unmarried Muslims with a partner in Germany. Low percentage of divorced Muslims in Thrace.

** High percentage of permanent partners in Muslims/Thrace.

*** Low percentage of students and high percentage of homemakers in Muslims/Thrace.

### Discussion

Comparative population-based information on contraceptive use for certain subpopulations can be used to guide the development of state programs and policies to decrease unintended pregnancies and the spread of sexually transmitted diseases. These data can identify groups within a state who are experiencing a greater unmet need for birth control and who might have barriers to birth control use. Low contraceptive prevalence within subgroups might suggest reduced access to birth control services or other barriers to contraceptive use. Data also might indicate gaps in contraceptive methods offered by providers. An analysis of the prevalence of birth control use by selected population characteristics can help target contraceptive programs to best meet the population. This information can be used to gain a better understanding of contraceptive use patterns among different sociodemographic groups [6].

Our study results reveal that there are behavioral differences between race/ethnic groups and minorities
regarding contraceptive practices which are probably due to different cultural, socioeconomic and educational factors. Similar data have been ascertained in other studies indicating that populations of women differ tremendously and patterns of sexual experience and contraception use, although modified by national trends, can differ extensively and widely from the national averages [5, 7]. It is well known that studies involving a large number of important variables categorized suitably combined with the appropriate analytical procedure will provide more valid and stable results [4]. The results of our study, based on small but representative samples, confirm that the use of contraceptives is affected by a host of individual and community characteristics.

Accurate knowledge is the key to making good decisions about one’s reproductive health. Studies show that women are able to make the right decisions and safe contraceptive choices as long as they are given and understand the necessary information [8-11]. A lack of knowledge of contraceptive methods or a source of supply, cost and poor accessibility are the barriers that exist mainly in populations of rural economy. The health concerns of these individuals also stop a lot of women and men from using modern contraceptive methods. Periodic abstinence and interrupted intercourse have the least health concerns but have frequent contraceptive failures. All these facts have been confirmed in studies performed on subpopulations of different demographic and socio-economic backgrounds in various countries or even in the same country [12-19]. In our study, modern contraceptive methods like the pill, the diaphragm or spermicides were used by women in urban areas, younger women and students or employed women. On the other hand, women in rural areas preferred old contraceptive methods like periodic abstinence and withdrawal.

The more information and counseling women receive on contraception, the more effectively they perform contraceptive practices. One way to inform women and their partners about family planning is through the mass media, including radio, TV, video and newspapers [20-
Table 9. — Use of spermicides according to women’s characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Use of spermicides (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muslims/Germany</td>
<td>4.0</td>
<td>0.264</td>
</tr>
<tr>
<td>Muslims/Thrace</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Christian Orthodox</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Residence place</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>2.3</td>
<td>0.327</td>
</tr>
<tr>
<td>Germany</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
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</tr>
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<td>Christian</td>
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</tr>
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<td>Muslim</td>
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<tr>
<td>Way of living</td>
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</tr>
<tr>
<td>Semi-Urban</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.243</td>
</tr>
<tr>
<td>≤ 20</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>≥ 36</td>
<td>–</td>
<td>0.077</td>
</tr>
<tr>
<td>Social status*</td>
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<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widow</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Unmarried with partner</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Permanent partner**</td>
<td></td>
<td>0.243</td>
</tr>
<tr>
<td>No</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Occupation***</td>
<td></td>
<td>0.063</td>
</tr>
<tr>
<td>Student</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Part-time employment</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Full-time employment</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

* Low percentage of married and unmarried Muslim women in Germany. High percentage of unmarried Muslim with partner in Germany. Low percentage of divorced in Muslims/Thrace.
** High percentage of permanent partner in Muslims/Thrace.
*** Low percentage of students and high percentage of homemakers in Muslims/Thrace.

22] which reaches many different groups, thus influencing family planning use among the married and unmarried, the literate and nonliterate, men as well as women. Reaching large and diverse audiences, the mass media is a valuable tool for family planning programs to improve the use of modern contraceptive methods. Typically, however, information in the mass media is not detailed enough to help people choose a specific family planning method and use it effectively. It seems that in our study the mass media did not play a crucial role in promoting family planning since the main source of information regarding contraception was the gynecologist. This should be seriously kept in mind in family planning programs and services organized by the state to improve contraceptive practices in these subpopulations. Attitudes toward contraception reflect the time and society in which individuals live. Actual and continuing efforts are needed to keep society informed and to plan for current and future family planning services.
Women’s health measures in two North Carolina regions sampled from the Basic Automated Birth Yearbook (BABY) datasets: experimental findings, methodological limits and future directions

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³Murphy Women’s Center, Murphy, NC
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Summary

Purpose: To compare selected characteristics in two North Carolina counties to document women’s health services at the geographical extremes of the state. Methods: Using aggregated 2004 data obtained from the North Carolina State Center for Health Statistics, obstetric and perinatal characteristics were experimentally analyzed for the westernmost and easternmost counties in North Carolina (Cherokee and Dare County, respectively). Findings: During the experiment period, 489 infants were delivered in Dare County (population 33,518), while 259 births were recorded in Cherokee County (population 25,289). Prenatal care was established by most women in both counties by the second gestational month. Women in Cherokee County were younger and less educated at delivery than women in Dare County, and smoking prevalence was higher in Cherokee County than in Dare County (31.3% vs 12.9%; p < 0.01). Cherokee County infants required assisted ventilation and other medical interventions more often than babies born in Dare County (p < 0.01) yet significantly fewer cesarean deliveries were performed in Cherokee County than Dare County (25.5% vs 35.2%; p = 0.04). Conclusion: This pilot study showed a significantly higher rate of tobacco use, and lower maternal education level in Cherokee County was associated with a higher incidence of multiple maternal complications and neonatal interventions compared to Dare County. Interestingly, the cesarean delivery rate was lower in Cherokee County despite these factors. We found < 10% of babies born in the study regions required any neonatal intervention. Early and almost universal access to prenatal care did not appear to be a problem at either site. Our preliminary comparison identified important limitations in this government-sponsored dataset that rendered logistic regression analysis methodologically impossible. Changes in process could improve surveillance based on patient-level data and facilitate multivariate analysis. Specific interventions to optimize women’s health services form the basis of future experimental research, including larger regional populations.

Key words: Perinatal outcomes; Women’s health; Rural; Appalachia.

Introduction

The rate of population growth in North Carolina over the past decade has magnified the public health challenges associated with provision of medical needs of individuals and families. This pilot experiment examined selected current obstetric and neonatal clinical features in North Carolina focusing on the Western and Eastern boundaries of the state, Cherokee and Dare Counties, respectively (Figure 1).

Materials and Methods

Data source

This report compares data derived from analysis of information submitted to the North Carolina Department of Health & Human Services, Division of State Health Statistics. Data were tabulated centrally based on formal entries on all birth certificates filed with the state from the two study counties in 2004. These data are compiled as the Basic Automated Birth Yearbook, providing a report stratified by county comprised of multiple cross-tabulations of various maternal and infant variables such as age, race, birth order, birth weight, and number of prenatal visits as well as medical conditions of both mother and newborn. As clinical information was not collected in a format permitting patient-specific comparisons for any parameters, it was not possible to perform logistic regression analyses.

For our study, live birth was defined as the complete expulsion or extraction from its mother of a product of conception irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or any definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached. Marital status for this population was determined as follows: ‘An unmarried’ mother was one who had never been legally married or who had been widowed or legally divorced from her husband for > 280 days. Birth weight for all infants was recorded in grams. A low-weight birth was defined as a live born infant weighing < 2500 g (i.e., 5 pounds, 8 ounces or less) at birth, irrespective of gestational age. Maternal age was the reported age in completed years at the mother’s last (most recent) birthday. Education of the mother was determined by the number of years of school completed at time of the birth.
Results

Table 1 summarizes recent federal census and geographic information for Cherokee and Dare County, North Carolina. Mean income was lower in Cherokee than Dare County, (median $33,768 vs $49,302, respectively), consistent with a significant difference in proportion of residents below the poverty line in these two respective areas (15.3% vs 8%; p < 0.01).

A total of 748 infants were delivered during the study period: 259 in Cherokee and 489 in Dare County. The number of medical practitioners providing prenatal and delivery services in the two counties during the study interval was quite dissimilar, with the hospital in Dare County having > 12 obstetricians on staff and the hospital in Cherokee County never having more than three (data not shown). Residents or other physicians-in-training did not work regularly in either location, although both counties maintained a public health clinic for individuals without health insurance. In 2004 few women from either county initiated prenatal care as late as the third month, and there were no recorded births in either study site resulting from pregnancy where prenatal care was entirely absent (Figure 9).

Discussion

Of North Carolina’s 100 counties, no two are further apart geographically than Cherokee and Dare. As the total population of North Carolina has grown in the past decade (at a pace exceeding the U.S. average), these two counties have registered their own substantial gains as well. Although at opposite ends of North Carolina and separated by more than 500 miles, Cherokee and Dare counties share some common characteristics. Neither county contains any large metropolitan center and both have only one hospital. Additionally, both counties are situated in rural areas with a generally low population density, both have a county health department that offers free women’s health services including prenatal care, and both counties are contiguous with at least one neighboring county with no hospital at all. Ours is the first study to describe representative features of these two North Carolina areas with an emphasis on women’s and infant health outcomes.

In general, these data show pregnant patients in Dare County to be older, better educated, and earlier in initiating prenatal care. Importantly, obstetric patients in Dare County to be older, better educated, and earlier in initiating prenatal care. Importantly, obstetric patients in Dare County to be older, better educated, and earlier in initiating prenatal care. Importantly, obstetric patients in Dare County to be older, better educated, and earlier in initiating prenatal care.
Figure 2. — Comparison of age distributions of pregnant women from Cherokee County (left) and Dare County (right), North Carolina.

Figure 3. — Education (highest level completed) among pregnant women from Cherokee County (left) and Dare County (right), North Carolina. E = elementary, HS = high school, HSG = high school graduate, COL = college, C+4 = college graduate, NS = not specified.

Figure 4. — Comparison of smoking status (black = % smoking) among pregnant women from Cherokee County (left) and Dare County (right), North Carolina.

Figure 5. — Comparison of maternal medical complications among pregnant women from Cherokee County (left) and Dare County (right), North Carolina. A = anemia, D = diabetes, H = hypertension, AO = any other, ≥ 1 = one or more complicating condition, U = unspecified.

Figure 6. — Comparison of infant birth weight from pregnant women delivering in Cherokee County (left) and Dare County (right), North Carolina. < 1500 g, INT = 1500-2499 g, ≥ 2500 g.

Figure 7. — Comparison of neonatal interventions performed on newborns delivered in Cherokee County (left) and Dare County (right), North Carolina. AV = artificial ventilation, AO = any other, ≥ 1 = one or more intervention, U = unspecified.
County were less likely to be smokers and their babies were less likely to require multiple neonatal interventions. Our observations parallel the findings of others [1, 2] who have noted an association between level of education and smoking status. Our analysis of these two North Carolina populations is in agreement with the confirmed deleterious impact of cigarette use during pregnancy and subsequent poor neonatal outcome [3, 4].

The rate of cesarean delivery in Dare County (35.2%) was significantly higher than in Cherokee County (25.5%) during a year (2004) when the national cesarean delivery rate was 29.1% [5]. While factors influencing cesarean delivery rate have been the focus of considerable study, there is little consensus on proper indications for this most frequently performed obstetrical surgery. It would be reasonable to expect a relatively high-risk obstetrical population to include an increased utilization of cesarean delivery, yet these data show a paradoxically lower cesarean rate in the location (Cherokee County) where women are more likely to have medical problems.

One explanation for this observation may be that, despite the higher prevalence of more complicated gestations in Cherokee County, the higher frequency of underweight babies delivered there leads to a lower cesarean delivery rate because cephalopelvic disproportion is encountered less often. The role of the relatively limited number of obstetricians in Cherokee County may also contribute to this finding, although the impact of this factor requires further study.

Measurement of the contributions of patient education level and affluence in the cesarean delivery equation represented an important challenge, and has frustrated epidemiologic efforts in other populations that sought to identify causes for cesarean delivery [5, 6]. The emerging concept of “cesarean delivery on maternal request” could also be a relevant factor, but as birth certificate data do not capture this as a recognized indication for cesarean delivery at present, the definitive answer remains elusive.

A comparison of operative vaginal delivery across the two regions was also performed, and important differences were identified. Choice of operative vaginal delivery method may be influenced by physician characteristics [7] including training and experience. For example, factors associated with operator preference for type of instrumental vaginal delivery (obstetrical forceps vs vacuum) has been studied previously [8, 9]. It may be that the number of physician providers in each county could contribute to the observed variance in operative vaginal delivery.

Our study anticipates further comparisons among larger groups in North Carolina, but was limited by several factors. The Basic Automated Birth Yearbook (BABY) databank (maintained by the North Carolina Department of Health & Human Services, Division of State Health Statistics) provides aggregate data only, and unfortunately is not presently configured for review of patient-level data. This rendered a more in-depth multivariate analysis of measured factors impossible and also made a robust statistical comparison between these two counties futile. The data also lacked sufficient detail to compare rate of multiple gestation, utilization of intrapartum anesthesia, frequency of maternal/neonatal blood transfusion, length of postpartum hospitalization, breastfeeding preference, or readmission within 48 hours of discharge. These parameters form the basis of further investigation at our institutions. Additionally, the source data could not identify how many pregnancies were established after ovulation induction, insemination, or advanced reproductive technologies. A higher a priori rate of primary cesarean delivery has been associated with antecedent infertility [10, 11] and could have impacted the cesarean delivery findings discussed above.

How could prenatal and perinatal care in these two North Carolina counties be improved? Having a database supporting a full range of statistical comparisons is vital for a definitive answer; at present this is not available in
North Carolina. Our descriptive study derived from aggregate data suggests that the rate of primary cesarean delivery in both counties (especially in Dare County) should be monitored and reduced. Institutional protocols are already in place to help achieve this objective. Furthermore, maternal tobacco use (particularly in Cherokee County) should be strongly discouraged and, if possible, eliminated. In this regard, the importance of antenatal smoking cessation counseling cannot be overstated. Previous investigators have demonstrated positive, enhanced clinical outcomes following implementation of a smoking cessation plan, particularly when initiated by the physician [12, 13]. With healthcare resources becoming acutely limited in these two counties and throughout North Carolina, cost savings resulting from such interventions would be especially welcome. Assessing the efficacy of these measures represents the aim of future studies.

References


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Misoprostol and first trimester pregnancy termination

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Summary

Objective: To investigate the efficacy of vaginal administration of 800 μg misoprostol as a single dose without performing post expulsion systematic curettage in first trimester pregnancy termination. Method: 113 women, aged 16-44, who requested first trimester pregnancy termination, received 800 μg of vaginal misoprostol. All examined women were divided into two groups depending on gestation age. The first group included of 67 women with up to nine weeks and the second of 46 with up to 12 weeks of pregnancy. Results: Abortion occurred within 24 hours and was completed in 74.3% of the cases. The mean induction-abortion interval was 5.9 ± 1.7 hours (median 5.5 hours). Side-effects were experienced by 24 women (21.2%). There was no significant difference between groups in the success rate, induction-abortion interval, number of previous deliveries and side-effects. Conclusion: Misoprostol is an effective agent for first trimester medical termination.

Key words: Misoprostol; Prostaglandins; Medical abortion; Surgical abortion; Uterine bleeding.

Introduction

Misoprostol is a synthetic prostaglandin E1 analogue that is commonly used for medical abortion. It can given orally vaginally and sublingually [1]. It was first developed in 1973 for the prevention or treatment of peptic ulcer disease caused by prostaglandin synthetase inhibition. Because this methyl ester of prostaglandin E1 is an effective uterine myometrium stimulant and binds selectively to EP-2/EP-3 prostaglandin receptors, misoprostol was quickly recognized as a potential therapeutic alternative to other available conventional prostaglandins [2, 3].

Abortion is one of the most common surgical applications worldwide. At present most patients and physicians seem to prefer surgical pregnancy termination [4]. Medical abortion is an alternative to the surgical procedure. Perceived benefits of medical abortion are the avoidance of surgery with its discomfort and morbidity and the increased privacy [5, 6]. In developing countries medical methods of abortion hold the potential to improve women’s health [7, 8]. Several medical methods for first trimester pregnancy termination have been developed by using misoprostol alone or in combination with methotrexate or mifepristone [9, 10].

The aim of this study was to certify the efficacy and safety of vaginal administration of 800 μg misoprostol as a single agent and single dose without performing post expulsion systematic curettage in first trimester pregnancy termination (7-12 weeks of gestation).

Patients and Methods

From January 2004 to December 2005, 135 women (age range 18-44 years; mean age 29 years) who requested medical termination of a pregnancy at 7-12 (mean 9) weeks of gestation were recruited for a prospective study. All of these women complied with the following inclusion criteria: ≥ 18 years of age, gestational age from 7 to 12 weeks, informed consent for medical abortion and for surgical abortion, and adequate hematological and biochemical profiles.

Twenty-two women were excluded from the study. Exclusion criteria were: hemoglobin level < 10 mg/dl, blood pressure ≥ 160/90 mmHg, poor general health for any cause, prior uterine bleeding, current genital infection and previous intolerance or allergy to prostaglandins.

The remaining 113 patients were divided into two groups depending on gestational age. The first group included participants from 7 to 9 weeks of gestation and the second more than nine weeks of gestation.

Gestational age was measured from the first day of the last menstrual period according to menstrual history and vaginal or abdominal ultrasonography. Blood samples were obtained to determine hemoglobin, hematocrit, blood group and Rhesus factor.

All women included were administered a single dose of 800 μg (four 200 μg tablets) by the vaginal route. The tablets were all placed in the left and right vaginal fornix, and were previously moistened with two to three drops of water for injection. If no abortion occurred in the next 24 hours, surgical abortion followed. An injection of 600 μg of paracetamol was given if needed to relieve pain. Patients were frequently examined for evaluation of the referred cramping, the abortion process, and the degree of bleeding. For these reasons the patients were hospitalized at least for 24 hours. Transvaginal ultrasound (TVS) was performed to confirm if abortion occurred.

Success was defined as complete evacuation of the endometrial cavity and cervix channel of the products of conception, whereas failure was considered as lack of abortion within 48 hours or as incomplete abortion. Failure led the patient to curettage.

Patients were also evaluated seven days after the expulsion or curettage by TVS and clinical examination of vaginal bleeding, and degree of pain and pelvic discomfort. Blood sample tests were also performed if considered necessary. All women were prescribed antibiotic and ergonovine treatment for three days after the abortion.
Pearson’s chi-square test was used to ascertain the independence between variables and obtained results. For comparison of hemoglobin levels before and after the application of misoprostol the t-test was used. In all cases p < 0.05 was considered significant. The study was approved by the Ethics Committee of the University Hospital of Alexandroupolis.

Results

The characteristics of the 113 subjects are presented in Table 1. Abortion occurred in all cases and was complete in 84 (74.3%). Suction curettage was performed in 17 women in group 1 (25.4%) and in 12 women in group 2 (26.1%). Bleeding began within 3.5 ± 0.75 hours (median 3.5 hours; range 1 to 5.5 hours) after misoprostol administration. The mean (± SD) induction-abortion time interval was 5.9 ± 1.7 hours (median 5.5 hours).

No statistically significant correlation was obtained concerning success/failure rates and any patient characteristics (Table 2). Moreover there were no significant differences between the two study groups regarding the success rate (p = 0.37), the induction-abortion interval (p = 0.47), the parity (p = 0.62) and the intensity of bleeding (p = 0.24).

Table 1. — Socio-demographic characteristics.

<table>
<thead>
<tr>
<th>Parameters studied</th>
<th>All cases</th>
<th>7-9 weeks group</th>
<th>10-13 weeks group</th>
<th>Significance between the 2 groups (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Religion-Christian</td>
<td>34.5%</td>
<td>31.3%</td>
<td>39.1%</td>
<td>0.173</td>
</tr>
<tr>
<td>Religion-Muslim</td>
<td>65.5%</td>
<td>68.7%</td>
<td>60.9%</td>
<td></td>
</tr>
<tr>
<td>History of deliveries</td>
<td>0</td>
<td>41.6%</td>
<td>38.8%</td>
<td>0.457</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>26.5%</td>
<td>28.4%</td>
<td>23.9%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16.8%</td>
<td>16.4%</td>
<td>17.4%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9.7%</td>
<td>11.9%</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.5%</td>
<td>4.5%</td>
<td>2.2%</td>
</tr>
<tr>
<td></td>
<td>≥ 5</td>
<td>1.8%</td>
<td>0%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Delivery</td>
<td>0</td>
<td>41.6%</td>
<td>38.8%</td>
<td>45.7%</td>
</tr>
<tr>
<td>VG</td>
<td>VG</td>
<td>48.7%</td>
<td>50.7%</td>
<td>45.7%</td>
</tr>
<tr>
<td>CS</td>
<td>7.1%</td>
<td>9%</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>VG+CS</td>
<td>2.7%</td>
<td>1.5%</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.19</td>
<td>28.58</td>
<td>30.07</td>
<td>0.252</td>
</tr>
</tbody>
</table>

Table 2. — Success-failure rate in patients.

<table>
<thead>
<tr>
<th>7-9 weeks</th>
<th>Incomplete abortion</th>
<th>17</th>
<th>25.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete abortion</td>
<td>50</td>
<td>74.6%</td>
</tr>
<tr>
<td>9-12 weeks</td>
<td>Incomplete abortion</td>
<td>12</td>
<td>26.1%</td>
</tr>
<tr>
<td></td>
<td>Complete abortion</td>
<td>34</td>
<td>73.9%</td>
</tr>
</tbody>
</table>

Table 3. — Side-effects observed.

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Group 1 (7-9 weeks)</th>
<th>Group 2 (&gt; 9-13 weeks)</th>
<th>Significance between the 2 groups (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25.4%</td>
<td>15.2%</td>
<td>0.871</td>
</tr>
<tr>
<td>Chills</td>
<td>13.4%</td>
<td>6.5%</td>
<td>0.448</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.9%</td>
<td>2.2%</td>
<td>0.695</td>
</tr>
<tr>
<td>Pelvic pain - mild</td>
<td>83.6%</td>
<td>78.3%</td>
<td>–</td>
</tr>
<tr>
<td>Pelvic pain - moderate</td>
<td>10.4%</td>
<td>17.4%</td>
<td>0.911</td>
</tr>
<tr>
<td>Pelvic pain - severe</td>
<td>6%</td>
<td>4.3%</td>
<td>–</td>
</tr>
<tr>
<td>Elevated temperature &gt; 38°C</td>
<td>4.5%</td>
<td>2.2%</td>
<td>0.789</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>4.3%</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>2.2%</td>
<td>0.829</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0%</td>
<td>2.2%</td>
<td>–</td>
</tr>
<tr>
<td>Mild bleeding</td>
<td>80.6%</td>
<td>89.1%</td>
<td>–</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>19.4%</td>
<td>10.9%</td>
<td>0.243</td>
</tr>
</tbody>
</table>

Table 4. — Hemoglobin levels before and after abortion.

| Hb (before) | 113 | 12.648 | 12.800 | 1.034 | p = 0.24 |
| Hb (after)  | 113 | 12.256 | 12.400 | 1.049 |

SD = standard deviation.

Incidence of all reported side-effects is shown in Table 3. The two groups did not differ significantly with respect to side-effects (incidence of pain, nausea, vomit, fever, headache, diarrhea and chill) (p = 0.871). None of the women presented severe bleeding. Only 4.4% of the patients asked for paracetamol to relieve pain. Incidence and severity of pain did not correlate with gestational age. We also did not observe significantly statistical differences concerning the amount and duration of post-expulsion vaginal bleeding. Finally there was no statistically significant correlation in decreased hemoglobin levels between the two studied groups (Table 4).

On the seventh day of examination none of the women who medically aborted had severe bleeding or pelvic distress, or any other discomfort. TVS examination showed no remains in the uterine cavity.

Discussion

Few drugs have been found to have as many potential applications in obstetric practice as misoprostol in the last 20 years [11]. For first trimester medical abortions misoprostol has been used extensively either alone or in combination with mifepristone and/or methotrexate. However, Greece is a country with no access to mifepristone and the use of methotrexate has many side-effects [12]. The main advantage of medical abortion is that it allows women to avoid the risks of surgery and anesthesia [13]. However the need for hospitalization, length of the process and time of bleeding, the multiple examinations and the potential for an after-hours intervention for bleeding or infection are perceived by many patients as negative [14]. On the contrary there are studies of women who have undergone medical pregnancy termination showing that they preferred medical over surgical termination [15, 16].

In our prospective study we found that medical termination of pregnancy using misoprostol alone was 74.6% in women with gestational age between seven and nine weeks of gestation and 73.9% in women with gestational age between nine and 12 weeks of gestation. Our results are not in contrast to those of previous studies that have shown that the efficacy of vaginally administered misoprostol is not affected by the duration of pregnancy [17].
Some authors have reported higher success rates (92% and 93.6%) with repeated dosing 48 hours apart for three vaginal doses of 800 μg [18]. In summary the studies on misoprostol alone for pregnancy termination indicate a success rate between 66% and 94% [19, 20].

In our study the overall incidence of side-effects was 25.4% lower than the respective one in other studies (34.9%-58.7%) [21, 22]. The two groups did not differ significantly with respect to side-effects, and none of the patients presented heavy bleeding – mainly due to the fact that a single dose of 800 μg of misoprostol was used. The episodes of bleeding were also shorter.

In conclusion this study showed that the abortive efficacy of a single vaginal dose of 800 μg of misoprostol is slightly lower than repeated administration of the drug but a significantly decreased incidence of observed side-effects established the safety of the method. It is clear that misoprostol alone is an inexpensive, readily available option for medical abortions as long as follow-up and a surgical termination back-up option are guaranteed. More detailed multi-center studies on the use of the method should be carried out to determine any aspects not yet clarified.

References


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Association study between catechol-O-methyltransferase polymorphisms and uterine leiomyomas in a Japanese population

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Summary

Purpose: To investigate a possible association between uterine leiomyomas and catechol-O-methyltransferase (COMT) polymorphisms in a Japanese population. Methods: We compared the allele frequencies and genotype distributions of the exon 4 NlaIII restriction site polymorphism (RSP), the P2 promoter HindIII RSP at -1217, and the exon 6 BglI RSP in the COMT gene in 250 leiomyoma cases and 182 controls using polymerase chain reaction-restriction fragment-length polymorphism analysis. Results: No significant differences in allele frequencies and genotype distributions of the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglI RSP were found between uterine leiomyoma cases and controls. Moreover, no associations were noted between these three polymorphisms in COMT genes and leiomyoma size or a family history of uterine leiomyomas. Conclusion: COMT gene polymorphisms are unlikely to be associated with an increased risk of uterine leiomyomas in a Japanese population.

Key words: Leiomyoma; Gene polymorphism; Polymerase chain reaction; Restriction fragment length polymorphism; Catechol-O-methyltransferase.

Introduction

Uterine leiomyomas are common benign neoplasms originating from smooth muscles in the myometrium, which frequently occur in premenopausal women [1]. This disease causes prolonged menstrual bleeding, dysmenorrhea, and reproductive dysfunction.

Accumulating evidence supports the concept that uterine leiomyomas are sex steroid hormone-dependent neoplasms. Leiomyomas increase with age during the premenopausal periods and typically regress and become asymptomatic with the onset of menopause [2, 3]. Tissue concentrations of estrogen are reported to be increased in leiomyoma tissues compared with those in the myometrium [4, 5]. Recent studies have demonstrated that the regulation of estrogen metabolizing enzymes may contribute to the pathogenesis of uterine leiomyomas [6].

Catechol-O-methyltransferase (COMT) is one of the enzymes that metabolize catechol estrogens [7]. This enzyme converts catechol estrogens, 2-hydroxyestradiol and 4-hydroxyestradiol, into inactive metabolites, 2-methoxy-estradiol and 4-methoxy-estradiol, respectively; 4-hydroxyestradiol activity was shown to be increased in human uterine leiomyomas compared with that in uterine myometrium [8]. This suggests that COMT may play an important role in the development and pathogenesis of uterine leiomyomas.

Polymorphisms in the COMT gene, especially the exon 4 NlaIII RSP (Val 108/158 Met polymorphism), have been studied as possible factors influencing susceptibility in several diseases. The Val/Val genotype in the exon 4 NlaIII RSP was reported to be associated with higher prevalence of systolic blood pressure compared with the Met/Met or Met/Val genotypes [9]. The Met/Met genotype was associated with increased risks of adenomyosis, sporadic breast cancer, and depressive disorders [10-12].

The exon 4 NlaIII RSP in the COMT (Val 108/158 Met polymorphism) was reported to be associated with an increased risk of uterine leiomyomas in African American, White, and Hispanic populations, suggesting that COMT gene polymorphisms may influence the establishment and development of this disease [13]. However, no additional studies that support such an association have been reported in other populations, and there is no information available regarding the P2 promoter HindIII RSP at -1217 and the exon 6 BglI RSP in the COMT gene.

In the present study, we investigated potential associations between uterine leiomyomas and the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglI RSP in the COMT gene in a Japanese population.
Materials and Methods

Subjects

The Medical Ethics Review Committee of Kobe University Graduate School of Medicine approved the study design, and written informed consent was obtained from all participants. The case group consisted of 250 unrelated, ethnically Japanese women who were pathologically diagnosed as having uterine leiomyomas after hysterectomy or myomectomy. Women were excluded from the study if they had undergone GnRH agonist therapy preoperatively or an unexpected pathology was found (e.g., adenomyosis).

The control group consisted of 182 healthy women who were confirmed to have no uterine leiomyomas by ultrasonography. We also performed an analysis on patients with regard to a family history of uterine leiomyomas. We defined a positive family history as the presence of a leiomyoma in a first-degree relative. The cases ranged in age from 24 to 73 years with a mean age of 44.0, and controls ranged in age from 26 to 57 years with a mean age of 46.7.

Genotyping

Genomic DNA was extracted from whole blood anti-coagulated with EDTA using the Wizard DNA purification kit (Promega, Madison, WI, USA). The exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene were determined using polymerase chain reaction-restriction fragment-length polymorphism (PCR-RFLP) analysis, as described previously [14]. Genotyping for the exon 4 NlaIII RSP was performed using the forward primer 5'-GCC CGC CTG CTG TCA CC-3' and the reverse primer 5'-CTG TGC TAC-3' and the reverse primer 5'-CCG GAG CCG CAG AAG GTC A-3', followed by digestion with the restriction enzyme NlaIII. Genotyping for the P2 promoter HindIII RSP at -1217 was performed using a PCR fragment amplified by the forward primer 5'-CTC TGCG CGG AAA GGA AT-3' and the reverse primer 5'-TCC GTG GGA AAA AG-3', followed by digestion with the restriction enzyme HindIII. Genotyping for the exon 6 BglII RSP was performed using the forward primer 5'-TGG GGA AGG GGA CAG TGC TAC-3' and the reverse primer 5'-CCG CGG CAG AAG GTG A-3', followed by digestion with the restriction enzyme BglII. The PCR conditions were as follows: PCR in a 20 μl reaction mixture containing 20 ng of genomic DNA, 10 pmol of each primer, 250 μM of dNTPs, and 1.0 unit of Taq gold DNA polymerase. The concentration of MgCl2 was 1.5 mM for all of these three polymorphisms. The PCR was conducted with an ABI 9700 thermocycler (PE Applied Biosystem, Foster City, CA, USA) using the following thermal profiles: an initial denaturing cycle at 96°C for 12 min, 30 cycles of denaturing cycle at 94°C for 30 sec, annealing at 60°C for 30 sec, extension at 72°C for 30 sec, and a final cycle of 72°C for 10 min for the exon 4 NlaIII RSP; an initial denaturing cycle of 96°C for 12 min, 35 cycles of denaturing cycle at 94°C for 30 sec, annealing at 53°C for 30 sec, extension at 72°C for 35 sec, and a final cycle of 72°C for 10 min for the P2 promoter HindIII RSP at -1217; an initial denaturing cycle of 96°C for 12 min, 35 cycles of denaturing cycle at 94°C for 30 sec, annealing at 60°C for 30 sec, extension at 72°C for 35 sec, and a final cycle of 72°C for 10 min for the exon 6 BglII RSP. Digestions with the appropriate restriction enzymes were performed at 37°C for 24 hours according to the manufacturer’s instructions (New England Biolabs, Beverly, MA, USA). DNA fragments were subjected to electrophoresis in a 4% NuSieve 3:1 agarose gels for the exon 4 NlaIII RSP, and in a 2% agarose gels for the P2 promoter HindIII RSP at -1217 and the exon 6 BglII RSP. Gels were stained with 0.1 g/ml ethidium bromide and visualized by ultraviolet illumination.

Statistical analysis

Genotypic distributions were examined for significant departure from the Hardy-Weinberg equilibrium by a goodness of fit χ2 test. The χ2 test was used to examine the differences in the genotype proportions of the polymorphisms between uterine leiomyomas patients and controls. The Fisher correction was applied when appropriate. Odds ratio (OR) and 95% confidence interval (CI) were used to compare categorical variables. The cases were subdivided into groups with or without a family history of uterine leiomyomas, and the distribution of the genotypes in these groups were analysed separately. The independent Student’s t-test was used to examine the relationship between the size of the largest leiomyoma and each genotype.

Results

The genotype distributions were confirmed to be in Hardy-Weinberg equilibrium in each group studied.

Typical gels are shown in Figure 1. The G allele of the exon 4 NlaIII RSP was not cleaved by NlaIII and had a single band of a fragment length of 114 bp (Figure 1A). The A allele was cleaved by NlaIII and yielded two small fragments of 96 bp and 18 bp (Figure 1A). The heterozygote had three bands of 114 bp, 96 bp, and 18 bp (Figure 1A).

The A allele of the P2 promoter HindIII RSP was not cleaved by HindIII and had a single band of a fragment length of 306 bp (Figure 1B). The G allele was cleaved by HindIII, yielding two fragments of 231 bp and 75 bp (Figure 1B). The heterozygote had three bands of 306 bp, 231 bp, and 75 bp (Figure 1B).

The C deletion allele of the exon 6 BglII RSP was not cleaved by BglII and had a single band of a fragment length of 277 bp (Figure 1C). The C insertion allele was cleaved by BglII and yielded two fragments of 196 bp and 82 bp (Figure 1C). The heterozygote had three bands of 277 bp, 196 bp, and 82 bp (Figure 1C).

Genotype distributions and allele frequencies of the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene in leiomyomas cases and the controls are shown in Tables 1, 2, and 3. The cutting allele frequencies of the exon 4 NlaIII RSP, the P2 promoter HindIII RSP, and the exon 6 BglII RSP were 32.2%, 31.6%, and 43.0% in the cases, and 30.2%, 28.9%, and 42.6% in the controls, respectively (Tables 1, 2, 3). No significant differences were found in either the allele frequencies or genotype distributions of the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in COMT gene in the cases and controls (Tables 1, 2, 3).

The allele frequency of the exon 4 NlaIII RSP in our cases were comparable with those in previous reports using a Japanese population (Table 4) [12, 15]. However, there has been no previous study that reported the allele frequencies of the P2 promoter HindIII RSP at -1217 and the exon 6 BglII RSP using a Japanese population. We investigated whether family history of uterine leiomy-
Table 1. — The exon 4 NlaIII RSP genotypes and alleles in leiomyoma cases and controls.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>G/G n (%)</th>
<th>G/A n (%)</th>
<th>A/A n (%)</th>
<th>P value versus controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma (n = 250)</td>
<td>121 (46.4)</td>
<td>97 (38.8)</td>
<td>32 (12.8)</td>
<td>p = 0.84</td>
</tr>
<tr>
<td>Leiomyoma with FH (n = 99)</td>
<td>53 (53.5)</td>
<td>36 (36.4)</td>
<td>10 (10.1)</td>
<td>p = 0.87</td>
</tr>
<tr>
<td>Leiomyoma without FH (n = 60)</td>
<td>28 (46.7)</td>
<td>25 (41.7)</td>
<td>7 (11.6)</td>
<td>p = 0.75</td>
</tr>
<tr>
<td>Controls (n = 182)</td>
<td>93 (51.1)</td>
<td>68 (37.4)</td>
<td>21 (11.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. — The P2 promoter HindIII RSP genotypes and alleles in leiomyoma cases and controls.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>A/A n (%)</th>
<th>A/G n (%)</th>
<th>G/G n (%)</th>
<th>P value versus controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma (n = 250)</td>
<td>117 (46.8)</td>
<td>108 (43.2)</td>
<td>25 (10.0)</td>
<td>p = 0.77</td>
</tr>
<tr>
<td>Leiomyoma with FH (n = 99)</td>
<td>49 (49.5)</td>
<td>39 (39.4)</td>
<td>11 (11.1)</td>
<td>p = 0.74</td>
</tr>
<tr>
<td>Leiomyoma without FH (n = 60)</td>
<td>25 (41.7)</td>
<td>30 (50.0)</td>
<td>5 (8.33)</td>
<td>p = 0.67</td>
</tr>
<tr>
<td>Controls (n = 182)</td>
<td>91 (50.0)</td>
<td>77 (42.3)</td>
<td>14 (7.69)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. — The exon 4 NlaIII RSP by PCR-RFLP (A). Lane 10 confirming 100 bp molecular wt marker is the best standpoint to prove the accuracy of RFLP analysis. Lane 2, 3, 5, and 6 are G/G. Lane 1, 4, 7, 8, and 9 are G/A. Lane 10 is A/A. The P2 promoter HindIII RSP at -1217 by PCR-RFLP (B). Lane 10 confirming 100 bp molecular wt marker is the best standpoint to prove the accuracy of RFLP analysis. Lane 1, 5, 6, and 10 are A/A. Lane 2, 7, 8, and 10 are A/G. Lane 3 and 4 are G/G. The exon 6 BglI RSP by PCR-RFLP (C). Lane 10 confirming 100 bp molecular wt marker is the best standpoint to prove the accuracy of RFLP analysis. Lane 1 is delC/delC. Lane 2, 3, 5, 6, 7, and 8 are delC/insC. Lane 1, 9 and 10 are insC/insC.

Figure 2. — The exon 4 NlaIII RSP and leiomyoma sizes (A). The P2 promoter HindIII RSP at -1217 and leiomyoma sizes (B). The exon 6 BglI RSP and leiomyoma sizes (C). Data on leiomyoma size and polymorphic status were collected as described in the results. Bars represent mean ± SEM.
Table 3. — The exon 6 BglII RSP genotypes and alleles in leiomyoma cases and controls.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Leiomyoma (n = 250)</th>
<th>Leiomyoma with FH (n = 99)</th>
<th>Leiomyoma without FH (n = 60)</th>
<th>Controls (n = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>delC/delC n (%)</td>
<td>delC/insC n (%)</td>
<td>insC/insC n (%)</td>
<td>delC/delC n (%)</td>
</tr>
<tr>
<td></td>
<td>259 (69.8)</td>
<td>24 (15.1)</td>
<td>61 (33.5)</td>
<td>61 (33.5)</td>
</tr>
<tr>
<td></td>
<td>254 (80.5)</td>
<td>23 (14.5)</td>
<td>59 (35.3)</td>
<td>87 (47.8)</td>
</tr>
<tr>
<td></td>
<td>124 (45.0)</td>
<td>24 (15.1)</td>
<td>66 (36.4)</td>
<td>34 (18.7)</td>
</tr>
<tr>
<td>p value versus controls</td>
<td>0.97</td>
<td>0.41</td>
<td>0.53</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>95% CI 0.68-1.22</td>
<td>95% CI 0.69-1.40</td>
<td>95% CI 0.64-1.47</td>
<td>95% CI 0.64-1.47</td>
</tr>
</tbody>
</table>

FH: family history.

Table 4. — Comparison of the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP alleles and genotypes in this study and previously published studies.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allele</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G n (%)</td>
<td>A/G n (%)</td>
<td>A/A n (%)</td>
</tr>
<tr>
<td>259 (71.2)</td>
<td>295 (71.2)</td>
<td>105 (28.9)</td>
</tr>
<tr>
<td>254 (80.5)</td>
<td>24 (15.1)</td>
<td>59 (35.3)</td>
</tr>
<tr>
<td>124 (45.0)</td>
<td>61 (33.5)</td>
<td>66 (36.4)</td>
</tr>
<tr>
<td>p value versus delC insC</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>95% CI 1.017-6.151</td>
<td>95% CI 1.017-6.151</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

In the present study, we investigated possible associations between the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene and uterine leiomyomas in a Japanese population using PCR-RFLP analysis. We could not find any associations in the allele frequencies and genotype distributions of these three polymorphisms in the COMT gene with uterine leiomyomas, irrespective of a family history and leiomyoma size. This is the first study to demonstrate no associations between uterine leiomyomas and the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene.

Previously, two authors investigated the association between the exon 4 NlaIII RSP and uterine leiomyomas in different populations [13, 16] with inconsistent results. Al-Hendy et al. investigated a possible association between the exon 4 NlaIII RSP in the COMT gene and uterine leiomyomas in African American, White, and Hispanic populations using PCR-RFLP analysis [13]. The G allele of the exon 4 NlaIII RSP was found to be significantly more frequent in uterine leiomyoma cases (63.7%) than in controls (45.1%). They demonstrated a positive association between this polymorphism and uterine leiomyomas in African American, White, and Hispanic populations, suggesting that the G/G genotype of the exon 4 NlaIII RSP was 2.5 times more likely to develop uterine leiomyomas than other genotypes (p < 0.001; 95% CI 1.017-6.151). In contrast, Denschlag et al. investigated the same association in a Caucasian population by performing pyrosequencing, but they could not find any association between the exon 4 NlaIII RSP and uterine leiomyomas [17]. Our results coincided with the data of Denschlag et al., who showed no significant differences in allele frequency and genotype distribution for the exon 4 NlaIII RSP (p = 0.3 and p = 0.6, respectively) between 128 cases and 139 controls [17].
There are several possible explanations for the discrepancy between our results and those of Al-Hendy et al. Firstly, one explanation is the relatively small sample sizes in the previous study. In the present study, we included 250 uterine leiomyoma cases and 182 controls, whereas Al-Hendy et al. used 81 cases and 22 controls in an African American population, 59 cases and 92 controls in a White population, and 46 cases and 28 controls in a Hispanic population. Although they evaluated totally 186 uterine leiomyoma cases and 142 controls in the admixture of the ethnic groups including African, White, and Hispanic women, the small sample size of each ethnic group may limit the power of their study to conclude the positive association of the exon 4 NlaIII RSP with the development of uterine leiomyomas.

Secondly, the discrepancy may be due to the differences between the ethnic populations examined because the exon 4 NlaIII RSP A allele frequencies vary among ethnic groups. Indeed, the frequency of the A allele is less frequent in a Japanese population (27-35%) [12, 15] than in a Caucasian population (50-61%) [18, 19]. In our study, the subjects examined had a homogeneous genetic background of Japanese origin alone. In complex traits, susceptibility differences between populations may be as dependent, if not more dependent, on the relative frequencies of polymorphisms conferring susceptibility as on environmental factors. Thus, the exon 4 NlaIII RSP might be associated with uterine leiomyomas in African American, White, and Hispanic populations, but not in those from other ethnic groups such as a Japanese population.

Thirdly, the discrepancy between our results and those of Al-Hendy et al. might be explained by the differences in the genotyping methods used. Both studies used the same PCR-RFLP method, but the sequences of the primers for PCR were different.

A significant association has been shown between the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene and various diseases, to date. Birgit et al. reported that the A allele of the P2 promoter HindIII RSP was significantly more frequent in cases with schizophrenia, bipolar disorder, and major depressive disorders [20]. A allele of the P2 promoter HindIII RSP was also reported to be associated with low COMT activity in lymphocytes [21]. On the other hand, the exon 6 BglII RSP was a deletion/insertion polymorphism immediately 3’ to the stop codon, thus the sequence variation at the 3’ end could have an effect on RNA stability or translational efficiency [22]. Maria et al. and Chia-Hsiang et al. investigated the association between the exon 6 BglII RSP and schizophrenia, but neither of the two studies found any significant differences in allele frequencies and genotype distributions between schizophrenic patients and controls [16, 22]. These two polymorphisms in the COMT gene have not been studied in relation to uterine leiomyomas. In the present study, we investigated for the first time the possible associations between uterine leiomyomas and the P2 promoter HindIII RSP at -1217 and the exon 6 BglII RSP in the COMT gene in a Japanese population. However, we could not identify any positive associations of these COMT gene polymorphisms with uterine leiomyomas.

COMT is present in a membrane bound form (M-COMT) and a soluble form (S-COMT), and plays a critical role in the metabolism of estrogen. COMT converts catechol estrogens, 2- and 4-hydroxyestradiol, into inactive metabolites, 2-methoxy- and 4-methoxy-estradiol; 4-hydroxyestradiol is similar to estradiol in its ability to bind to and activate the estrogen receptor and is hormonally active for stimulating uterine growth [23]. A high activity of 4-hydroxyestradiol was demonstrated in human uterine leiomyomas compared with uterine myometrium [8]. On the other hand, 2-methoxyestradiol exerts an antiproliferative effect on human leiomyoma cells by inhibiting DNA and collagen synthesis, and induces G0/M cell cycle arrest and apoptotic cell death [24]. Taken together, low COMT activity might up-regulate 4-hydroxyestradiol levels and down-regulate 2-methoxyestradiol levels, thereby inducing cell proliferation and down-regulation of DNA and collagen synthesis, and inhibiting apoptotic cell death in human leiomyomas.

COMT is genetically polymorphic caused by autosomal codominate alleles resulting in nearly a fourfold difference in enzyme activity [25]. A polymorphism of a G-to-A transition at codon 158 of S-COMT gene results in a valine-to-methionine substitution [26]. Homozygosity for 158Met leads to a 3-4-fold reduction in enzymatic activity, compared with homozygosity for 158Val [26]. Met/Met genotype was associated with an increased risk of adenomyosis (p = 0.006; OR = 3.2; 95% CI 1.3-7.8) [10]. Met/Met genotype was associated with an increased risk of sporadic breast cancer in premenopausal Turkish women (p = 0.005; OR = 2.28; 95% CI 1.27-4.12) [11]. Moreover, the presence of A allele (Met) was significantly associated with depressive disorders (p = 0.012; OR = 2.19; 95% CI 1.19-4.03) [12].

Considering these data, we hypothesized that the Met allele of the exon 4 NlaIII RSP and the A allele of the P2 promoter HindIII RSP that were reported to be associated with low enzyme activity might have an increased risk for the development of uterine leiomyomas. However, we could not find any positive associations between the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene and uterine leiomyomas.

In conclusion, we could not demonstrate any associations between the exon 4 NlaIII RSP, the P2 promoter HindIII RSP at -1217, and the exon 6 BglII RSP in the COMT gene and uterine leiomyomas in a Japanese population. Further studies will be needed to elucidate the relation of estrogen-metabolizing gene polymorphisms with uterine leiomyomas, since our results can not rule out the involvement of other estrogen-metabolizing single nucleotide polymorphisms in the development of uterine leiomyomas.
References


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Vaginal cysts: a common pathologic entity revisited

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1Pathology Laboratory, 2nd Clinic of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital, Athens (Greece)

Summary

Purpose: To further study the clinicopathological features of benign vaginal cysts. Methods: We retrospectively studied all cases of benign vaginal cysts diagnosed in our laboratory over the last decade. Pathological findings were correlated with the clinical records of the patients and histochemistry results. Results: Forty cases of benign vaginal cysts were retrieved. There were 12 cases of mullerian cysts (30.0%), 11 cases of Bartholin’s duct cysts (27.5%), ten cases of epidermal inclusion cysts (25.0%), five cases of Gartner’s duct cysts (12.5%), one endometrioid cyst (2.5%) and one unclassified cyst (2.5%). Patient age ranged from 20 to 75 years with a mean of 35 years, and a peak incidence between 31-40 years (13 cases, 32.5%). The majority of patients were asymptomatic (31 cases, 77.5%). The cyst type which was more frequently associated with symptoms was Bartholin’s duct cyst. Most lesions were located in the left-lateral vaginal wall (13 cases, 32.50%). Mullerian cysts were lined by columnar endocervical-like or cuboidal epithelium, whereas Gartner’s duct cysts were all lined by cuboidal epithelium. Epidermal inclusion cysts were lined by stratified non-keratinizing squamous epithelium. Bartholin’s duct cysts were lined by transitional, mucin-rich columnar or squamous epithelium and were frequently accompanied by inflammation. Conclusion: Benign vaginal cysts are in the majority of cases asymptomatic and are often incidentally discovered during gynecological examination for other purposes. The differential diagnosis between Mullerian and Gartner’s duct cysts requires histochemical evaluation of epithelial mucin production. The pathogenesis of most types of vaginal cysts remains to be clarified.

Key words: Vaginal cysts; Mullerian; Gartner’s duct; Bartholin’s duct; Epidermal inclusion; Endometriosis.

Introduction

The vagina is a remarkable organ with many unexplored properties, both structural and functional. However, as described elegantly by Schmidt, “the vagina attracts too little serious or sustained study. It seems almost an afterthought in the minds of most pathologists, a structure serving only to connect other far more interesting reproductive organs which harbor more curious and challenging diseases” [1]. Indeed, a review of the relevant literature reveals mostly case reports of rare neoplasms or other unusual pathologic conditions [1]. Clinicopathological studies of common vaginal lesions, such as vaginal cysts, are only scarcely conducted.

Vaginal lesions are generally classified into the following types of disorders: developmental, infectious inflammatory, noninfectious inflammatory, cystic, neoplastic and those that follow trauma, surgery and radiation [2]. Vaginal cysts in particular can be divided into several different types according to their lining epithelium: Mullerian, epidermal inclusion, Bartholin’s duct, Gartner’s duct (mesonephric) cysts, and other rarer cystic lesions such as emphysematous vaginitis, endometriosis, dermoid and urothelial cysts [2, 3]. The majority of these lesions produce mild symptoms, if any, and present as incidental findings in women with other complaints. However, they may also be the cause of pain, dyspareunia or inflammation or even grow large enough to cause vaginal pressure and urinary obstruction [4]. Although clinical history, physical examination and – to a lesser degree – radiological imaging techniques are essential in the initial evaluation of the patient, permanent histopathology of the operative specimen is the only accurate method of establishing the final diagnosis. The choice of the adequate treatment depends mostly on the severity of symptoms [4].

The aim of the present study was to review the clinicopathological features of all benign vaginal cysts diagnosed in our laboratory over the last decade and compare our findings with those of previously published series.

Materials and Methods

After reviewing the archival files of our laboratory for the last 10-year period (1996-2005), we retrieved 40 cases of vaginal cystic lesions. The relative clinical records were also retrieved, reviewed and correlated with the pathological findings (both gross and histological). Representative slides for each case were reexamined by two independent pathologists. Additional sections were obtained in nine cases, and stained by mucicarmine stain.

Results

Clinical features: age, symptoms, location and treatment of lesions

A summary of the clinical findings of all cases included in our study is provided in Table 1.

Age and symptoms: The patients’ age ranged from 20 to 75 years with a mean of 35 years, and a peak incidence between 31-40 years (13 cases, 32.5%). The majority of patients were asymptomatic (31 cases, 77.5%) and were diagnosed with a vaginal cyst while being examined for
symptoms or conditions related to various other gynecologic disorders including incomplete abortion, cervical dysplasia, endometrial hyperplasia or carcinoma, leiomyomatous uterus and uterine prolapse (total of 20 cases) or during their routine gynecological examination (11 cases).

In the remaining symptomatic cases, dyspareunia (7 cases, 17.50%) and pain (6 cases, 15%) were the commonest clinical manifestations. The cyst type which was more frequently associated with symptoms was Bartholin’s duct cyst, where the majority of cases (6 out of 10) presented with pain and/or dyspareunia. With the exception of two patients with epidermal inclusion cysts which presented with pain, none of the remaining patients reported any symptoms related to the vaginal cyst.

**Location:** Most lesions were located in the left-lateral vaginal wall (13 cases, 32.50%), followed by the right lateral wall (6 cases, 32.50%), the anterior wall (8 cases, 20%), the posterior wall (6 cases, 15%) and, finally, the posterior fornix (1 case, 2.5%) (Table 1). The location of epidermal inclusion cysts in particular correlated in the majority of cases (6 out of 10) with an area of previous surgical trauma (obstetrical procedure in 4 cases, hysterectomy in 2).

**Treatment:** All cases were treated with local excision of the lesion: 32 cases (80%) were clinically evident during physical examination, while the remaining eight cases (20%) were incidentally discovered in vaginal biopsies or hysterectomy specimens removed for other reasons. The latter were asymptomatic and smaller than 1 cm in diameter.

**Pathologic (gross and microscopic) features. Histochemistry results**

**Size:** On gross examination, the size of the cysts ranged from 0.4 to 5.5 cm (mean 2.19 cm), with most lesions (25 cases, 62.5%) measuring 1-2 cm in diameter. The mean size per histological type of lesion was as follows: 1.78 cm for Mullerian, 2.7 cm for epidermal inclusion, 2.34 cm for Bartholin’s duct cysts and 2.1 cm for Gartner’s duct cysts. The endometriotic cyst and the unclassified cyst measured 2 cm and 1 cm, respectively.

**Gross findings (other than size):** The cysts were filled with serous, mucinous or purulent-like fluid. Their inner and outer surfaces were smooth, and the thickness of their walls ranged from 0.1 to 0.3 cm.

**Histological and histochemical findings:** Table 2 presents the pathologic classification of our study material after combining the results of microscopic and histochemical examination. Mullerian duct cysts were lined by columnar endocervical-like or cuboidal epithelium (Figure 1), whereas Gartner’s duct cysts were all lined by cuboidal epithelium (Figure 2). Mucus secretion was microscopically evident in eight cases, initially typed as Mullerian. The performance of histochemistry (mucicarmine stain) revealed the presence of mucus-secreting epithelium in four additional Mullerian cysts, which were initially misinterpreted as Gartner’s duct cysts. Mucicarmine stain was negative in five cases which were finally diagnosed as Gartner’s duct cysts.

**Table 1. — Clinical findings in 40 patients with benign vaginal cysts.**

<table>
<thead>
<tr>
<th>Cyst type*</th>
<th>No. of cases (%)</th>
<th>Mean age (years)</th>
<th>Symptoms (no. of cases)</th>
<th>Location (no. of cases)</th>
<th>Mean size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullerian</td>
<td>12 (30.0%)</td>
<td>40.89</td>
<td>None (12)</td>
<td>Ant (3)</td>
<td>1.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LL (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RL (2)</td>
<td></td>
</tr>
<tr>
<td>Bartholin’s gland</td>
<td>11 (27.5%)</td>
<td>41.40</td>
<td>Dysp (5)</td>
<td>LL (5)</td>
<td>2.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RL (6)</td>
<td></td>
</tr>
<tr>
<td>Epidermal inclusion</td>
<td>10 (25.0%)</td>
<td>48.22</td>
<td>None (8)</td>
<td>Ant (2)</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gartner’s duct</td>
<td>5 (12.5%)</td>
<td>34</td>
<td>None (5)</td>
<td>Ant (3)</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LL (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fornix</td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1 (2.5%)</td>
<td>26</td>
<td>None (1)</td>
<td>Post (1)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fornix</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>1 (2.5%)</td>
<td>43</td>
<td>None (1)</td>
<td>Post (1)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain (6/15.5%)</td>
<td>Ant (8/20%)</td>
<td>2.19</td>
</tr>
<tr>
<td>Total</td>
<td>40 (100%)</td>
<td>35</td>
<td>None (3/7.5%)</td>
<td>Post (7/17.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dyse (5/12.5%)</td>
<td>LL (13/32.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RL (12/30%)</td>
<td></td>
</tr>
</tbody>
</table>


*As proven by histological examination.

Epidermal inclusion cysts were lined by stratified non-keratinizing squamous epithelium and were filled with keratin (Figure 3). Cyst rupture with a granulomatous reaction was noticed in two cases, accompanied by stromal calcifications in one.

Bartholin’s duct cysts were lined by transitional, mucin-rich columnar or squamous epithelium (Figure 4). Chronic and/or acute inflammation was noted in the majority of cases (7 out of 10).

Diagnosis of endometrioid cysts was based on the presence of endometrial glands and endometrial stroma. Hemosiderin-laden macrophages, suggesting old hemorrhage, were also noted.

We failed to identify the presence of epithelium in one cyst, which was thus coded as “unclassified”.

**Discussion**

According to previous studies and literature reviews, benign vaginal cysts are typically encountered in women of reproductive age, most commonly in the third and fourth decades of life, while the occurrence in other age...
Vaginal cysts: a common pathologic entity revisited

groups (infants, children, adolescents and postmenopausal patients) is relatively rare [1, 5, 6]. In the majority of cases these lesions are asymptomatic and are discovered during physical examination for irrelative symptoms or even as incidental histopathologic findings in vaginal biopsies or hysterectomy specimens surgically excised for other pathologic conditions [5, 6]. Symptomatic cases may present with a feeling of abdominal discomfort, vaginal pain or bleeding, dyspareunia or urinary symptoms such as incontinence or obstructive voiding symptoms [5, 6]. The presence and severity of this symptomatology is directly related to the cyst size, with larger lesions more frequently warranting excision [5]. In our study, the peak incidence was noted between 31-40 years of age, and the large majority of women were totally asymptomatic, with the notable exception of six patients with Bartholin’s gland cysts and two patients with epidermal inclusion cysts, who presented with pain and/or dyspareunia.

The embryology of the vagina has been the object of significant controversy in the past. In contrast to the initial statement expressed by Schmidt [1] that all of the vaginal epithelium is of urogenital sinus origin, it is now generally agreed that both the mullerian ducts and the urogenital sinus contribute to the formation of the vagina [2, 7-10]. The vagina is therefore considered an organ of dual origin, with a native lining of mullerian-type columnar cells that are retained unless there is a contribution of squamous cells from the urogenital sinus [2]. Some vaginal cysts are believed to be embryological derivatives, and are classified by some researchers under the “congenital” category (versus the “acquired” type), which mainly comprises two types of cysts: those of the mesonephric duct (Wolffian duct, Gartner’s duct) and those of paramesonephric duct (Mullerian duct) origin [1]. Although the differential diagnosis of these congenital remnants is of limited clinical significance, with no effect whatsoever on the prognosis and treatment of the patient, it is of great theoretical interest with regard to embryology. Most authors suggest that among the congenital cysts, Mullerian duct cysts predominate while Gartner’s duct cysts are rare, and that mullerian cysts may be found in various locations in the vagina, while Gartner’s duct cysts are typically found in the anterolateral area [2, 6, 11]. Nevertheless, these features do not allow an accurate differential diagnosis, and the only way to properly classify these cysts is the evaluation of epithelial mucin production [12]. Deppisch [11] in his study of 64 vaginal cysts, as well as Pradhan and Tobon [6] in
their review of 41 cases, suggested that mucicarmine histochemical staining may safely differentiate mullerian mucus-producing cysts from those of Gartner’s duct which are devoid of cytoplasmic mucin. Our own results reaffirm this view, since four of our cases, which were originally classified as Gartner’s duct cysts were found to be Mullerian in origin after the performance of histochemistry (mucicarmine stain was positive in the epithelium lining the cysts). Furthermore, the mullerian cyst was the predominant cyst type found in our series, accounting for 30% of the total of cases.

The differential diagnosis of mullerian cysts should further include Bartholin’s gland cysts originating in an acinus, which are also lined by mucus secreting epithelium [5, 6, 13]. Bartholin’s gland cysts arising from the main duct are lined by transitional or squamous epithelium [5]. Cysts that are in the area of the Bartholin gland commonly result from dilatation of Bartholin’s duct due to ductal obstruction, associated with either a highly viscous thick mucoid secretion or gland infection, and are typically located in the lateral introitus [2, 5]. Histologically, chronic and/or acute inflammation are relatively common findings, and were also found in most of our cases. From the clinician’s point of view, it should be emphasized that those lesions associated with pain or introital obstruction require surgical treatment, with marsupialization representing the treatment of choice, while in cases with recurrent abscess formation, excision of both gland and cyst may be useful [2, 4, 5].

Epidermal inclusion cysts are often secondary to obstetrical or other surgical procedures, and are considered as the most common nonembryological type of vaginal cysts [2, 5, 12]. Our results, as well as those of Pradhan and Tobon confirmed these observations: in the latter study as well as in our own, the locations of the reported epidermal inclusion cysts correlated with the sites of a previous surgical trauma [6]. Epidermal inclusion cysts are easily recognized microscopically by the presence of stratified squamous, non-keratinising epithelium, which may show evidence of neoplastic changes, when the prior surgery was done for intraepithelial lesion of the cervix or the vagina [1]. Cyst rupture may result in a granulomatous reaction, as previously reported and as noted in two of our cases [1].

Primary endometriosis of the vagina is rare, and usually represents a manifestation of pelvic disease [5, 12]. Nevertheless, in our case there was no clinical evidence or any history of endometriosis located elsewhere in the pelvis. Endometrioid cysts are usually located in the posterior fornix of the vagina and have a typical chocolate-like appearance [5]. The histological criteria required for the diagnosis of endometriosis include the presence of the following three characteristics: endometrial glands, endometrial stroma and hemosiderin-laden macrophages [5]. Treatment usually involves excision of larger lesions and destruction of the smaller ones by laser vaporization [5, 12]. The risk of malignant transformation, although small, cannot be ignored, thus posing the need for early diagnosis and treatment of these lesions [12, 14-16].

In the absence of an epithelial lining no proper classification of the cyst can be made. According to Pradhan and Tobon [6], this category could be classified as simple cysts, in a way analogous to ovarian cysts lacking discernible epithelium. However, when the cyst is small, it is practically impossible to verify that the absence of epithelium is not due to the technical procedures employed during surgical excision and pathologic processing of the tissue. Thus we preferred to retain the term “unclassified” for the single case of a vaginal cyst without apparent epithelium.

In conclusion, the results of our study reaffirm those of previous series. However, further research is needed to enrich the existing data regarding the clinicopathological features of benign vaginal cysts and to shed more light on the pathogenesis.

References


Frequency of rate of body temperature chart at mid cycle in pregnant women and the subsequent effect on pregnancy

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Summary

Purpose of investigation: To determine if changes in basal body temperature (BBT) during the ovulatory phase are related to subsequent effects on pregnancy. Methods: BBT records from 216 pregnant women in a spontaneous cycle or a clomiphene citrate cycle during a recent 6-year period were studied. The last day of low phase (LDLP) and the number of days until high phase (NDHP) were determined for all subjects. Results: In the spontaneous cycle group, medium-cycle cases were most frequent and long-cycle cases were most frequent in the clomiphene cycle group. The NDHP ranged between one and three days in 82.8% of the subjects in the spontaneous cycle group and in 86.1% of the subjects in the clomiphene cycle group. Conclusions: Our findings demonstrate the importance of properly evaluating an NDHP of two or even three days in a BBT-based assessment of ovarian function in the ovulatory phase.

Key words: Basal body temperature; Clomiphene citrate; Ovulatory phase.

Introduction

Basal body temperature (BBT) elevation brings about the action of progesterone [1]. BBT can also be affected by sleep duration and sleep environmental factors, such as noise and climate [2], by living environment variables such as daytime work and physical exercise, and by seasonal changes in ambient temperature. Changes in ambient temperature are also subject to geography. Finally, the dramatic changes in lifestyle and living environment that have occurred during the past quarter of a century cannot be disregarded.

The measurement of BBT is not required in current clinical practice, but is nevertheless utilized by almost all gynecological patients with infertility in the early course of ambulatory care at hospitals in Japan, because it is reasonably accurate in predicting ovulation [1, 3, 4], and is inexpensive and minimally invasive [5-7]. However, there are concerns that it is too inaccurate to be used for predicting ovulation [6, 8-10]. Although there have been attempts to evaluate the BBT records of pregnant women in whom ovulation and ovarian function were easy to investigate [11, 12], these reports were published more than 20 years ago and may not reflect our present-day living environment. Medical techniques have also immensely improved, resulting in improvements in examinations and treatment. In the present study, we investigated shifts of BBT during the ovulatory phase and the subsequent effect on pregnancy and, compared our findings to those of studies published 20 years earlier [11].

Materials and Methods

The BBT records of 216 pregnant women that were followed at our hospital or affiliated hospitals during the 6-year period from January 1999 to December 2004 were studied. Patients who conceived during a spontaneous cycle or clomiphene citrate cycle were included; those who became pregnant after hMG-hCG or Gn-RHa therapy or by means of in vitro fertilization-embryo transfer (IVF-ET) were excluded from the study. All women who had received progesterone supplementation in the luteal phase were also excluded. The last day of low phase (LDLP) and the number of days until high phase (NDHP) were determined in all BBT records by two gynecologists, each with over ten years of experience. In the event of a disagreement, the mean of the two estimates was used. All assessments were based on their professional judgment.

Results

Gestation was spontaneous in 133 women (spontaneous cycle pregnancy group) and clomiphene citrate-induced in 76 women (clomiphene cycle pregnancy group). The BBT pattern was classified as biphasic in all these cases. The opinions of the two gynecologists differed for 18 patients who conceived after spontaneous ovarian cycles (13.0%) and 12 who conceived after clomiphene citrate cycles (15.4%). The rate of agreement was thus approximately 86% (186/216). The difference between the two opinions was one day in nearly all inconsistent cases.

The duration of the follicular phase was determined in the two groups and classified as a short, medium, or long cycle [13]. In patients with ongoing pregnancies in the spontaneous cycle pregnancy group, medium-cycle cases were most frequent (42.0%), followed by long-cycle cases (36.1%). Long-cycle cases were most frequent (40.6%) in the clomiphene-cycle pregnancy group, fol-
lowed by medium-cycle cases (39.1%) (Table 1). In the
patients who miscarried the frequencies of long-cycle
cases and medium-cycle cases resembled those of the
spontaneous group. Short cycle cases comprised only
3.4% of spontaneous cycle pregnancies and 3.1% of
clophene citrate cycle pregnancies. No short cycle
pregnancy ended in miscarriage.

Table 1. — Duration of follicular cycle in spontaneous and
clophene-induced pregnancies.

<table>
<thead>
<tr>
<th>Follicular phase</th>
<th>Ongoing (%)</th>
<th>CC</th>
<th>Spontaneous abortion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>4 (3.4)</td>
<td>2 (3.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>12 - 16</td>
<td>50 (42.0)</td>
<td>25 (39.1)</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>17 - 22</td>
<td>43 (36.1)</td>
<td>26 (40.6)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>23 ≥</td>
<td>22 (18.5)</td>
<td>11 (17.2)</td>
<td>2 (14.3)</td>
</tr>
</tbody>
</table>

CC: clomiphene citrate.

In ongoing pregnancies, the number of days until high
phase (NDHP) was one day in 44 women (37.9%) from
the spontaneous cycle pregnancy group, and one to two
days in 73 women (62.9%). In the clomiphene pregnancy
group, the NDHP was one day in 36 women (45.6%), and
one to two days in 58 women (73.4%). The NDHP was
one to three days in 96 women (82.8%) from the sponta-
neous cycle pregnancy group and in 68 women (86.1%)
from the clomiphene pregnancy group. In contrast, in the
miscarriage group NDHP was one day in six women (40%)
from the spontaneous-cycle pregnancy group, one
to two in nine women (60%), and one to three days in 12
women (80%). In the clomiphene cycle group, NDHP
was one day in seven women (58.3%), one to two days
in nine women (75%), and one to three days in ten women
(83.3%) (Table 2).

Table 2. — NDHP in spontaneous and clomiphene-induced
pregnancies.

<table>
<thead>
<tr>
<th>NDHP</th>
<th>Ongoing (%)</th>
<th>CC</th>
<th>Spontaneous abortion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44 (37.9)</td>
<td>36 (45.6)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>1-2</td>
<td>73 (62.9)</td>
<td>58 (73.4)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>1-3</td>
<td>96 (82.8)</td>
<td>68 (86.1)</td>
<td>12 (80)</td>
</tr>
</tbody>
</table>

CC: clomiphene citrate.

Discussion

Evaluation of BBT records in daily clinical practice is
based on the judgment and skill of gynecologists. Com-
puterized evaluation of records has been attempted [14],
but the results were disappointing. Human sensory judg-
ment has proven to be a superior and substantial agree-
ment in the evaluations of appraisers has also been docu-
mented [4]. In the present study, the rate of agreement
between the two gynecologists was approximately 85%.
This relatively high rate is most likely attributable to the
fact that the present series of subjects were pregnant
women with stable ovarian function. Cases with in-
consistencies might have anomalies in BBT. Therefore, 85%
agreement is probably the maximum limit for BBT
records used alone.

Variations in the duration of the follicular phase were
evident in women with spontaneous cycles. This phe-
nomenon was conspicuous in the clomiphene cycle preg-
nancy group (Table 1). Comparing the number of cases
with a follicular phase of 23 days or longer, there were
very few cases with a follicular phase shorter than 11
days. Check et al. reported that a short follicular phase
per se reduces fecundity [15]. The present study findings
support this hypothesis.

Ovulation and stable ovarian function is most easily
monitored in women with successful pregnancies. Indeed,
existence of a pregnancy indicates that ovarian
function is stable, to say nothing of the presence of
ovulation. It may be said that these requirements have
already been demonstrated in pregnant women. On this
premise, Luciano et al. [8], Fedele et al. [9], Robert et al.
[11], and Matthews et al. [12] used BBT to determine
LDLP and changes in the ensuing course of BBT in preg-
nant women. As for the number of days until NDHP, in
the present study 44 women (37.9%) in the spontaneous
cycle pregnancy group and 36 women (45.6%) in the
clomiphene pregnancy group were “category 1” i.e.,
those with the most rapid rise in BBT (Figure 1). This
category corresponds to “type 1” (fairly steep) in the
report by Robert et al., who reported this pattern in 50% of
their cases.

Figure 1. — BBT records of a representative NDHP category 1
case.

LDLP is generally regarded as the day of LH surge [16-
18]. Ovulation occurs within 36 hours of the LH surge
[9]. The day after the last day of low phase does not nec-
essarily correspond with the beginning of the high phase
because the progesterone level is reportedly 4 to 5 ng/ml
during the high phase of BBT [8, 19, 20], and also
because the period during which the LH surge occurs
varies. Instead, it is likely to be an intermediate day,
neither low phase nor of a high phase. Therefore, it is
highly probable that BBT progresses to the high phase
over a period of two days. If so, it may be acceptable to
categorize the NDHP “category 2” cases in the present
Frequency of rate of body temperature chart at mid cycle in pregnant women and the subsequent effect on pregnancy

References


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Conclusion

Our findings demonstrate the importance of properly evaluating a NDHP of two or three days in a BBT-based assessment of ovarian function in the ovulatory phase.

study as patients with a rapid rise in BBT (Figure 2). The presence of an intermediate day(s) (NDHP) has been characterized as a gradual stepwise rise (type 2) or more than one temperature nadir (type 3) by Robert et al. [11], and as a slow pattern by Matthews et al. [12]. In the present study, NDHP category “1” and “2” cases comprised 73 women (62.9%) in the spontaneous cycle pregnancy group and 58 women (73.4%) in the clomiphene pregnancy group. These percentages are still lower than the percentage of type 1 cases in Robert et al. In the present series the number of cases in NDHP categories “1” to “3” was 96 (82.8%) in the spontaneous cycle pregnancy group and 68 (86.1%) in the clomiphene pregnancy group. Guida et al. reported that BBT-determined ovulation days were scattered between day -1 to day +3 of actual ovulation [1]. Moreover, they found no difference between women with ongoing pregnancies and those who miscarried.

Temperature-controlled environments are much more common than they were two decades ago. The view of life and the lifestyle itself of present-day women have become more positive and active, thereby making their daily living more complicated. A rapid elevation in BBT during the gestational cycle should occur in most women, but BBT may not be as accurate in assessing ovarian function in present-day women living in cities. The accuracy of BBT records for ovulation stage is eventually reduced because the starting points of BBT elevation are to be read. BBT however, has the great advantage of being minimally invasive and allows continuous assessment of ovarian function, thus it can hardly be abandoned as the majority of patients use it to keep records. Although definitive results cannot be expected from the application of BBT for future treatment or in the early stage of treatment with low-dose clomiphene citrate, further analysis and use of the BBT records will continue in the foreseeable future.
Clinical symptoms and histopathological findings in subjects with adenomyosis uteri

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Summary
Objective: The purpose of this study was to compare the clinical symptoms and histopathological findings in subjects with adenomyosis uteri. Method: Infiltration depth and spread of adenomyotic foci together with clinical symptoms and findings were compared in a total of 103 subjects who had undergone hysterectomy and were diagnosed with adenomyosis uteri through histopathological examinations. Results: The spread of adenomyotic foci in myometrial tissues was observed to significantly increase as the depth of myometrial infiltration increased in subjects with adenomyosis (p < 0.05). It was observed that there was significantly higher myometrial infiltration depth in subjects with dysmenorrhea and severe anemia, and diffuse adenomyotic foci in subjects with menometrorrhagia (p < 0.05). Conclusion: Increased infiltration depth and spread of adenomyotic foci in myometrial tissues in subjects with adenomyosis uteri were studied. When clinical symptoms and findings in subjects with adenomyosis, such as dysmenorrhea, anemia and menometrorrhagia are compared with these histopathological findings, infiltration depth and spread of adenomyotic foci appear to determine the clinical severity of adenomyosis.

Key words: Adenomyosis uteri; Symptoms; Histopathology.

Introduction
Adenomyosis refers to the presence of islands of endometrial glands and stroma within the myometrium [1]. However, two important issues have to be mentioned within this description: 1) that the adenomyotic site is located away from the endometrial-myometrial junction at a distance further than 25% of full myometrial thickness, and 2) this site is surrounded by a myometrial hypertrophy, which does not exist at the endometrial-myometrial junction [2].

Symptoms associated with adenomyosis, such as dysmenorrhea, menometrorrhagia, dyspareunia and chronic pelvic pain have been considered to be related to adenomyotic foci within the myometrium. Although symptoms associated with adenomyosis such as dyspareunia, menstrual irregularities and pelvic pain are believed to be related to the depth of adenomyotic tissue within the myometrium, results of the studies on this topic are contradictory [3-6].

Recently interest on adenomyosis has increased because of the results of recent studies in which adenomyosis was reported to have similar symptoms to endometriosis, such as pelvic pain, dysmenorrhea and bleeding disorders, as well as being involved in etiologies of infertility and early abortion. However, the number of studies on adenomyosis is rather less when compared with those on endometriosis. In this study we aimed to investigate the comparison of clinical symptoms and histopathological findings in women with adenomyosis.
smoking habits; early pregnancy loss and infertility; symptoms such as bleeding disorders, chronic pelvic pain, dysmenorrhea and dyspareunia; history of previous uterine surgery, anemia and gynecological conditions accompanying adenomyosis.

The study data were statistically analyzed using SPSS software. The chi-square test was used for the comparison of categorical values, while a special test, namely Fisher’s exact test was used when the tables were in a 2 x 2 situation. Significance was determined as p < 0.05.

**Results**

The infiltration depth and spread of adenomyotic foci in 103 subjects is presented in Table 1. It can be seen that the rate of diffuse adenomyotic foci within myometrial tissue showed a significant increase together with the myometrial infiltration depth (p < 0.05). Patient characteristics and symptoms are summarized in Table 2. The mean age of all women was 50.3 ± 10.4, and no significant difference was observed between age, infiltration depth and spread of adenomyotic foci in subjects with adenomyosis (Table 1). Due to the estrogen effect on the etiopathogenesis of adenomyosis, the “cumulative time” with estrogen effect was calculated by considering the total duration of the reproductive periods of subjects, and the mean value of the duration of the reproductive period was determined as 33.91 ± 13.3 years in patients with adenomyosis (Table 2). Although it was not significant, spread of adenomyotic foci was found to be higher in subjects who had a longer duration of the reproductive period, while no significant difference was observed between the total duration of reproductive period and depth of infiltration (Table 3).

<table>
<thead>
<tr>
<th>Table 1. — Relationship between depth of infiltration and spread of adenomyotic foci.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltration depth of adenomyotic foci (n: 103)</td>
</tr>
<tr>
<td>Focal (n: 47)</td>
</tr>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>Group II</td>
</tr>
<tr>
<td>Group III</td>
</tr>
<tr>
<td>Group IV</td>
</tr>
</tbody>
</table>

*p < 0.05.

<table>
<thead>
<tr>
<th>Table 2. — Summary of patient characteristics and symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Reproductive period (years)</td>
</tr>
<tr>
<td>Menopause (%)</td>
</tr>
<tr>
<td>Oligomenorrhea (%)</td>
</tr>
<tr>
<td>Regular menstruation (%)</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
</tr>
<tr>
<td>History of previous uterine surgery (%)</td>
</tr>
<tr>
<td>One previous uterine surgery (%)</td>
</tr>
<tr>
<td>Two previous uterine surgeries (%)</td>
</tr>
<tr>
<td>Three previous uterine surgeries (%)</td>
</tr>
<tr>
<td>Four previous uterine surgeries (%)</td>
</tr>
<tr>
<td>Primary infertility (%)</td>
</tr>
<tr>
<td>Secondary infertility (%)</td>
</tr>
<tr>
<td>Early pregnancy loss (%)</td>
</tr>
<tr>
<td>Anemia (%)</td>
</tr>
<tr>
<td>Severe anemia (%)</td>
</tr>
<tr>
<td>Blood transfusion (%)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Menometrorrhagia (%)</td>
</tr>
<tr>
<td>Pelvic pain (%)</td>
</tr>
<tr>
<td>Dystmenorrhea (%)</td>
</tr>
<tr>
<td>Dyspareunia (%)</td>
</tr>
</tbody>
</table>

Thirty-three patients (32.04%) complained of pelvic pain (Table 2). The infiltration depth of adenomyotic foci was significantly higher in these subjects (p < 0.05; Table 3). When the subjects were evaluated with respect to their menstrual patterns, regular menstruation was found in 21 patients (20.4%), menopause in 31 patients (30.1%), menometrorrhagia in 47 patients (45.6%), and oligomenorrhea in four patients (3.9%) (Table 2). Diffuse adenomyotic foci were significantly higher in subjects with menometrorrhagia (p < 0.05; Table 3). Although not significant, infiltration depths of adenomyotic foci were found to be higher in women with menometrorrhagia.

Dysmenorrhea was observed in 26 patients (25.2%), while dyspareunia was observed in 19 patients (18.4%) (Table 2). Infiltration depth was found to be significantly higher in women with a history of dysmenorrhea (p < 0.05; Table 3) whereas the rates of diffuse adenomyotic foci were insignificantly higher in these women. No significant difference was found between dyspareunia, infiltration depth, and spread of adenomyotic foci. However, dyspareunia was determined to be more common in women with higher infiltration depth (groups C and D) and diffuse adenomyotic foci (Table 3).

When the subjects were evaluated with respect to parity, it was found that 22 subjects (21.4%) were nulliparous (Table 2). The difference between parity, infiltration depth, and spread of adenomyotic foci was not significant. However, the rate of diffuse adenomyotic foci observed in multiparous subjects was higher than that in nulliparous women (58% vs 42%, respectively).

Rate of smoking was found as 35.9% (37) among subjects (Table 2). Although not significant, it was observed that smoking was related to lower myometrial infiltration depth (groups A and B) and higher rates of focal adenomyotic foci (p > 0.05).
It was found that 63 (61.2%) of the subjects had a history of previous uterine surgery, such as pregnancy evacuation, uterine curettage and cesarean section, which would have a traumatic effect on the endometrial-myometrial junction (Table 2). Previous cesarean section, transcervical endometrial curettage or uterine evacuation were recorded only if performed more than six months prior to hysterectomy. The rate of diffuse adenomyotic foci with a high infiltration depth (groups C and D) was observed to be insignificantly higher in subjects with a history of previous uterine surgery. No significant difference was found between the number of previous uterine surgeries, spread, and infiltration depth of adenomyotic foci (Table 4).

Table 4. — Number of previous uterine surgeries in subjects with adenomyosis.

<table>
<thead>
<tr>
<th>No. of previous uterine surgeries</th>
<th>Infiltration depth of adenomyotic foci</th>
<th>Spread of adenomyotic foci</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n: 34)</td>
<td>0 (n: 44)</td>
<td>17.90%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Group II (n: 27)</td>
<td>1 (n: 34)</td>
<td>28.63%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Group III (n: 28)</td>
<td>2 (n: 34)</td>
<td>30.65%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Group IV (n: 14)</td>
<td>3 (n: 28)</td>
<td>32.45%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Focal (n: 47)</td>
<td>4 (n: 68)</td>
<td>29.75%</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Diffuse (n: 56)</td>
<td>5 (n: 80)</td>
<td>26.35%</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Table 5. — Indications for hysterectomy.

<table>
<thead>
<tr>
<th>Indications for hysterectomy</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoma uteri</td>
<td>47 (46%)</td>
</tr>
<tr>
<td>Associated gynecological conditions*</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Uterine prolapse</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Adnexal mass</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Menometrorrhagia+</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Cervical dysplasia</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Other gynecological malignancies</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

*: patients having more than one indication (myoma uteri, endometrial hyperplasia, menometrorrhagia, adenomyosis, endometriosis, adnexal mass, pelvic pain); +: medical therapy-resistant.

Table 6. — Histopathological findings of subject.

<table>
<thead>
<tr>
<th>Histopathological findings</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomyosis + myoma uteri</td>
<td>52 (50.48%)</td>
</tr>
<tr>
<td>Pure adenomyosis</td>
<td>25 (24.27%)</td>
</tr>
<tr>
<td>Adenomyosis + endometrial hyperplasia</td>
<td>9 (8.74%)</td>
</tr>
<tr>
<td>Adenomyosis + endometrial carcinoma</td>
<td>5 (4.85%)</td>
</tr>
<tr>
<td>Adenomyosis + endometriosis</td>
<td>3 (2.91%)</td>
</tr>
<tr>
<td>Adenomyosis + benign adnexal mass</td>
<td>3 (2.91%)</td>
</tr>
<tr>
<td>Adenomyosis + endometrial polyp</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Adenomyosis + cervical dysplasia</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Adenomyosis + other gynecological malignancies</td>
<td>2 (1.9%)</td>
</tr>
</tbody>
</table>

When we evaluated the women with respect to their infertility histories, we observed that two (1.9%) subjects had primary and five (4.6%) subjects had secondary infertility (Table 2). Eleven subjects (10.67%) had a history of early pregnancy loss (Table 2). Although not significant, spread and infiltration depth of adenomyotic foci were observed to be higher in women with a history of early pregnancy loss and infertility.

Anemia (hgb level < 12 g/dl) due to menometrorrhagia was observed in 27 patients (26.3%) (Table 2). No significant difference was observed between anemia, spread, and infiltration depth of adenomyotic foci. During the preoperative period, 14 subjects required a blood transfusion due to severe anemia (hgb level < 10 g/dl) (Table 2). Infiltration depth of adenomyotic foci was significantly related to preoperative requirement of blood transfusion (p < 0.05), where no significant difference was observed between the spread of adenomyotic foci and preoperative requirement of blood transfusion.

Indications for hysterectomy and histopathological findings in descending order of frequency are shown in Tables 5 and 6, respectively. According to the results of histopathological examinations, 25 (24.3%) out of 103 subjects had pure adenomyosis, while the remaining 78 subjects with adenomyosis had other associated gynecological conditions. The results obtained with histopathological examination of the subjects were in accordance with the operation indications, where myoma uteri was the most common histopathological diagnosis (52 subjects; 50.48%). The rate of diffuse adenomyosis was higher in subjects with pure adenomyosis than in subjects with adenomyosis-associated gynecological conditions, but the difference was not significant. The prevalence of endometriosis was 2.91% [3].

The mean uterus weight was 222.23 g in 103 subjects, whereas mean uterus weight in 25 (24.3%) subjects with pure adenomyosis and in 78 subjects with adenomyosis-associated gynecological conditions was 153.09 g and 242.31 g, respectively (p < 0.05). No significant difference was found between uterus weight, infiltration depth and spread, which determine the severity of the disorder.

Discussion

The mean age of women with adenomyosis has been reported to be between 40 and 60 years [7-9]. In a study where magnetic resonance imaging (MRI) was used for the evaluation of infertility, adenomyosis was most frequently seen in women in the second and third decades [10]. It has been reported that incidence of adenomyosis was about 17% in women who had undergone hysterectomy following cesarean section [11]. This study included women who had histopathologically confirmed adenomyosis. The mean age of the women was 50.3, which was also the average age group for hysterectomy operations. Through advancement and extensive use of alternative diagnostic methods for adenomyosis, apart from histopathological examination of hysterectomy material, the age groups in which adenomyosis is more frequently seen could be more accurately determined with MRI.

Adenomyosis is a condition in which ectopic endometrial glandular and stromal structures are embedded within the myometrium, while surrounded by a hyperplastic and hypertrophic myometrium layer. Symptoms associated with adenomyosis such as dysmenorrhea, menometrorrhagia, dyspareunia and chronic pelvic pain...
have been considered to be related to adenomyotic foci within the myometrium. The spread of these foci has been reported to be related to myometrial invasion depth in several studies [3, 4]. In the present study, the rate of diffuse adenomyotic foci with higher myometrial infiltration depth (groups C and D) showed a significant increase.

The results of immunohistochemical studies emphasize the influence of estrogen and progesterone on the etiology of adenomyosis [1, 12-15]. This hypothesis is supported by the fact that adenomyosis can be associated with pathologies such as leiomyoma, endometrial hyperplasia, endometrial cancer and endometrial polyps which are considered to have an estrogen effect in their etiology [7, 8, 16]. Similarly in this study, pure adenomyosis was observed in only 25 (24.3%) out of 103 adenomyotic cases. We observed that women with adenomyosis-associated gynecological conditions had diffuse adenomyotic foci with a higher infiltration depth (groups C and D) (in which the etiopathogenesis high estrogen activity is known to play a role, such as myoma uteri, endometrial polyps, endometrial hyperplasia and endometrial cancer, when compared with subjects with pure adenomyosis).

Although adenomyosis is generally associated with other gynecological conditions such as leiomyoma and endometrial hyperplasia, which are known to be related to high levels of estrogen, it is rarely seen together with endometriosis. This finding supports the idea that endometriosis and adenomyosis are two distinct pathologies [8, 17, 18]. Similarly in this study, pure adenomyosis was observed in only 24.27% [25] of the cases, while the most common histopathologic findings accompanying adenomyosis were descendingly ordered as myoma uteri 50.48% (52), endometrial hyperplasia 8.74% (9), endometrial cancer 4.85% (5), endometriosis 2.91% (3) and endometrial polyps 1.9% (2).

It has been suggested that early menarche, late menopause and bleeding disorders are related to adenomyosis. However, contradictory results have been reported in different studies. Some authors suggest that there is no relationship between adenomyosis and menstrual cycle patterns, age of menarche and menopause [7], while others believe that there is a strong correlation between adenomyosis and menstrual patterns [8].

The relation between total duration of the reproductive period and adenomyosis was evaluated in this study. Although duration of the reproductive period might be affected by conditions such as obesity, medications and pregnancy, it is the parameter that shows the whole period where the hormonal effects under suspicion in etiology do exist. High infiltration depth of of adenomyotic foci (groups C and D) was observed in women with longer reproductive periods. Additionally, low infiltration depth of adenomyotic foci (groups A and B) were determined in women where adenomyosis was not associated with any other gynecological conditions related to estrogen effects. These findings, which seem to support each other, were not significant.

Subjects with adenomyosis are reported to be asymptomatic with a rate of 35%. The most commonly observed findings, which are termed the adenomyosis triad, consist of menorrhagia (50%), dysmenorrhea (30%), and sensitive, symmetrically expanded uteri. Other less commonly seen symptoms that follow may be dyspareunia and chronic pelvic pain. These symptoms observed in adenomyosis are non-specific symptoms, and are also seen in gynecological conditions that may be associated with adenomyosis [12].

The reasons for menorrhagia in subjects with adenomyosis include impaired uterus contractions during menstruation due to affected myometrium, increased endometrial surface area, excessive secretion of prostaglandin and hyperestrogenism, while uterine irritability secondary to blood loss and pseudodesidual edema occurring around adenomyotic foci are reported to be causes of dysmenorrhea [4].

The most commonly observed symptoms in subjects with adenomyosis were menometrorrhagia, pelvic pain, dysmenorrhea, and dyspareunia in this study. There are many studies where the relationship between symptoms associated with adenomyosis and prevalence of the disorder and infiltration depth within the affected site have been investigated. It was reported that frequency of dysmenorrhea was directly related to infiltration depth [5, 6], while the extent of adenomyosis was correlated with dysmenorrhea-related menorrhagia with respect to spread and infiltration depth [4] in these studies.

A significant relationship was observed between infiltration depth and menometrorrhagia, and between infiltration depth and dysmenorrhea in this study. The rate of adenomyotic foci with high infiltration depth was significantly increased in subjects where a preoperative blood transfusion was required.

Adenomyotic foci do not consist of functional endometrium. However, a higher tendency for bleeding has been reported in adenomyotic foci with profound myometrial inhabitance, without any definitive explanation for this condition [19, 20]. This is in accordance with the findings in this study that there was a significantly high infiltration depth (groups C and D) in subjects who required blood transfusions during the preoperative period.

Contradictory results of studies where a relationship between symptoms and spread, and infiltration depth of adenomyotic foci in subjects were evaluated might be due to the fact that associated pathologies such as myoma uteri, endometrial hyperplasia, endometrial cancer and endometriosis were present with various frequencies in the women who took part in these studies.

It was reported that the uterus could reach a weight of 80-200 g in women with adenomyosis [12]. In a study where uterus weight was evaluated together with symptoms and histopathological findings, uterus weight in subjects only with adenomyosis was found to be significantly lighter than those in subjects with leiomyoma [21]. Mean uterus weight in subjects with adenomyosis was found as 222.23 g in this study. In subjects with pure adenomyosis and adenomyosis-associated gynecological
conditions, mean uterus weight was observed as 153.09 g and 242.31 g, respectively, p < 0.05. This difference, which is in accordance with the studies in the literature, appears to result from myoma uteri as an associated pathology. There was no significant relationship between uterus weight, infiltration depth and spread, which determine the severity of the disorder.

It has been reported in many studies that adenomyosis is more frequently seen in multiparous subjects [7-9, 16]. It was stated that aggressive trophoblastic activity during pregnancy could lead to an increase in adenomyotic sites within the myometrium, and this could also be predisposed by hormonal status during pregnancy [7].

In accordance with the literature, multiparous women were more frequently observed than nulliparous subjects with adenomyosis in this study (78.6% vs 21.4%, respectively). There was no significant difference between parity, spread and infiltration depth of adenomyotic foci, however, in accordance with the above-mentioned studies, in which prevalence of the disorder has been reported to increase during pregnancy, extensive adenomyosis was more frequently observed in multiparous subjects.

It has been stated that estrogen levels were lower in smokers, and accordingly adenomyosis was less commonly seen in smokers. Also the risks of myoma uteri and endometrial cancer were lower in smokers due to decreased levels of estrogen [7]. History of smoking was evident in 35.9% of the subjects with adenomyosis in this study. Although not significant, subjects who smoked had focal adenomyotic foci with a low infiltration depth (groups A and B). It seems to be characterized by focal adenomyotic foci and low infiltration depth (groups A and B) in smokers with adenomyosis.

There are studies where interferences such as early pregnancy termination and cesarean section are suggested to play a role in the etiology of adenomyosis and to cause iatrogenic weakness within the endometrial-myometrial junction, leading to invasion of endometrial glandular and stromal structures into the myometrium [2, 8, 17]. On the other hand, there are also studies where such interferences were shown to have no relationship with the development of adenomyosis [7]. The rate of subjects with a history of previous uterine surgery was found to be 61.2% in this study. Diffuse adenomyotic foci with high infiltration depth (groups C and D) were found in subjects with a history of previous uterine surgery. However, no significant differences were observed between the number of previous uterine surgeries and adenomyosis, with respect to both spread and infiltration depth of involvement.

The endometrial-myometrial junction consists of basal endometrium and subendometrial myometrium. This is the functional unit necessary for sperm transportation, embryonic implantation, placental development and menstruation [22]. Adenomyosis, whose etiology is considered to be effected by weakness in the endometrial-myometrial junction due to congenital or acquired factors [14-15, 23], might have a relationship with early abor-


tions and infertility. Moreover, patients with adenomyosis have also been shown to have high levels of nitric oxide which have a negative effect on embryonic implantation and the spermatozoon [24, 25].

Today, considerable advancements through technological developments have been achieved in infertility and the average age for the first pregnancy has increased. Therefore, adenomyosis can be diagnosed during investigations for infertility. It was reported in one study that adenomyosis was diagnosed by using magnetic resonance imaging in 14 (53.8%) out of 26 patients who were being examined for infertility, menorrhagia and dysmenorrhea [22].

The subjects evaluated in this study were often multiparous patients in the fourth or fifth decades. Therefore, histories of infertility and early abortion were also investigated. However, subjects with a history of infertility or early abortion were rather few in number. Seven subjects (6.5%) had a history of infertility, while 11 (10.8%) had a history of early abortion. Diffuse adenomyotic foci with high infiltration depth (groups C and D) were found to be insignificant in these subjects with histories of early abortion and infertility.

As a result, the relationship between adenomyosis and conditions under discussion could be further cleared up with higher numbers of subjects included in studies [26].

References

Clinical symptoms and histopathological findings in subjects with adenomyosis uteri


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Laparoscopic management of adnexal masses in postmenopause

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Summary
The study included 64 postmenopausal women with adnexal masses. The selection criteria included menopausal status, an ultrasound scan indicating a benign mass and serum levels of CA-125 below the cutoff (35 U/ml). The results of the study confirm that the removal of a cystic mass in postmenopausal patients with laparoscopic surgery is a more valid and acceptable alternative to traditional surgery.

Key words: Postmenopause; Adnexal mass; Laparoscopic surgery.

Introduction
In young fertile women, laparoscopic surgery is usually the treatment of choice for adnexal tumors. Indeed, laparoscopic surgery is a minimally invasive, effective technique with reduced risk of complications in both the short and long term. From a therapeutic viewpoint, postmenopausal women with adnexal masses present some problems that are mainly associated with a higher incidence of neoplastic disease in older women. Until a few years ago, the approach to ovarian masses in this class of patients was exploratory laparotomy, which allowed an earlier diagnosis and subsequent treatment of ovarian cancer [1]. Very often, even in the case of a benign ovarian tumor, it was customary to remove the uterus and adnexes as prophylaxis of neoplastic disease [2]. In recent years the improvement in ultrasonographic diagnostics has made it possible to define the morphological criteria indicative of a benign mass in the evaluation of adnexal lesions [3]. In addition, the introduction into clinical practice of tumor markers, especially the CA-125 marker [4,5], has made it possible to extend the laparoscopic approach with certain assuredness to the treatment of ovarian pathology also in postmenopausal women. The purpose of this study was to evaluate the feasibility and efficacy of laparoscopic surgery in this class of women through analyses of data collected in our clinic.

Materials and Method
The study was conducted on 64 women with adnexal masses who were admitted in our department for evaluation and treatment. The selection criteria included menopausal status, an ultrasound scan indicative of a benign mass, and serum levels of CA-125 below the threshold value of 35 U/ml. The patients enrolled in the study were between 48 and 81 years old. The mean age was 63.9 years with 56 patients older than 50 years of age (87.5%) and eight (12.5%) under 50. Seven were nulliparous (10.9%) and 57 pluriparous (81.1%) with the number of births ranging from one to five. All the patients were in menopause (range 1-30 years; mean 11.5 years). Patient weight ranged from 52 to 120 (mean 66.7 kg). Ten patients had been treated with interventions in the genital area: six had had a hysterectomy (abdominal or vaginal) for benign uterine pathologies preserving one or both of the ovaries, three had had cesarean sections, and one had undergone removal of an ovarian cyst. From a clinical standpoint, 34 patients (53.1%) reported abdominal pain and/or pelvic pain of varying intensity. Five women (7.8%) reported uterine bleeding, thus hysteroscopic evaluation of the endometrium was carried out giving negative results. Two patients (3.1%) reported urinary tract problems, while 23 patients (35.9%) were asymptomatic, with the adnexal mass being incidentally discovered by clinical or ultrasound (US) examination during a routine checkup. The week before hospitalization all patients were submitted to gynecological examination with an endovaginal ultrasound probe and blood tests for determination of CA-125 levels. Presurgical standard tests were carried out together with a new US examination to define the size and characteristics of lesions. The criteria used for the presumptive diagnosis of a benign mass were those proposed by ACOG (diaper less than 10 cm, no irregularities or thickening of the wall or large septum or endocystic excrescences, and absence of ascites) [6]. Serum samples of CA-125 were implemented using CA-125 Cobas Core Ria (Roche, Switzerland) with the value of 35 U/ml as the threshold (values less than 35 U/ml were considered normal). After obtaining written informed consent from all patients who met the requirements for surgery, laparoscopy under general anesthesia with endotracheal intubation was performed, always by the same medical team. After removal of the cystic mass, it was placed in a laparoscopic endobag after having been partially aspirated. All samples were sent for contemporaneous histological evaluation. The final anatomo-pathological assessment was performed by a pathologist blinded to the results of the US and...
CA-125 values. The decision to remove the entire uterus and adnexes or only the tumor was left to the surgeon, depending on the clinical situation. Surgery included unilateral salpingo-oophorectomy in 21 cases (32.8%), bilateral ovariectomy in 16 cases (25.0%), bilateral salpingo-oophorectomy in 25 cases (39.1%), and removal of only the mass in two cases (3.1%). Due to pelvic adhesions, additional adhesiolysis was performed in ten patients. The duration of the intervention was calculated by taking the time between the first surgical incision and the last suture point. All patients were submitted to the same protocol of postoperative care and were considered to be feverish when their body temperature was above 38°C two times or more during the postoperative 24-hour period.

Results

Laparotomic conversion was necessary for only one of the 64 patients who underwent laparoscopic surgery (1.6%), due to technical difficulties related to an extensive secondary adhesion syndrome, most probably associated with a previous laparotomic intervention. Adnexal masses had variable echographic sizes: diameters ranged between 4 and 12 cm, with a mean of 6.8 cm. The serum value of CA-125 ranged between 2.9 and 34.2 U/ml, with a mean of 15.5 U/ml. In 35 cases the pelvic mass was located in the right adnexa (54.6%), in 27 cases in the left (42.2%), while in two cases (3.2%) there also was a small lesion in the contralateral adnexa. Histological examination of the surgical specimen showed no pathological alteration with evidence of malignancy in any case. Histological reports showed 24 serous cysts, 12 serous cystadenomas, six mucinous cystadenomas, six dermoid cysts, eight fibrothecomas, three inclusion cysts, two paraovarian cysts, two endometriotic cysts, and one cystic lymphangioma. Interventions varied from 40 to 70 minutes with a mean duration of 55 min. There were no intraoperative complications except for one case which was converted to laparotomy due to difficulties previously mentioned. There were also no important postsurgical complications and patients were discharged the day after the operation, except for eight women who were discharged two days after as they lived far away. All patients were asked to report any symptoms arising on the day after the operation, except for eight women who were discharged two days after as they lived far away. All patients were submitted to the same protocol of postoperative care and were considered to be feverish when their body temperature was above 38°C two times or more during the postoperative 24-hour period.

Discussion

Today, much attention is focused on the menopausal period and the use of ultrasound techniques which allow easier identification of expansive adnexal pathology in menopausal and postmenopausal patients. Until a couple of years ago, an adnexal mass required a laparotomic intervention which almost always ended up in demolitive surgery. This approach, even after great progress in the anesthesiological, surgical, and medical fields, can in some circumstances become burdensome and risky due both to the age of the patient and to her clinical condition. Although the first application of laparoscopic surgery in postmenopausal patients dates back more than 15 years ago [7], there are still few data in the literature. In many cases, these data do not meet the criteria for homogeneity because they do not exclusively include postmenopausal patients, rather, they also include women with biochemical and ultrasonographic characteristics suspicious for malignancy. When confronted with an unexpected malignant neoplasia, the laparoscopic approach to adnexal masses is still a major controversy for a number of diagnostic and therapeutic problems related to the failure of the diagnosis of ovarian malignancy, tumor rupture, inadequate staging and surgical treatment, and delay in chemotherapy [8, 9]. In our study, using specific US criteria for a benign mass and values of CA-125 below the threshold allowed us to have a careful selection of patients eligible for laparoscopy. The validity of this association is confirmed by the negative histological results for malignancy. In light of the importance of adopting strict criteria for the evaluation of adnexal masses, especially in menopausal and postmenopausal women, the results of our study and others confirm the reliability of the combination of ultrasonographic and biochemical data in the evaluation of this type of pathology [10-12]. In our study, the percentage of conversions from laparoscopic surgery to laparotomy was slightly lower than that found in the literature, which ranges from 5% to 8% [13]. This result is probably due to the homogeneity of data, the fact that our study is the most recent and reflects continuing improvements in the laparoscopic technique, the small number of enrolled patients and, last but not least, the rigorous selection of the patients that were submitted to endoscopic treatment. Data related to the duration of intervention (55 min), postoperative complications, and shorter hospital stay are similar to data reported in the international literature – some small differences are probably dependent on the healthcare organization [14]. Thus the laparoscopic approach for this type of pathology comprises a reduced hospital stay, lower incidence of complications, and a faster return to normal activities. Laparoscopic surgery also offers significant medical and psychological advantages in this category of women resulting in better acceptance by the patient and a lower impact on the health economy. In conclusion, we can confirm that laparoscopic surgery for benign adnexal masses in postmenopausal women can be a viable alternative, provided...
that these patients are submitted to a thorough ultrasonographic evaluation and to tumor-marker evaluation, which can reassure us as to the benign nature of these tumors.

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Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomized, prospective, controlled clinical trial in female smokers

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Summary

Objective: To compare the efficacy of three progestin regimens in perimenopausal menorrhagia. Design: One hundred thirty-two women with menorrhagia were included in this prospective, randomized, comparative trial. Women were randomized to three groups of 44 in each, either to get a single shot of depot medroxyprogesterone acetate, intramuscularly (Group 1), or medroxyprogesterone acetate in a daily dose of 5 mg orally (Group 2), or the levonorgestrel releasing intrauterine system (LNG-IUS) (Group 3). The Mann-Whitney U-test was applied to compare independent groups. Results: Pictorial blood loss assessment chart (PBAC) score, the duration of bleeding and mean hemoglobin level were improved in all groups. Comparing the groups we noted that for the PBAC, there was no statistically significant difference between groups 1 and 2, while group 3 was superior to both groups 1 and 2 (p < 0.05 and p < 0.05, respectively). Mean duration of menstruation showed no differences among the groups. Hemoglobin levels were no statistically significant differences between groups 1 and 2, while group 3 was superior to both groups 1 and 2 (p < 0.05 and p < 0.05, respectively). Conclusion: The efficacies of oral and intramuscular medroxyprogesterone acetate in the treatment of menorrhagia were comparable each other, however, the efficacy of LNG-IUS was superior to both.

Key words: Menorrhagia; Perimenopause; Progestin; Medroxyprogesterone acetate; LNG-IUS.

Introduction

Dysfunctional uterine bleeding is one of the most common complaints during the perimenopausal transition [1]. It is defined as abnormal bleeding in the absence of pelvic organ disease or systemic disease and therefore is a diagnosis of exclusion. It is estimated that a woman has a life-time chance of 1: 20 to consult her gynecologist for complaints due to dysfunctional uterine bleeding [2]. Twenty-five percent of all gynecologic operations center around the clinical problem of abnormal uterine bleeding during this period [3]. Perimenopausal bleeding disorders can be challenging for the clinician. The differential diagnosis in recent years is vast, as anatomic, hormonal, and metaplastic processes have a higher incidence.

Dysfunctional uterine bleeding can be anovulatory, characterized by irregular unpredictable bleeding, or ovulatory, characterized by heavy but regular periods (i.e., menorrhagia) [4]. On the other hand, anovulation can manifest in different ways, ranging from amenorrhea to intermittent spotting to erratic, prolonged, heavy menses. This further adds to the difficulty of the diagnosis and the management. Ten to thirty percent of menstruating women experience menorrhagia during their reproductive lives, especially at the both ends of the reproductive period [5].

Since only 40-50% of the women who complain of heavy menstrual bleeding suffer from objective menorrhagia, it is important to quantify the amount of menstrual blood loss. To obtain a semi-quantitative measurement of menstrual blood loss, Higham et al. developed a pictorial blood loss assessment chart [6]. Jansen et al. investigated the usefulness of a modified pictorial chart in a large study, and recommended a cut-off score of 185 for the diagnosis of menorrhagia [7]. Although the use of a pictorial chart might implicate misclassification of menorrhagia, the method is clearly more accurate than history alone. Menstrual blood loss can be measured objectively by the alkaline hematin method, which defines a cut-off score for menorrhagia of 80 ml per cycle. However, patient selection in dysfunctional uterine bleeding trials is often not defined, such as blood loss in excess of 80 ml or as increase in pictorial chart score.

Progestins are the cornerstone of most hormonal treatments of menorrhagia. Progestins mediate downregulation of endometrial estrogen receptors to blunt proliferation. They facilitate the conversion of estradiol to less potent estrone through activation of 17-β hydroxysteroid dehydrogenase [8]. Progestin treatment in dysfunctional uterine bleeding can be given in various forms and dosages and protocols [9-11]. For the last decade, progestin-delivering intrauterine devices have introduced a novel modality for progestin treatment. The levonorgestrel releasing intrauterine system (LNG-IUS) was developed for contraceptive purposes, but also provides...
several noncontraceptive health benefits. Experience in women using Mirena (releasing 20 mcg levonorgestrel a day) for contraception demonstrated a significant decrease in menstrual flow [12].

The objective of the present trial was to compare the efficacy of continuous oral or intramuscular medroxyprogesterone acetate to levonorgestrel-releasing intrauterine system in perimenopausal women with menorrhagia.

Material and Method

Patient selection

Four hundred and five perimenopausal patients were admitted to our center because of irregular and/or heavy vaginal bleeding between August 2005 and May 2006. The term “peri-menopause” refers to women over age 40 in this study. The diagnosis of menorrhagia was established after the following diagnostic work-up: Hemogram, modified pictorial blood loss assessment chart, prothrombin time, activated partial thromboplastin time, ALT, AST, hormonal profile including FSH, LH, estradiol, prolactin, β-HCG, sTSH, T₄, T₃, Pap smear, endometrial biopsy, transvaginal sonography and saline infusion sonography, and diagnostic office hysteroscopy when needed. Patients were not included in the study when an organic pathology was found.

Using this evaluation protocol, 32 women were excluded because they were having only irregular bleeding but were non-menorrhagic; they were given cyclic progestin treatment. Of the rest, 229 patients were nonsmokers and were given combined oral contraceptive pills; they were not included in the study. One hundred and forty-four women were diagnosed as menorrhagic, but 12 of them refused to participate in the study. One hundred and thirty-two were included in the study. Institutional Review Board approval and signed informed consents were obtained.

Baseline demographic characteristics were as follows: mean age was 43.8 ± 2.9 years, mean parity was 1.9 ± 0.6, mean BMI was 27.9 ± 4.7 kg/m², and the percentage of smokers was 100% because the non-smokers were given combined oral contraceptive pills. Occasional smokers were also excluded. Forty-four patients were scheduled for each arm of the study. Randomization was performed by a predefined application order. The first applicant to the first group, the second applicant to the second group and the third applicant to the third group, and so on.

Treatment groups

Group 1 consisted of 44 women who were given a single shot of depot medroxyprogesterone acetate (DMPA) (Depo Provera ampoule, Eczacibasi, Istanbul, Turkey) intramuscularly on the first day of the cycle.

Group 2 consisted of 44 women who were given daily medroxyprogesterone acetate (MPA) (Farlutal tablets, Deva, Istanbul, Turkey) in a dose of 5 mg orally every day, starting on the first day of the cycle.

Group 3 consisted of 44 women who received the LNG-IUS (Mirena, Schering, Berlin, Germany) on the second or third day of the cycle. Patients were not prescribed iron supplements and were advised to stay on their usual diet.

Demographic characteristics of the patients randomized to groups are given in Table 1.

Patients continued to give blood samples for hemograms every month and continued to record a modified pictorial blood loss assessment chart (PBAC) score for each treatment cycle.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>43.1 ± 1.6</td>
<td>42.6 ± 1.9</td>
</tr>
<tr>
<td>Mean parity (number)</td>
<td>1.8 ± 0.4</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>27.1 ± 4.4</td>
<td>26.4 ± 3.9</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

MPA: medroxyprogesterone; DMPA: depot medroxyprogesterone; LNG-IUS: levonorgestrel releasing intrauterine system.

When the menstrual blood loss score was > 185 on the PBAC in the second treatment cycle it was considered as unresponsiveness to the treatment. Response was pre-defined as a score < 185 in the modified PBAC and stabilization and/or any increase of hemoglobin level.

Patients were followed-up for six months. No drop-outs occurred in any arm of the study.

Statistical analysis

Statistical analyses were performed using SPSS 10.0 (Chicago, USA). Pretreatment values were compared to treatment cycle 2 values. The Mann-Whitney U-test was applied to compare two independent groups. A p value of < 0.05 was accepted as statistically significant.

Results

In group 1 the treatment was successful in 33 of 44 women (75%). The modified pictorial blood loss assessment chart score decreased significantly in the second treatment cycle, from 284 ± 50 units to 146 ± 21 units (p < 0.001). The duration of bleeding was 9 ± 2 days pretreatment, which decreased to 7 ± 1 days in the second cycle of the treatment (p < 0.001). Mean hemoglobin level was 9.7 g/dl pretreatment and it increased to 10.2 g/dl in the second cycle of the treatment (p < 0.01) (Table 2).

<table>
<thead>
<tr>
<th>Group 1 (DMPA)</th>
<th>Group 2 (daily MPA)</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.7 ± 0.4</td>
<td>10.2 ± 0.4</td>
</tr>
<tr>
<td>Mean duration of menstruation (days)</td>
<td>7-11</td>
<td>5-8</td>
</tr>
</tbody>
</table>

In group 2 the treatment was successful in 30 of 44 women (68%). The modified PBAC score decreased significantly at the second treatment cycle, from 230 ± 36 units to 154 ± 30 units (p < 0.001). The duration of bleeding was 9 ± 1 days pretreatment, which decreased to 5 ± 1 days in the second cycle of the treatment (p < 0.001). Mean hemoglobin level was 10.2 g/dl pretreatment and it increased to 10.8 g/dl in the second cycle of the treatment (p < 0.01) (Table 3).

In group 3 the treatment was successful in 38 of 44 women (86%). The modified PBAC score decreased significantly in the second treatment cycle, from 287 ± 57 units to 77 ± 41 units (p < 0.001). The duration of bleed-
Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system etc. 59

Table 3. — Results in the daily medroxyprogesterone acetate (MPA) group.

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Cycle 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pictorial blood loss score (units)</td>
<td>230 ± 36</td>
<td>154 ± 30</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Mean duration of menstruation (days)</td>
<td>9±1</td>
<td>5±1</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.2 ± 0.7</td>
<td>10.8 ± 0.7</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Willing to continue 25/44 (56.8%) 19/44 (43.1%) 38/44 (86.3%)

Breast tenderness 9/44 (20.4) 12/44 (27.2) 6/44 (13.6)

Irregular bleeding 9/44 (20.4) 12/44 (27.2) 6/44 (13.6)

Table 4. — Results in the LNG-IUS group.

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Cycle 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pictorial blood loss score (units)</td>
<td>287 ± 57</td>
<td>77 ± 41</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Mean duration of menstruation (days)</td>
<td>9 ± 2</td>
<td>5 ± 2</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.1 ± 0.4</td>
<td>10.9 ± 0.4</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Comparing the groups, we noted that there was no statistically significant difference between groups 1 and 2 in PBAC score while group 3 was superior to both groups 1 and 2 (p < 0.05 and p < 0.05, respectively). For mean duration of menstruation there was no difference among the groups. For hemoglobin levels there was no statistically significant difference between groups 1 and 2, while group 3 was higher to both groups 1 and 2 (p < 0.05 and p < 0.05, respectively). Comparisons are given in Table 5.

Table 5. — Comparisons between groups.

<table>
<thead>
<tr>
<th></th>
<th>DMPA vs daily MPA</th>
<th>DMPA vs LNG-IUS</th>
<th>Daily MPA vs LNG-IUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pictorial blood loss score (units)</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Mean duration of menstruation (days)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>NS</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Common side-effects of progestin treatment are irregular bleeding and mineralocorticoid effects as manifested by breast tenderness. Side-effects are shown in Table 6. There were no significant differences between DMPA and daily MPA groups (20.4% vs 27.2%), while there were fewer side-effects in the LNG-IUS group (13.6%). Patients were asked whether they were willing to continue the treatment. Twenty-one in group 1 (56.8%), 19 in group 2 (43.1%), and 38 in group 3 (86.3%) agreed to continue the treatment.

Table 6. — Side-effects.

<table>
<thead>
<tr>
<th></th>
<th>DMPA (%)</th>
<th>Daily MPA (%)</th>
<th>LNG-IUS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular bleeding</td>
<td>9/44 (20.4)</td>
<td>12/44 (27.2)</td>
<td>6/44 (13.6)</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>9/44 (20.4)</td>
<td>12/44 (27.2)</td>
<td>6/44 (13.6)</td>
</tr>
<tr>
<td>Willing to continue</td>
<td>25/44 (56.8%)</td>
<td>19/44 (43.1%)</td>
<td>38/44 (86.3%)</td>
</tr>
</tbody>
</table>

Discussion

Several theories have been proffered to elucidate the hormonal mechanisms responsible for perimenopausal bleeding. In one theory, ovulation occurs but with a longer follicular phase, during which there is a slow rise in the estrogen level. This slow rise in proliferative stimulus from estrogen causes the endometrium to proliferate excessively. This lengthened follicular/proliferative phase thus leads to a heavier/longer menstruation after progestosterone is withdrawn [13]. A prospective analysis using age matched controls for perimenopausal women over the age of 40 with menometrorrhagia determined that higher levels of serum estradiol (0.55 vs 0.24 nmol/l) were noted in the abnormal group, but with no significantly different FSH levels [14].

Progestins are able to induce a secretory transformation in otherwise estrogen-stimulated proliferative endometrium. Progestins halt endometrial growth and allow for an organized sloughing of the endometrium. They also increase the PGE2/PgE ratio by stimulating arachidonic acid formation in the endometrium, which may also contribute to decreasing abnormal uterine bleeding [11]. Continuous progestin is administered with the rationale of inducing endometrial atrophy and preventing estrogen stimulated endometrial proliferation, resulting in diminished blood loss during menopause.

It is almost routine practice to give a hormonal treatment regimen for perimenopausal dysfunctional uterine bleeding. For hormonal treatment of menorrhagia, women can be offered either oral contraceptives or progestins. The decision between oral contraceptives and progestins is often based on contraindications to estrogen, most commonly smoking. In our group the percentage of smokers was 100% because the non-smokers were allocated to another mode of treatment.

To our knowledge, there is no study evaluating the continuous use of progestins for meno-metrorrhagia. Most studies in the literature compare regimens such as antifibrinolytics, nonsteroids, combined contraceptives, and the LNG-IUS to norethindrone, administered in the luteal phase of women having menometrorrhagia. Because menometrorrhagia is not due to a deficiency of progestin, studies comparing norethisterone to mefenamic acid [15], danazol [16], and tranexamic acid [17] all suggest that there is no benefit to administering oral progestin in the luteal phase.

Given as a 21-day course from cycle days 5-26, a low-dose (2.5 mg/day) medroxyprogesterone acetate reduced blood loss substantially [18]. When 5 mg of norethindrone was given three times a day, menstural blood loss was reduced by 87%. However, this therapy was poorly tolerated; 78% of women refused to continue the therapy beyond three months [19]. Daily low-dose (2.5-5 mg/day) medroxyprogesterone has been used to treat women with ovulatory menorrhagia with anecdotal success; but there has been no clinical trial yet. In our study 5 mg of daily medroxyprogesterone acetate showed a comparable effect on menorrhagia with depot medroxyprogesterone acetate and LNG-IUS.
Continuous systemic therapy with depot medroxyprogesterone acetate is generally more effective, better tolerated, and longer acting than high-dose oral progestins. DMPA effectively suppresses ovarian steroidogenesis and thus reduces estrogen stimulation of the endometrium. DMPA exerts powerful atrophic effects on the endometrial cells. There are no published studies testing the impact of DMPA in women with menorrhagia, although it is often used in clinical practice for this indication. Our results show for the first time that DMPA can be successfully used in the treatment of menorrhagia.

The efficacy of the LNG-IUS in the treatment of menorrhagia has been studied in numerous clinical trials. In a study in which it was the sole treatment for menorrhagia, the LNG-IUS caused an 86% decrease in menstrual blood loss in the third month after insertion and a 97% decrease in the 12th month [12]. Five other studies that investigated the effects of the LNG-IUS on menorrhagia confirmed the effectiveness of the LNG-IUS in markedly reducing menstrual blood loss from 85% to 97% for up to three years after insertion [20]. In addition, the LNG-IUS increased hemoglobin and serum ferritin levels [21].

The LNG-IUS has demonstrated superiority over other medical therapies in comparative clinical trials. In their 2005 Cochrane review, Lethaby et al. concluded that the LNG-IUS is more effective than cyclical norethisterone (for 21 days) as a treatment for heavy menstrual bleeding [22]. Milsom et al. [23] compared the LNG-IUS directly with oral medications. Flurbiprofen and tranexamic acid reduced menstrual blood loss by 21% and 44%, respectively, while the LNG-IUS reduced menstrual blood loss by 82% after three months, 88% after six months, and by 96% after 12 months. Irvine found that the LNG-IUS and oral norethisterone given days 5-26 in the cycle reduced blood loss significantly, but more women in the LNG-IUS group were amenorrheic and willing to continue the therapy at the end of the trial [18]. When Reid compared the LNG-IUS with mefenamic acid in a 6-month trial, he found that LNG-IUS users had a greater decrease in blood loss, but no higher rates of discontinuation [24]. In our study, menstrual blood loss was significantly lower in the LNG-IUS group.

Although the power of the study does not allow us to draw strong conclusions, the results of the current study are considerable, because to the best of our knowledge this is the only study comparing all the different modes of delivery of progestins in menorrhagia.

In conclusion, the efficacies of oral and intramuscular medroxyprogesterone acetate in the treatment of menorrhagia were comparable each other. However, the efficacy of the LNG-IUS was superior to both. Moreover, patient compliance was much better in the LNG-IUS group.

References


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Cervicovaginal fetal fibronectin (FFN) for prediction of preterm delivery in symptomatic cases: a prospective study

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Department of Obstetrics and Gynecology, Perinatology Unit, Eskisehir Osmangazi University School of Medicine, Eskisehir (Turkey)

Summary

**Objective:** To assess the clinical value of cervicovaginal fetal fibronectin (FFN) in the prediction of preterm delivery (PTD) in women with signs and symptoms of preterm labor (PTL). **Method:** This investigation prospectively studied a cohort of 65 women with symptoms of PTL, between 24 and 37 weeks’ gestation with < 3 cm of cervical dilatation and intact membranes. Cases were evaluated in terms of maternal demographic characteristics like age, body mass index, number of parities, previous PTL history, Bishop scores at admission, gestational age at delivery, mode of delivery, use of tocolytic or steroids, presence of histologic chorioamnionitis, neonatal outcomes and delivery before 34 weeks’ gestation as well as within seven days of admission. **Results:** A total number of 68 cases were included in the study. There were no statistically significant differences between positive and negative FFN groups in terms of maternal characteristics, mode of delivery and adverse neonatal outcomes. However, FFN + cases had higher Bishop scores on admission (3.4 ± 1.2 vs 2.5 ± 0.3, p = 0.03) and lower gestational age at delivery (33.4 ± 3.1 weeks vs 36.8 ± 2.1 weeks, p = 0.002). Likelihood ratio (LR) for positive results was 1.83 (95% CI: 1.61-2.26) for predicting birth before 34 weeks’ gestation, with a corresponding negative LR of 0.62 (95% CI: 0.3-1.2). LR for positive results was 4.34 (95% CI: 3.65-5.12) for predicting birth within seven days of testing, with a corresponding negative LR of 0.3 (95% CI: 0.2-0.5). **Conclusion:** Based on the results of cervicovaginal FFN, positive tests represent an increased likelihood of PTD among women with symptoms of threatened preterm labor.

**Key words:** Preterm labor; Fetal fibronectin; Preterm delivery; Prediction.

Introduction

Preterm labor complicates 8% to 12% of all deliveries and is responsible for 70% of perinatal mortality and morbidity [1]. The prediction and prevention of preterm birth have proven to be an obstetric challenge. The identification of women at risk of preterm delivery would allow the initiation of important interventions to delay delivery and to improve perinatal outcome, such as maternal transfer to a tertiary-care center, tocolysis and corticosteroid therapy [2]. Current evidence supports the screening of preterm delivery by maternal obstetric history, cervical ultrasonography, and several biomarkers in the serum and cervicovaginal secretions [3-5]. These above-mentioned markers have been extensively studied. Other markers like the presence of bacterial vaginosis, interleukin (IL)-6, ferritin, and granulocyte colony-stimulating factor levels have also been assessed, several of which have predictive values potentially useful for clinical practice [5, 6].

Fetal fibronectin (FFN) is a glycoprotein found in amniotic membranes, decidua, and cytotrophoblasts. The appearance of FFN in cervicovaginal secretions in the late second and early third trimester represent disruption of the chorio-decidual surface, leading to spontaneous preterm birth [7]. This prospective cohort study was conducted to assess the previously described association of FFN with preterm delivery (PTD) in women with symptoms suggestive of premature labor in whom no prior tocolytic treatment was initiated.

Materials and Methods

Approval for this study was obtained from the Institutional Ethical Board and all the authors conformed to the Declaration of Helsinki during the study period. This investigation prospectively studied a cohort of 65 women with symptoms of PTL, between 24 and 37 weeks’ gestation with < 3 cm cervical dilatation and intact membranes, from January 2004 to July 2006. Symptoms suggestive of preterm labor included regular uterine contractions, low back pain, minimal vaginal bleeding and increased vaginal discharge. Cases were excluded if they had cervical cerclage, massive vaginal bleeding, tocolysis at admission, or cervical manipulation such as vaginal douche, intercourse or digital examination within the previous 24 hours, preeclampsia, diabetes mellitus, hyperthyroidism or asthma. Symptomatic treatment included intravenous ritodrine hydrochloride or magnesium sulphate. Ritodrine hydrochloride was given as an intravenous infusion of 50-100 μg/min in a 5% dextrose solution in water and increased by 50 μg/min every 20 min until adequate tocolysis was achieved or up to a maximum dose of 350 μg/min. Magnesium sulphate was given as a bolus dose of 4 g in 100 ml saline solution, followed by a maintenance dose of 2 g/hour as an intravenous infusion. A total intramuscular dose of 24 mg betamethasone was given (12 mg) twice daily to enhance fetal lung maturation. Mode of delivery was dependent on obstetric indications. During the initial physical examination, a speculum was introduced into the vagina before digital examination. The FFN specimen collection kit (QuickCheck iPTN, Adea Biochemical Cooperation, Sunnyvale, CA) contains a dacron® swab (Dupont, Kinston, NC) an a buffer-filled collection tube. The dacron
polyester swab was rolled against the posterior lip of the cervix. The collected specimen was placed in a buffer solution and sealed within the collection tube. All samples were sent to the hospital laboratory and the FFN was processed by monoclonal antibody ELISA rapid assay (Adeza), with results available within 30 minutes. All the digital examinations were made by a single experienced physician.

Results were blinded to managing obstetricians during the study. Decisions on tocolytic and steroid use after specimen collection were made by managing physicians. Positive and negative FFN cases were evaluated in terms of maternal demographic characteristics like age, body mass index (BMI), number of parities, previous PTL history, smoking status, number of pregnancies from assisted reproductive techniques (ART), Bishop scores at admission, gestational age at delivery, mode of delivery, use of tocolytics, antibiotics or steroids, presence of histologic chorioamnionitis, neonatal outcomes such as birthweight, Apgars scores, days in the neonatal intensive care unit (NICU), newborn sepsis, neonatal death, and delivery before 34 weeks' gestation as well as within seven days of admission. A positive test was defined as a fetal fibronectin concentration > 50 ng/ml. Histological chorioamnionitis was defined by the criteria of Salafia et al. [7].

Statistical analysis was performed using the SPSS 10.0 (SPSS10.0, Chicago, IL, USA) statistical package. Results are presented as the mean ± standard deviation. Patient demographic characteristics were analyzed by the Student’s t-test, and the chi-square test was used for discrete variables. Univariate and multivariate logistic regression analyses were performed to evaluate the association of various confounding variables and FFN with the outcome of pregnancy. Kaplan-Meier curves were compared with the Wilcoxon log-rank test. Statistical significance was assumed at p < 0.05. The sample size was predetermined using a power analysis. We calculated 68 patients would be required to demonstrate a significant association between FFN and the outcome of pregnancy. Kaplan-Meier curves were determined by univariate analysis of confounding factors to determine deliveries < 34 weeks' gestation.

### Table 1. Maternal and neonatal characteristics of cases with cervicovaginal positive and negative FFN (ns: not significant).

<table>
<thead>
<tr>
<th>FFN test</th>
<th>(+) (n = 36)</th>
<th>(−) (n = 32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.5 ± 3.5</td>
<td>28.3 ± 2.3</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 1.2</td>
<td>26.7 ± 1.2</td>
<td>ns</td>
</tr>
<tr>
<td>Gravity (n)</td>
<td>2.1 ± 1.2</td>
<td>2.2 ± 1.4</td>
<td>ns</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>0.69 ± 0.7</td>
<td>0.69 ± 0.2</td>
<td>ns</td>
</tr>
<tr>
<td>Abortion (n)</td>
<td>1.7 ± 0.6</td>
<td>1.5 ± 0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Gestational age on admission (weeks)</td>
<td>31.1± 2.5</td>
<td>30.6 ± 2.3</td>
<td>ns</td>
</tr>
<tr>
<td>History of abortion (n)</td>
<td>10</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td>Tocolytic use (n)</td>
<td>34</td>
<td>29</td>
<td>ns</td>
</tr>
<tr>
<td>Cesarean delivery (n)</td>
<td>14</td>
<td>15</td>
<td>ns</td>
</tr>
<tr>
<td>Vaginal delivery (n)</td>
<td>21</td>
<td>18</td>
<td>ns</td>
</tr>
<tr>
<td>Histological chorioamnionitis (n)</td>
<td>11</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Bishop score on admission</td>
<td>3.4 ± 2.1</td>
<td>2.5 ± 2.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Cervical dilatation on admission (cm)</td>
<td>1.8 ± 1.2</td>
<td>1.4 ± 1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Cervical effacement on admission (%)</td>
<td>32.2±10.5</td>
<td>29.0 ± 10.3</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of tocolysis (days)</td>
<td>7.1 ± 1.3</td>
<td>5.9 ± 2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>33.4 ± 3.1</td>
<td>36.8 ± 2.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Time from admission to delivery (days)</td>
<td>10.3±4.5</td>
<td>23.2 ± 9.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Apgar score (1 min)</td>
<td>6.5 ± 2.1</td>
<td>6.9 ± 2.2</td>
<td>ns</td>
</tr>
<tr>
<td>Apgar score (5 min)</td>
<td>8.4 ± 1.5</td>
<td>8.6 ± 1.7</td>
<td>ns</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2514 ± 716</td>
<td>2796 ± 784</td>
<td>0.04</td>
</tr>
<tr>
<td>Days in NICU</td>
<td>4.96 ± 5.9</td>
<td>4.51 ± 6.1</td>
<td>ns</td>
</tr>
<tr>
<td>Newborn sepsis (n)</td>
<td>2</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Neonatal death (n)</td>
<td>3</td>
<td>1</td>
<td>ns</td>
</tr>
</tbody>
</table>

NICU: neonatal intensive care unit.

### Table 2. Univariate analysis of confounding factors to determine deliveries < 34 weeks' gestation.

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.86-1.11</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.07</td>
<td>0.93-1.24</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>1.70</td>
<td>0.38-7.55</td>
</tr>
<tr>
<td>History of PTL</td>
<td>4.89</td>
<td>1.21-19.76</td>
</tr>
<tr>
<td>pH IGFBP-1 +</td>
<td>55.2</td>
<td>9-335</td>
</tr>
<tr>
<td>Bishop score</td>
<td>1.16</td>
<td>0.87-1.55</td>
</tr>
<tr>
<td>Cervical dilatation</td>
<td>1.31</td>
<td>0.76-2.55</td>
</tr>
<tr>
<td>Cervical effacement</td>
<td>1.02</td>
<td>0.98-1.03</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>1.03</td>
<td>0.9-1.9</td>
</tr>
<tr>
<td>Histological chorioamnionitis</td>
<td>1.38</td>
<td>0.32-5.86</td>
</tr>
</tbody>
</table>

### Table 3. Univariate analysis of confounding factors to determine the deliveries within 7 days of admission.

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.83-1.12</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.91</td>
<td>0.81-1.03</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>0.60</td>
<td>0.16-2.22</td>
</tr>
<tr>
<td>History of PTL</td>
<td>3.23</td>
<td>0.86-12.09</td>
</tr>
<tr>
<td>FFN (+)</td>
<td>14.6</td>
<td>4.3-49.9</td>
</tr>
<tr>
<td>Bishop score</td>
<td>1.30</td>
<td>1.01-1.66</td>
</tr>
<tr>
<td>Cervical dilatation</td>
<td>1.63</td>
<td>1.03-2.57</td>
</tr>
<tr>
<td>Cervical effacement</td>
<td>1.02</td>
<td>0.99-1.05</td>
</tr>
<tr>
<td>Tocolysis</td>
<td>0.24</td>
<td>0.02-2.44</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>0.61</td>
<td>0.20-1.80</td>
</tr>
<tr>
<td>Histological chorioamnionitis</td>
<td>0.82</td>
<td>0.24-2.75</td>
</tr>
</tbody>
</table>

Results

In this cohort, the rate of preterm delivery before 37 and 34 weeks was 19.1% (13/68) and 8.8% (6/68), respectively. As shown in Table 1, there were no statistically significant differences between FFN positive and negative groups in terms of maternal characteristics, mode of delivery and adverse neonatal outcomes. However, positive FFN cases had higher Bishop scores on admission (p = 0.04) and longer duration of tocolysis (p = 0.01) but lower gestational age at delivery (p = 0.002), time from admission to delivery (p = 0.003 and birthweight (p = 0.04). As shown in Table 2, univariate analysis showed that the strongest predictors of PTD < 34 weeks’ gestation was FFN positivity (RR: 55.2, 95% CI: 9-335, p < 0.001) and the history of PTL (RR: 4.89, 95% CI: 1.21-19.76, p = 0.02). For deliveries within seven days of admission, FFN positivity (RR: 14.6, 95% CI: 4.3-49.9, p < 0.0001), Bishop score (RR: 1.3, 95% CI: 1.01-1.66, p = 0.03) and cervical dilatation on admission (RR: 1.63, 95% CI: 1.03-2.57, p = 0.03) were found to be statistically significant (Table 3).
As depicted in Table 4, for deliveries < 34 weeks' gestation, the FFN test had a sensitivity, specificity, PPV, NPV, positive LR and negative LR of 57.1%, 69.2%, 66.7%, 70%, 1.8 and 0.6, respectively. For deliveries within seven days of admission, the corresponding figures were: 68.6%, 84.4%, 52.8%, 82.4%, 4.3 and 0.3, respectively. As shown in Figure 1, Kaplan-Meier survival analyses showed that a higher percentage of women with positive FFN delivered within 14 days of sampling, compared to those with negative FFN (Mantel-Cox, log-rank analysis, \( \chi^2 \) value: 12.1, \( p < 0.001 \)).

Table 4.— Sensitivity, specificity, PPV, NPV, positive and negative LR's of cervicovaginal FFN for predicting deliveries < 7 days, and < 14 days of admission as well as < 34 weeks' gestation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>&lt; 7 days</th>
<th>&lt; 14 days</th>
<th>&lt; 34 weeks' gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>68.6</td>
<td>60.7</td>
<td>57.1</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>84.4</td>
<td>66.7</td>
<td>70.0</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>52.8</td>
<td>66.7</td>
<td>70.0</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>82.4</td>
<td>70.0</td>
<td>70.0</td>
</tr>
<tr>
<td>LR +</td>
<td>4.3 (2.1-9.8)</td>
<td>2.2 (1.4-3.1)</td>
<td>1.83 (1.61-2.26)</td>
</tr>
<tr>
<td>LR -</td>
<td>0.3 (0.2-0.5)</td>
<td>0.2 (0.1-0.5)</td>
<td>0.62 (0.3-1.2)</td>
</tr>
</tbody>
</table>

As shown in Table 4, the high NPV of cervicovaginal FFN for the prediction of deliveries within seven days of admission may indicate less intervention and avoid unnecessary medical procedures in women with threatened preterm labor. Swamy et al. [11] also concluded that the NPV of FFN was found to be 98% in 46 subjects with positive FFN. They also found that time to delivery and gestational age at delivery were lower in women with positive tests, conforming with our results. In contrast to the above-mentioned study, the present study showed no significant differences among women with positive or negative FFN in terms of the frequency of therapeutic interventions. In a recent study by Eroglu et al. [12] that compared the predicting value of different cervicovaginal biomarkers with cervical length in 51 women between 24 to 35 weeks' gestation, NPV of fetal FFN was found to be 91.9%. In the present study, although the number of admissions and length of hospital stay were not mentioned, several studies did find a significant difference in admissions to the antepartum service and length of stay in the antepartum ward with a negative FFN compared to positive FFN, emphasizing the reduction of unnecessary interventions and hospital stay, thus leading to a substantial cost savings [13, 14]. Similar to our results, in a recent study by Skoll et al. [15], of 149 women with symptoms suggestive of preterm labor tested, a negative FFN result was associated with a 97.4% likelihood of delivering more than seven days after testing and with a 91.4% chance of delivering after 34 weeks.

Both acute placental inflammation and positive mid-gestational cervico-vaginal fetal fibronectin assays have been independently correlated with preterm delivery [16]. However, in the present study, women with positive assays were no more likely to have histological evidence of acute inflammation noted at birth than women with negative FFN results. The same result was also observed in the study by Akers et al. [17]. Similar to our results, Rizzo et al. [18] found that a positive fetal fibronectin > 50 ng/ml was not associated with the presence of histological chorioamnionitis in women with intact membranes and signs suggestive of preterm labor. Hence, FFN is not a sensitive marker in identifying women at risk for the presence of histological chorioamnionitis.

The present study was an intent-to-treat study since the authors were blinded to the FFN results. However, the incidence of preterm birth was found to be higher in symptomatic women with negative FFN [19]. In contrast, blind sampling from the vagina for FFN was found to yield a sensitivity of 52% and specificity of 94.5% with a NPV of 99.1% in pregnant women at high risk for preterm delivery but without any symptoms [20].

Finally, based on the results of our study, the FFN test appears to provide useful information in the preterm delivery risk assessment in women with symptoms suggestive of preterm labor.
References


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A prospective randomized trial of labor induction with vaginal controlled-release dinoprostone inserts with or without oxytocin and misoprostol+oxytocin

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Summary

Objective: This study was designed in an aim to compare the efficacies of three labor induction methods, dinoprostone (PGE2) vaginal insert with or without concomitant oxytocin and misoprostol (PGE1) combined with oxytocin infusion. Methods: This was a prospective observational trial of nulliparous women undergoing labor induction from December 2006 to January 2007. Inclusion criteria were: gestational age between 36 to 42 weeks, singleton cephalic presentation of the fetus, intact membrane and unfavorable cervical Bishop score < 6, and absence of spontaneous uterine contractions. Participants were then randomly assigned to pre-induction cervical ripening with a dinoprostone vaginal insert (10 mg) administered into the posterior fornix for a total of 12 hours without oxytocin (group I); with oxytocin (group II), and with misoprostol (50 μg) intravaginally in the posterior fornix with repeat dosing at 6-hour intervals with a maximum dose of four with oxytocin (group III). Results: A total number of 106 women met the inclusion criteria without distribution for 19 cases in group I, 44 and 43 cases in groups II and III, respectively. There were no statistically significant differences in terms of the demographic characteristics, indication of labor induction, interval from-induction-to-delivery, cardiotocographic abnormalities and neonatal outcomes and mode of deliveries among the three groups (p > 0.05). Conclusions: Three methods of labor induction were equally efficient in achieving successful delivery without any maternal and fetal adverse outcomes.

Key words: Labor induction; Oxytocin; Controlled-release dinoprostone vaginal insert: Misoprostol.

Introduction

Labor induction is an obstetric challenge for women with an unfavorable cervix. The aim of labor induction is straightforward vaginal delivery within 12-24 hours of induction. In an attempt to optimize labor induction, there has been a concerted effort to elucidate the role of several agents available for cervical ripening in achieving a successful vaginal delivery, including mechanical and pharmacological methods like cervical stripping, an extra-amniotic Foley catheter, oxytocin, a controlled-release dinoprostone vaginal insert (PGE2), misoprostol (PGE1), and mifepristone [1-5]. Prostaglandin analog studies in the last decade have demonstrated that both oral and local administration of these compounds shortened induction-to-delivery intervals, and lowered maximum dose of oxytocin compared to a placebo [6-8]. However, the most significant adverse effects of PGE or PGE2 were uterine hyperstimulation and systemic side-effects [1, 5, 9].

The ideal agent must effectively induce labor, needs to be safe, easy to administer, and acceptable to the patient. The most frequent pharmacological method for labor induction is intravenous oxytocin [1].

The purpose of this study was to determine whether the administration of a controlled-release dinoprostone vaginal insert with or without oxytocin and misoprostol with oxytocin would result in shorter induction times, and to assess the undesirable outcomes of each regimen such as uterine hyperstimulation, vaginal delivery not achievable within 24 hours, fetal heart rate abnormalities, neonatal morbidity assessed by Apgar score, and admission to the neonatal intensive care unit (NICU).
uterine contractions. A cervical Bishop score was assigned on admission by a single-blinded physician for all patients. Prior to cervical ripening, all ultrasound examinations were made by using a Toshiba Sonolayer SSA 250 (Toshiba, Tokyo, Japan) ultrasound machine equipped with a 5 MHz transvaginal probe by a single-blinded investigator. Ultrasound measurement of cervical length was made in the sagittal plane along the length of the endocervical canal with simultaneous visualization of the internal and external cervical os. The shortest of three measurements was taken as the cervical length. Randomization was done independently through the hospital pharmacy by random allocation. Administration of labor induction agents was made by an on-call physician in the labor ward and not by the physician who assigned the Bishop scores.

The controlled-release PGE2 vaginal insert was a 0.8 mm thick semi-opaque polymeric insert, consisting of a biodegradable polymeric drug delivery device with a constant rate of 0.3 mg/hours or a total dose of 5 mg over the recommended dosage period of 12 hours [9]. All nulliparous women allocated to prostaglandin analogs remained in bed for two hours following insertion. Cardiotocographic (CTG) recordings were continued during the first hour of insertion and thereafter when the contractions occurred. Prostaglandin analogues were inserted into the posterior fornix of the vagina.

CTG tracings were independently reviewed by a blinded investigator and abnormalities were coded as hypertonus, tachysystole, and hyperstimulation. Hypertonus was defined as a single contraction with duration of at least two minutes; tachysystole as the presence of at least six contractions in ten minutes for two consecutive ten minute periods; and hyperstimulation as the presence of at least six contractions in ten minutes for a total of 24 hours (10 mg every 12 hours) without oxytocin (group I), with oxytocin (group II), and with misoprostol (Cytotec®, 200 μg tablets, Ali Raif, Turkey) 50 μg intravaginally (group III). If the Bishop score was ≥ 5 oxytocin was started followed by amniotomy. Oxytocin (Synpitan forte®, 5 IU, Deva, Turkey) was started with a dose of a 2 mU/min increment at 20-min intervals to a maximum of 30 mU/min for all cases with Bishop scores > 6 following cervical ripening with prostaglandin analogues.

Demographic characteristics, mode of delivery, time from induction-to-delivery, indications of induction, CTG abnormalities and neonatal outcomes were determined. Neonatal complications noted were Apgar scores of < 7 at 5 min and the rate of admission to NICU.

Statistical analysis was performed using the SPSS 10.0 (SPSS10.0, Chicago, IL, USA) statistical package. Results are presented as the mean ± SD or median with 25th-75th percentile values, where appropriate. Test of normality was performed by the one-way Kolmogorov-Smirnov test. Patient demographic characteristics were analyzed by the Student’s t-test and the chi-square and Fisher’s exact test or Wilcoxon rank sum test where appropriate. One-way ANOVA was used for group comparisons of continuous variables. Kaplan-Meier curves were compared by using the Wilcoxon log-rank test. A two-sided p value < 0.05 was set to be statistically significant.

Results

A total number of 106 women met the inclusion criteria without distribution for 19 cases in group I, 44 and 43 cases in groups II and III, respectively. There were no statistically significant differences in terms of demographic characteristics and indication of labor induction (Table 1), as well as fetal and neonatal characteristics, cardiotocographic abnormalities and neonatal outcomes, and mode of deliveries among the three groups (Table 2). Duration of oxytocin use and time interval from induction to delivery also did not differ among the three groups (p > 0.05) (Figure 1). Interestingly, in all three groups high percentages of abnormal CTG patterns (hypertonus, tachysystole or hyperstimulation) were observed. In terms of number of patients that remained undelivered within 24 hours of labor induction, no statistically relevant differences were depicted between three groups (Mantel-Cox log-rank, \( \chi^2 \geq 1.5, df = 2, p = 0.454 \)).

### Table 1. Characteristics of women who received a controlled-release dinoprostone vaginal insert only (group I), dinoprostone + oxytocin (group II) and misoprostol + oxytocin (group III).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 19)</th>
<th>Group II (n = 44)</th>
<th>Group III (n = 43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (yrs)</td>
<td>29.1 ± 2.3</td>
<td>29.4 ± 3.2</td>
<td>27.9 ± 1.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>82.2 ± 3.4</td>
<td>84.2 ± 2.5</td>
<td>82.3 ± 1.8</td>
<td>0.54</td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>39.3 ± 1.7</td>
<td>38.6 ± 2.1</td>
<td>39.4 ± 1.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Indications for induction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postdates</td>
<td>5</td>
<td>11</td>
<td>10</td>
<td>0.55</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>0.63</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>8</td>
<td>18</td>
<td>17</td>
<td>0.76</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>0.32</td>
</tr>
<tr>
<td>Term PROM*</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>0.79</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>7</td>
<td>8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*premature rupture of membrane.

### Table 2. Labor characteristics and neonatal outcome in groups I, II and III, respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 19)</th>
<th>Group II (n = 44)</th>
<th>Group III (n = 43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3270.3 ± 482.8</td>
<td>3210.3 ± 562.4</td>
<td>3186.6 ± 534.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Bishop score (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>18</td>
<td>44</td>
<td>36</td>
<td>0.80</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Initial cervical length (mm)</td>
<td>33.7 ± 3.7</td>
<td>33.0 ± 1.8</td>
<td>30.3 ± 4.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Duration of oxytocin use (hr) median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25th-75th percentiles)</td>
<td>–</td>
<td>6 (4-9)</td>
<td>6 (5-8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Vaginal delivery n (%)</td>
<td>10 (52.6)</td>
<td>27 (61.4)</td>
<td>25 (58.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cesarean delivery n (%)</td>
<td>9 (47.4)</td>
<td>17 (38.6)</td>
<td>18 (41.9)</td>
<td></td>
</tr>
<tr>
<td>Time from induction to delivery (hrs) median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25th-75th percentiles)</td>
<td>10 (4-15)</td>
<td>10 (7-18)</td>
<td>11 (8-15)</td>
<td>0.50</td>
</tr>
<tr>
<td>Abnormal CTG tracings*</td>
<td>17</td>
<td>33</td>
<td>35</td>
<td>0.40</td>
</tr>
<tr>
<td>5 min Apgar score &lt; 6</td>
<td>1</td>
<td>2</td>
<td>–</td>
<td>0.39</td>
</tr>
<tr>
<td>NICU** stay (days)</td>
<td>3.1 ± 0.2</td>
<td>4.1 ± 1.2</td>
<td>3.9 ± 0.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Maternal hospital stay (days) median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25th-75th percentiles)</td>
<td>4 (2-6)</td>
<td>3 (2-3)</td>
<td>4 (2-6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*hypertonus, tachysystole or hyperstimulation; **neonatal intensive care unit.
cesarean delivery. From induction-to-delivery and reduced the incidence of significant increased Bishop score, shortened the time
that prostaglandin analogues with or without oxytocin prostaglandin analogues and oxytocin with each other or randomized controlled studies in the literature comparing the three groups.
and induction-to-delivery interval did not differ among outcomes. As seen in Table 1, duration of oxytocin dose hours of infection with similar adverse maternal and fetal similar efficacy in achieving vaginal delivery within 24 oxytocin and misoprostol with oxytocin protocols had
differences were similar between the two groups, as also found eutopic pregnancies that underwent labor induction at
last, the authors emphasized that this issue is more important
in tropical countries.

In a systematic review by Crane et al. [20], misoprostol (oral or vaginal) in women at term with an unfavorable cervix and intact membranes was more effective than dinoprostone (intracervical or vaginal) in achieving vaginal delivery within 24 hours. The same authors stated that misoprostol increased the rates of tachysystole and hyperstimulation. In a recent randomized study, comparing the safety and efficacy of vaginal misoprostol versus dinoprostone vaginal inserts for cervical ripening and labor induction, 200 cases were randomized to either 50 μg intravaginal misoprostol every three hours or a 10 mg dinoprostone insert every 12 hours for a maximum dose of 24 hours [21]. In contrast to the results of the current investigation, the authors concluded that misoprostol resulted in a shorter interval from induction to delivery with a high rate of non-reassuring fetal heart rate tracing. In a prospective randomized controlled trial by Rowland et al. [22], comparing misoprostol versus dinoprostone for cervical ripening in 126 women recruited into the study, there was no difference in the percentage of women who delivered vaginally or by cesarean section, but more hyperstimulation was observed in the misoprostol group. Again, neonatal outcome in respect to low cord pH or Apgar score as well as admissions to NICU were similar between the two groups.

Similar to the present investigation, Bolnick et al. [23] studied pregnancies that underwent labor induction at ≥ 37 weeks of gestation with an unfavorable cervix (Bishop score, ≤ 6) were randomly assigned to receive vaginally either a single dose of sustained-release dinoprostone (Cervidil) with concurrent low-dose oxytocin or multi-dosing of misoprostol (25 μg every 4 hours) followed by high-dose oxytocin. They concluded that neither mean time from the initiation of induction to vaginal delivery nor the percentage of patients who were delivered vaginally differed between the two groups. CTG abnormalities were similar between the two groups, as also found in the current investigation.

Discussion
Based on the results of the current investigation, a dinoprostone controlled release vaginal insert with or without oxytocin and misoprostol with oxytocin protocols had similar efficacy in achieving vaginal delivery within 24 hours of infection with similar adverse maternal and fetal outcomes. As seen in Table 1, duration of oxytocin dose and induction-to-delivery interval did not differ among the three groups.

There are considerable numbers of prospective, randomized controlled studies in the literature comparing prostaglandin analogues and oxytocin with each other or a placebo [1, 11-15]. These studies have demonstrated that prostaglandin analogues with or without oxytocin significantly increased Bishop score, shortened the time from induction-to-delivery and reduced the incidence of cesarean delivery.

In a retrospective analysis by Lapair et al. [16], 98 patients were retrospectively analyzed. A total of 47 patients received 3 mg dinoprostone suppositories every six hours (max 6 mg/24 h) whereas 51 patients in the misoprostol group received either 50 μg misoprostol vaginally every 12 hours. The authors concluded that there was a three-fold chance for vaginal delivery in the misoprostol than in the dinoprostone whereas more cesarean sections were performed in the dinoprostone group due to failed induction without any significant differences in adverse maternal outcome. However, in contrast to the results of the present study, more neonates of the dinoprostone group were admitted to the NICU.

The potential development of uterine hyperstimulation is of particular concern with regard to prostaglandin analogues. Ramsey et al. [17], through a study of 111 cases randomized to 50 μg misoprostol every six hours for two doses and 0.5 mg dinoprostone gel every six hours for two doses, found that CTG abnormalities occurred more frequently following misoprostol administration compared to dinoprostone analogues. One distinct advantage of vaginally inserted dinoprostone compared to tablet form was stated to be the easy removal of the drug and reversibility of uterine hyperstimulation, as well as a single dosing scheme [18]. Although the present study did not show any difference in CTG abnormalities, dinoprostone vaginal inserts seemed to confer a benefit over misoprostol. Le Roux et al. [7] conducted a multicenter, randomized control trial for 573 women admitted for induction of labor and randomized to vaginal misoprostol (50 μg every 6 hours x 4 doses) or dinoprostone gel (1 mg), and stated that despite there being no difference in the rates of vaginal delivery within 24 hours of induction between the two groups, more tachysystole and cesarean section for fetal distress were performed compared to the dinoprostone group. However, they also pointed out that oral misoprostol resulted in fewer cesarean deliveries without any increased CTG abnormalities. Although the current investigation yielded a similar efficacy of different prostaglandin analogues for successful labor induction, Nanda et al. [19] concluded that misoprostol is cheaper, stable at room temperature, has a shorter mean induction-to-delivery interval and requires less oxytocin. As for the last, the authors emphasized that this issue is more important in tropical countries.

Figure 1. — Percentage of nulliparous women in groups I, II and III who remained undelivered (y-axis) within 24 hours of labor induction (x-axis). (Mantel-Cox log-rank, χ²: 1.5, p = 0.454).

Table 1: Duration of oxytocin dose hours of infection with similar adverse maternal and fetal outcomes.
The cost-benefit of misoprostol over dinoprostone also has to be taken into account. Although it was not the intention of the present study to do a comparison of the three groups in terms of cost, the duration of hospital stay was found to be lower in the dinoprostone-oxytocin group, compared to the dinoprostone only and misoprostol + oxytocin groups. Although not shown in this study, the hospital cost of cases in group III (misoprostol + oxytocin) was lower compared to the dinoprostone groups (groups I and II).

Ramsey et al. [24] compared the relative efficacy and cost of three commercially available prostaglandin analogues, intravaginal misoprostol (50 μg dose at 6-hour intervals), and dinoprostone inserts (10 mg for a total time of 12 hours), as labor preinduction agents in 111 women with an unfavorable cervix who underwent labor induction. They finally concluded that induction-to-delivery intervals, however, were significantly shorter among women who were treated with misoprostol compared with dinoprostone inserts. Moreover, the overall mean cost per patient that was incurred by labor induction was significantly less for the misoprostol group compared to the dinoprostone insert group which is an important finding that needs further evaluation in detail.

In conclusion, although there were no differences in the efficacy of labor induction and neonatal outcomes among the three groups, a more detailed analysis regarding the cost-effectiveness of each regimen needs to be determined in a larger case series with sufficient power. In addition, the use of prostaglandin analogues with different dosage and way of administration (oral, intracervical, intravaginal) have to be evaluated. Moreover, although different from the current investigation, the concurrent use of oxytocin with prostaglandin analogues needs to be assessed. The latter issue seems to be beneficial in shortening the delivery time without considerable maternal and perinatal adverse outcomes [25].

References


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Ellis-van Creveld (EvC) syndrome, or chondroectodermal dysplasia, is a rare genetic disorder associated with chondrodysplasia, ectodermal dysplasia, polydactyly, and congenital cardiac malformations. The disorder is due to an autosomal-recessive mutation mapped to chromosome 4p16. It may occur with different phenotypes. The case of an ovarian endometriotic cyst in a patient suffering from EvC syndrome is reported.

Key words: Ovarian cyst; Ellis-van Creveld’s syndrome.

Introduction

Ellis-van Creveld (EvC) syndrome is a rare autosomal recessive disease also known as chondroectodermal dysplasia [1]. EvC is characterized by a tetrad of manifestations including disproportionate dwarfism, ectodermal dysplasia, cardiac malformations, and polydactyly [2]. The physical features of patients suffering from this disease are typical and characteristic: long trunk with short limbs, dystrophic nails, extra fingers/toes, teeth malformations (taurodontism, missing incisors), harelip, narrow rib cage (barrel chest with short ribs), single atrium (interatrial and interventricular defects), delayed endochondral ossification, and nephrotic syndrome. The chromosome alteration appears as a mutation of the short arm (p) of chromosome 4 (cr4p16). The heterozygous condition involves polydactyly and cardiac malformations, but not necessarily short stature [3]. It can be diagnosed echographically from the 27th week of pregnancy and is not a life threatening disorder. Prenatal diagnosis is important both for family pathology and for early surgical correction of cardiac defects and osteochondrodysplastic abnormalities. As with all diseases, there are variants of the classic symptomatology. In the literature, variants have been described which were associated with kidney and liver abnormalities, changes in the central nervous system, and mucormetrocolpos [4]. We report a case of a 19-year-old patient suffering from an ovarian cyst associated with EvC syndrome, both being dysontogenetic disorders.

Case Report

A 19-year-old hexadactyly patient with a history of cardiac disorders and suffering from EvC syndrome was admitted to our hospital to undergo a laparoscopic intervention for removal of an ovarian cyst. Anamnestic data indicated a familial propensity for heart disease. Surgical correction of the cardiopathy (partial AV channel, single atrium, unroofed superior vena cava, no venous innominate trunk) had been performed when the patient was 12 years old. Subsequently, her bilateral hexadactyly with dystrophic toenails was also corrected. The patient was 1.60 m in height as her case of heterozygous EvC syndrome was not associated with disproportionate dwarfism. She presented the typical craniofacial morphology: small posterior cranial base, small jaw, and large lower jaw with an increased angle (malocclusion). Dental anomalies could be observed: shovel-shaped incisors, claw pointed teeth, reduced size of the crown and supernumerary teeth.

When admitted to the hospital the patient underwent electrocardiography and hematochemical tests which showed normal parameters and negative tumor markers. Pelvic echography showed a 58 x 47 cm right adnexal ovular nonhomogeneous mass consisting of both non-echogenic and echogenic areas with irregular but clear margins. There was fluid in the pouch of Douglas. After receiving preventive antibiotic therapy, the patient underwent laparoscopic removal of the endometriotic cyst in the right ovary. No complications were observed during the surgical intervention or postoperatively. She was discharged after 24 hours. Pathological examination confirmed the diagnosis of ovarian endometriosis. Cytological and bacteriological examinations of the peritoneal fluid were negative.

Discussion

Given that the etiology of endometriosis is considered by some to be a genetic immune disorder, it is interesting to note that in this case this etiology was associated with an autosomal recessive disorder [5]. It is important that researchers describe cases associated with rare syn-
dromes that even through today, given the advances in surgery, particularly heart surgery, are no longer life threatening. Patients with pathologies, once described as very rare, are today becoming more common. Our patient, in addition to the esthetic damage due to the median thoracotomy and polydactyly, could in the future have had more problems related to endometriosis: infertility, chronic pelvic pain and, as the disease progresses, dysmenorrhea, dysuria, dyschezia, and pelvic adhesion syndrome.

In this case the endometriosis was still in an early stage (Ib), the patient’s pelvis had no tenacious adhesions and thus stripping the cystic wall was easy. We believe that the publication of this unusual case will be useful as we found no reports in the literature describing any association of these diseases [6-9].

References


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Anaesthetic burns

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2Department of Obstetrics and Gynaecology, Brooklyn Hospital Centre, New York (USA)

Summary

Patients frequently complain of numbness after surgery via the Pfannensteil incision. The two cases in this report demonstrate clear evidence of impaired sensory perception following such an incision. While this is often regarded as a trivial complication, a brief warning to patients should help avoid such superficial burns.

Key words: Transverse suprapubic incision; Pfannensteil incision; Superficial burn.

Introduction

A lower suprapubic incision is commonly used in many gynaecological procedures as it provides for good pelvic access and leaves an aesthetic scar. Nerve injuries can occur which can cause sensory impairment in some patients. We report two cases in which the patients received burns postoperatively from placing hot water bottles over the abdominal skin that had been anaesthetised. It is important patients and clinicians be made aware of this potential complication.

Case Reports

Case 1

A 48-year-old Eritrean woman underwent a myomectomy via a suprapubic incision for a large fibroid uterus. The postoperative course was uneventful. While at home, two weeks after the operation, a hot water bottle was used to alleviate abdominal discomfort while she was recuperating from her operation. She sustained a partial thickness skin burn when she fell asleep (Figure 1).

Case 2

A 53-year-old English woman underwent an abdominal hysterectomy with bilateral salpingo-oophorectomy for an 8 cm right ovarian cystadenoma which was found on scan when she presented with postmenopausal bleeding. The abdomen was opened via a suprapubic incision. She made an uneventful recovery from the procedure and her wound healed well. She too sustained a superficial burn from a hot water bottle that she had used to comfort her symptoms postoperatively. Her general practitioner provided treatment for the burn, which had almost healed when she attended for a follow-up appointment at the gynaecology outpatient clinic.

Discussion

The lower transverse abdominal incision, described by Hans Hermann Johannes Pfannensteil, was popularised in 1900 [2]. It is the incision of choice for many gynaecological procedures and has stood the test of time. Advantages to this incision are lower incisional hernia rates, less wound infection, haematoma formations, and postoperative pain, as well as better cosmetic results [1]. The incision traverses the skin, subcutaneous fat, rectus sheath, and extends through the fascia of the internal and external oblique muscles before entering the inguinal canal. These nerves can be damaged while gaining pelvic access via a Pfannensteil incision, leading to sensory impairment. Injury to these nerves is more likely to occur because of the nerve’s superficial course.

Complications of nerve damage occur most commonly when the incision is extended too far laterally [2]. If the incision needs to be extended more laterally, the nerve should be identified and preserved. Additionally, the iliohypogastric nerve can be avoided if the incision passes at least 5 cm cranial to the inguinal ligament [3].

In addition to avoiding direct damage, it is important to recognise that the nerves can become entrapped during the suturing of abdominal layers, or by scar tissue formation [1]. The classic triad of nerve entrapment includes burning pain that radiates to the region supplied by the nerve, evidence of sensory...
impairment to the affected area, and pain relieved by application of anaesthetic [4]. This complication is reported in 3.7% of cases [1].

Although most experienced gynaecological surgeons are aware of the anaesthetic effect of this incision, a review of the literature does not reveal any previous publication of this complication. It is important for patients, especially in colder climates, to be made aware that numbness can occur following this incision, so they can avoid unwanted superficial burns as experienced by our patients.

References


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Conservative treatment of an early ectopic pregnancy in a cesarean scar with systemic methotrexate - case report

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Summary

Purpose of investigation: Pregnancy implanted in a cesarean scar is rare, and is a life-threatening condition due to high risk of uterine rupture, hemorrhage, hysterectomy, and maternal mortality. Case report: We describe a 26-year-old woman who presented with five weeks of amenorrhea and a serum hCG level of 10,440 mIU/ml. Transvaginal sonography revealed a gestational sac of 15 x 11 mm containing a yolk sac located in a previous cesarean scar. She was successfully treated conservatively with multi-dose methotrexate. No side-effects were encountered. The serum hCG levels were undetectable in 58 days. The patient had normal menstrual cycles afterwards.

Conclusions: In the view of increasing cesarean rates, healthcare professionals should be aware of the possibility of a scar pregnancy and the potentially life threatening sequelae. Early diagnosis by transvaginal sonography can improve outcome and minimize the need for emergent surgery. Conservative treatment with systemic methotrexate is an effective option in selected patients.

Key words: Methotrexate; Ectopic pregnancy; Cesarean section scar.

Introduction

Pregnancy developing within a previous cesarean section scar is a rare type of ectopic pregnancy that carries a high risk of uterine rupture, hemorrhage, hysterectomy, and maternal mortality [1]. With increasing use of transvaginal ultrasonography (TVS), this condition may be diagnosed earlier and treated more conservatively avoiding the need for emergent surgery. We report a case of ectopic pregnancy in a cesarean scar diagnosed by TVS and successfully treated conservatively with systemic methotrexate (MTX) without performing a dilatation and curettage procedure.

Case Report

A 26-year-old Caucasian woman (gravida 1, para 1) after five weeks of amenorrhea was referred to our institution because of a preliminary diagnosis of ectopic pregnancy. She had no other symptoms. Her obstetric history revealed a previous cesarean section, performed with a low transverse uterine incision due to breech presentation, 18 months before. The physical examination was unremarkable; she had a normal-sized uterus and no adnexal masses were palpated. TVS revealed a normal uterus. The endometrium measured 13 mm in thickness and there was an anechoic collection near the isthmic area 5 x 5 mm in size. The left ovary was normal. At the lateral margin of the right ovary, a cystic mass measuring 17 x 19 mm in diameter was seen. No free fluid was seen in the cul-de-sac. Laboratory data revealed a quantitative serum human chorionic gonadotropin (hCG) level of 5,995 mIU/ml. The patient was admitted to the hospital with the differential diagnosis of ectopic pregnancy and intrauterine pregnancy. Observation of vital signs and serial hCG level monitorization was planned. A repeat quantitative hCG level of 7,670 mIU/ml was obtained 48 hours later. The repeat TVS findings were similar. Forty-eight hours later the hCG measured 10,440 and the patient was reevaluated. There was tenderness over the anterior wall of the uterus. On TVS, the endometrium measured 15 mm in thickness and contained an irregular anechoic fluid collection. Over the cesarean scar on the isthmic portion of the uterus, a gestational sac of 15 x 11 mm containing a yolk sac was visualized (Figure 1). A slight amount of free fluid was seen in the cul-de-sac. The diagnosis of a cesarean scar ectopic pregnancy was established and the patient was informed about treatment options, possible risk of uterine rupture and profuse bleeding which may require emergent hysterectomy. After discussion, conservative treatment with MTX was chosen because the patient had no symptoms, wanted to preserve her fertility, hCG levels were around 10,000 IU/ml, the gestational sac was small in diameter, and no signs of internal bleeding were observed.

Figure 1. — Gestational sac and yolk sac located in the previous cesarean section scar.
bleeding were observed. She was given multiple doses of MTX which included four doses of 75 mg (1 mg/kg) intramuscular MTX given on days 0, 2, 4, and 6 with leucovorin rescue given on days 1, 3, 5, and 7. No-side effects were observed. The quantitative hCG levels continued to rise initially to 15,538 until day 4 and then decreased to 5,370 on day 7. The patient was discharged from the hospital on day 9 with a hCG level of 3,975. Fifty-eight days later, the hCG level decreased to 0.3 IU/ml and the mass on the anterior wall of the uterus had disappeared completely. The patient had normal menstrual cycles.

Discussion

Although its true incidence has not been determined, pregnancy implanted in a cesarean scar is commonly cited as the rarest form of ectopic pregnancy and a life-threatening condition. A review of the English literature between 1978 and 2001 revealed only 18 cases while the number of reported cases has increased up to 66 since 2002 [2]. This increase may reflect both the increasing number of cesarean procedures currently being performed [3] as well as earlier detection of such pregnancies due to widespread use of TVS [4].

Among the theories for explaining the occurrence of pregnancy implanted in a cesarean scar, a blastocyst entering the myometrium through a microscopic dehiscent tract, is the most probable and reasonable. Such tract is believed to be created through a trauma that occurred in association with a previous uterine surgery or trauma like cesarean delivery, curettage, myomectomy, metroplasty, hysteroscopy, manual removal of placenta, and IVF [1, 5]. It has also been suggested that the interval between such trauma and a subsequent pregnancy may affect implantation events [6]. The time interval between the last cesarean delivery and the diagnosis of scar pregnancy ranges from six months to 12 years in the literature [5]. Our patient’s history was remarkable for a spontaneously conceived pregnancy terminated by a planned cesarean section. Neither curettage nor any type of uterine surgery for gynecologic disease was noted. Hence, cesarean section seems to be the only predisposing factor in our patient and the time interval between cesarean delivery and the diagnosis of scar pregnancy was 18 months, suggesting that complete healing of the uterine scar must have occurred by that time. The interesting association between cesarean section for breech presentation and the subsequent occurrence of pregnancy in the resultant scar, proposed by Maymon et al. [7], was also present in our case. Later in their review of scar pregnancies [2], they proposed that this association might not be merely coincidental and healing processes after elective procedures performed in a non-developed lower uterine segment (like for breech deliveries) might facilitate implantation of the blastocyst within the scar. It is also interesting to see this relationship in the first case of scar pregnancy encountered at our university. We agree with Maymon et al. that changing surgical techniques, indications for cesarean section and surgery in non-developed lower uterine segments might have an impact on the occurrence of scar pregnancies. This intriguing association needs to be examined further.

We first used transvaginal and then transabdominal ultrasound with a full bladder, as proposed by Ravhon [8], for diagnosis. According to Vial [9], three sonographic criteria should be present: 1) the trophoblast must be mainly located between the bladder and the anterior uterine wall; 2) on sagittal view of the uterus running through the amniotic sac, a discontinuity in the anterior wall of the uterus should be demonstrated; 3) no fetal parts must be visible in the uterine cavity. Since an early diagnosis of ectopic scar pregnancy was made at five gestational weeks in our case, the fetal pole was not visible; instead all of the gestational sac and yolk sac was located inside the previous cesarean scar. Although MRI is used for diagnosis in some reports, we found a combined approach of (transabdominal plus transvaginal) ultrasound scan accurate and cost-effective in our patient.

It is prudent to consider and offer termination of pregnancy after explaining the risks of uterine rupture with life-threatening hemorrhage as soon as the diagnosis is made. Because of its rarity, there is no universal treatment guideline to manage this condition. Surgical treatment includes excision of the gestational sac and repair of the cesarean scar, which has been successfully performed by both laparotomy and laparoscopy. However, this operative approach still carries a significant risk of uncontrolled hemorrhage that has led to hysterectomy and loss of reproductive function in some of the reported cases [4]. Dilatation and curettage has a high risk of severe vaginal bleeding which may necessitate hysterectomy and it should not be considered the first choice of therapy as proposed by some authors [10, 11]. Treatment with MTX is an option which is both effective in treatment of the disease and in preserving the uterus and future fertility. Local and systemic MTX treatments are described, but local MTX injection is technically more difficult, especially in a case like ours, where the gestational sac is 6-8 mm in dimension. Thus, we chose systemic MTX to avoid the risks associated with other treatment methods. Some authors have proposed that systemic absorption of MTX may be limited which may delay the absorption of the gestational sac [1, 8], because the cesarean scar pregnancy is surrounded by fibrous scar tissue rather than a normally vascularized myometrium. Whether local MTX would have resulted in a shorter treatment and a shorter time for normalization of hCG levels in our case, one cannot know; but absorption of systemic MTX was enough to treat our case. It is also important that no curettage or other additional treatment was necessary after this therapy. Normalization of hCG levels and disappearance of the ectopic mass occurred within two months of the therapy. Although multi-dose systemic MTX treatment may result in failures requiring laparotomy [12], the pregnancies in that case series were bigger and hCG levels were higher than our case, which may explain the reason for failure of MTX.

In view of the increasing cesarean rates and use of TVS, healthcare professionals should be aware of the possibility of a scar pregnancy and its potentially life threatening sequelae. Early diagnosis and conservative treatment...
options are effective in reducing morbidity and preserving fertility. Today there are many suggested conservative treatment options, but a consensus in treatment has not been developed yet. We propose that conservative treatment with systemic methotrexate alone may be a good choice of therapy in selected patients diagnosed early.

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Congenital cystic adenomatoid lung malformation: report of two cases and literature review

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Summary

Congenital cystic adenomatoid malformations of the fetal lung (CCAM) are rare embryonic developmental abnormalities. They are considered as benign hamartomatous or dysplastic lung tumors characterized by overgrowth of the terminal respiratory bronchioles at the expense of the saccular spaces. A minority of cases may not be identified by prenatal imaging techniques and the pulmonary lesions are recognized postnatally. Two cases of congenital cystic adenomatoid malformation of the fetal lung diagnosed in our institution during the last four years are reported. The ultrasonographic and pathologic findings of these cases are discussed.

Key words: Congenital cystic adenomatoid lung malformation; Type II; Ultrasound; Prenatal diagnosis.

Introduction

Congenital cystic adenomatoid malformation of the lung (CCAM) is an extremely uncommon fetal developmental anomaly characterized by an abnormal proliferation of the terminal bronchioles. [1].

CCAM of the lung is usually unilateral and involves part or all of one fetal hemithorax, with up to 15% of cases having bilateral involvement [1]. Polyhydramnios, fetal hydrops and hypoplasia of the contralateral lung may also be present due to compression from the abnormal lung tissue [1]. The cysts within the mass may be macrocystic (cysts ≥ 5 mm) or microcystic (cysts < 5 mm) [2]. The vascular supply for a CCAM mainly arises from the pulmonary vessels. Some communication may exist between the mass and the surrounding normal lung tissue.

The ultrasound differential diagnosis is based on the morphology of the cysts, the location of the lesion, the vascular supply as assessed by color Doppler analysis, and the lesion’s effects on adjacent tissues and structures. The differential diagnosis includes various congenital abnormalities of the lung, such as pulmonary sequestration, bronchogenic cysts, diaphragmatic hernia, mediastinum cystic teratoma, and, less commonly, congenital lobar emphysema [2, 3].

In 1949, Chin and Tang [4] first reported a case of CCAM. The current descriptions are founded on studies from Stocker et al. [5] and Adzick et al. [6]. The Stocker classification is based on certain histologic findings but mainly the cyst dimensions, whereas the Adzick classification is based on the sonographic appearance of the cysts and cyst size. The prognosis varies from spontaneous resolution of the lung lesions in utero to perinatal death or no neonatal morbidity [1]. Sonography is essential for the prenatal diagnosis.

Two cases of congenital cystic adenomatoid malformation of the fetal lung that were diagnosed in our institution during the last four years are presented. The ultrasonographic findings, postmortem pathology and etiology of this entity are discussed and the international literature is reviewed.

Case Reports

Case 1

The first patient was a 27-year-old, gravida 4, nulliparous, rhesus negative woman who was admitted to the 2nd Obstetrics and Gynecology Department of Aretaieion Hospital at 24 weeks of gestation suffering from vaginal bleeding and possible spontaneous rupture of the membranes. Her personal history included three spontaneous miscarriages. The course of her pregnancy up to that point had been uneventful.

From the ultrasonographic examination a single fetus was found, fetal movements were normal and the placenta was adhered to the posterior uterine wall. There was a partial placental abruption and a hematoma had formed at the sight of the abruption. The biometric measurements were as follows: fetal biparietal diameter (BPD) 58 mm, head circumference (HD) 199.20 mm, fetal abdominal circumference (FAC) 153.31 mm and fetal femur length (FL) 33.20 mm. Ultrasonographically, the gestational age was calculated to be 20 weeks and four days and the gestational weight was estimated to be 482 g. Amniotic fluid was within normal levels. No fetal anomalies such as congenital diaphragmatic hernia, ascites, pericardial effusion were present. The left lung appeared to be full of small cystic lesions and the maximum diameter of these cysts was approximately 0.5 cm. Displacement of the fetal heart was also recognized. The right lung was not affected. These findings were considered to be a type-II congenital cystic adenomatoid malformation of the lung (Figure 1). During the following days there was a spontaneous rupture of the membranes and a male rhesus-positive fetus was delivered, weighing 465 g. Three hundred micrograms of Rh immunoglobulin (RhIgG) were administered to the mother.

Histopathology confirmed the above diagnosis of congenital
cystic adenomatoid malformation of the lungs. A retroplacental hematoma and recent infarcts were also confirmed. The cross section of the fetal thorax showed areas that contained cysts of 0.4 to 0.5 cm in diameter, surrounded by normal pulmonary parenchyma. The cysts resembled terminal bronchioles and were lined by ciliated cuboidal to columnar epithelium (Figure 2). Distended alveoli were present between the epithelium-lined cysts (Figure 3). The karyotype results showed 46, XY.

Case 2

The second patient was a 28-year-old, primigravida, rhesus-positive woman who was admitted to the 2nd Obstetrics and Gynecology Department of Aretaieion Hospital at the 25th week of gestation with the symptom of spontaneous rupture of the membranes. Her personal history included a tonsillectomy, an appendectomy and hypothyroidism under treatment. The course of her pregnancy up to that point had been uneventful.

From the ultrasonographic examination a single fetus was found, fetal movements were diminished and the placenta was adhered to the anterior uterine wall. The biometric measurements were as follows: BPD 60 mm, HD 205.70 mm, FAC 197.92 mm and FL 41 mm. Ultrasonographically the gestational age was calculated to be 23 weeks and two days and the gestational weight was estimated to be 635 g. Amniotic fluid was absent. No fetal anomalies such as diaphragmatic hernia, ascites, or pericardial effusion were present. Due to the complete absence of amniotic fluid the couple had to terminate the pregnancy, which was carried out by means of misoprostol. A female rhesus-positive fetus was delivered, weighing 639 g.

Histopathology showed a congenital cystic adenomatoid malformation of the lungs, which was classified as type II. The cross section of the fetal thorax showed areas that contained cysts of 0.1 to 0.2 cm in diameter, surrounded by normal pulmonary parenchyma (Figure 4). The cysts resembled terminal bronchioles and were lined by ciliated cuboidal to columnar epithelium. Distended alveoli were present between the epithelium-lined cysts (Figure 5). The karyotype results showed 46, XX.

Discussion

Chin and Tang first described the most common intrinsic intrathoracic lesion that can be defined antenatally, CCAM, in 1947 [4]. Since then, it has been regarded as a rare cause of neonatal respiratory distress, and most of the reported clinical data have derived from postmortem and surgically excised material [5]. Although, the exact incidence of CCAM is unknown, there are reports that estimate the incidence of CCAM to be approximately one in 25,000 pregnancies [7].

Histopathologic classification of CCAM was first described in 1977. Stocker et al. classified congenital cystic malformations of the lung into three types based on certain criteria but mainly on the cyst dimensions [5]. All three are characterized by an abnormal proliferation of the terminal bronchioles, increased elastic tissue and polypoid columnar or cuboidal epithelial proliferation:

(A) Congenital cystic adenomatoid malformations of the fetal lung type I: The most commonly seen CCAM lesion is the Stocker type I, which accounts for 50-70% of the diagnosed cases [5]. This defect is composed of single or multiple large cysts (2 to 7 cm in diameter), that are confined to one lobe, and are filled with air or fluid. The cysts are lined by ciliated pseudo-stratified columnar epithelium. The wall of the cysts is quite thick and contains prominent smooth muscle and elastic tissue. Mucous-producing cells can be identified in one-third of the cases and cartilage in the wall can rarely be recognized. Relatively normal alveoli may be seen between the cysts. It is not unusual for these lesions to communicate with the normal bronchial tree. These lesions frequently result in mediastinal herniation. Only 11% of these lesions are complicated with associated anomalies. It has been estimated that 90% of these patients survive. Also the prognosis of the infant is good after the resection of the lesion [5].

(B) Congenital cystic adenomatoid malformations of the fetal lung type II: CCAM Stocker type II lesions are found in 18%-40% of the diagnosed cases, and are characterized by multiple evenly distributed, medium sized cysts (< 1.0 cm in diameter) that resemble terminal bronchioles [5]. The cysts are lined by cuboidal to tall columnar ciliated epithelium. The wall of the cysts has a thin layer of loose connective tissue and contains discontinuous bands of smooth muscle and elastic tissue. Strands of striated muscle fibers can be recognized. Distended alveoli are found between the epithelium-lined cysts. There is no identification of mucous cells and cartilage. CCAM type-II lesions have been associated with a higher incidence (50%) of other congenital anomalies and have a poor prognosis. These congenital anomalies include renal agenesis, bilateral renal dysgenesis, pulmonary sequestration, and congenital heart disease [5].

(C) Congenital cystic adenomatoid malformations of the fetal lung type III: Congenital cystic adenomatoid malformations of the fetal lung type III are identified in about 10% of the cases. These lesions are characterized by a large, bulky lesion with evenly distributed small
cysts involving the whole lung or even both lungs. Mediastinal displacement is extremely common. CCAM type-III lesions have the worst prognosis [5].

An expanded concept of CCAM has been presented by Stocker, who has divided CCAM into five different categories based on the site of the defect in the tracheobronchial tree: 1) type 0 - acinar dysplasia, 2) type I - multiple large cysts or a single dominate cyst, 3) type II - multiple evenly spaced cysts, 4) type III - bulky firm mass, 5) type IV - peripheral cyst type.

In our cases the postmortem examination showed a congenital cystic adenomatoid malformation of the lungs, which was histopathologically classified as type II.

Congenital cystic adenomatoid malformations of the fetal lung can lead to pulmonary hypoplasia, mediastinal shift, polyhydramnios and hydrops, especially when the abnormally developed lung tissue reaches large proportions in utero [1, 2]. The development of fetal hydrops is a poor prognostic feature [1, 2]. Fetal hydrops is probably the result of a mass effect by the size of the CCAM on fetal swallowing (due to compression of the fetal esophagus) or decreased venous return following vena cava compression by the pulmonary mass or decreased myocardial contractility due to the extreme mediastinal shift caused by the lesion [1]. In these cases the prognosis of the fetus is adversely affected [1]. Polyhydramnios may also be present due to compression of the fetal esophagus or from increased fetal lung fluid production by the abnormal lung tissue [1]. In our cases there was no development of fetal hydrops, pulmonary hypoplasia, mediastinal shift or polyhydramnios.

The exact mechanism causing congenital cystic adenomatoid lung malformation is not clear, although this abnormality is considered to be the result of hamartomatous changes in the tertiary bronchioles or an arrest in their embryologic development between seven and 17 weeks of gestation [1, 3, 7]. The development of the fetal lung has been subdivided into five distinct periods based on the anatomical changes that occur in lung morphology: embryonic (3-7 weeks), pseudoglandular (7-17 weeks), canalicular (8-20 weeks), saccular (18 weeks), and terminal (20 weeks).
Congenital cystic adenomatoid lung malformation: report of two cases and literature review

Congenital cystic adenomatoid lung malformations may also be found [1]. The risk of recurrence of congenital cystic adenomatoid lung malformations in future pregnancies appears minimal since this embryonic developmental abnormality represents in most cases as a sporadic non-hereditary lesion [1]. In addition, this malformation is associated with certain genetic syndromes such as trisomy 18 [1]. In the cases we studied the fetal karyotypes were normal.

In the past, years before the advent of prenatal ultrasound imaging, the diagnosis of CCAM was made at autopsy or during investigation of respiratory disease in childhood. Garrett et al. made the earliest recorded ultrasound imaging diagnosis of CCAM in 1975 [8]. Improvements in ultrasound technology have led to an increase in the number of cases of CCAM diagnosed prenatally. In addition, the diagnoses are more precise and are made at earlier gestational ages.

The current sonographic descriptions are based on studies from Adzick et al. [6]. They classified congenital cystic malformations of the lung into two subgroups based on the sonographic appearances of the cysts and cyst dimensions: macrocystic CCAML, with cysts ≥ 5 mm and microcystic CCAML, with cysts < 5 mm. Reported prenatal prognostic features for CCAM include the size and type of the lesion, laterality, progression or resolution of the cysts, cardiac axis deviation, presentation with or development of hydrops, and findings of other structural anomalies [7]. The microcystic type tends to have a more adverse prognosis. On the other hand, lesions that regress have a better prognosis [7].

Prenatal ultrasound imaging demands special attention to the echogenicity of the lungs to detect fetal lung lesions. Disappearance of the lung lesions with spontaneous resolution in utero has been reported [9]. The initial size of the thoracic lesion may not always be helpful in predicting outcome since shrinkage of the lesion due to decompensation of fetal lung fluid through abnormal channels to the bronchi and the gastrointestinal tract has been reported. Another possible explanation is that the pulmonary lesions outgrow their vascular supply and involute [1].

The identification of CCAMs as either cystic or solid is quite practical because it provides more useful categories for determining options and prognosis [6]. The majority of fetuses with CCAM detected antenatally have a good prognosis but continuous surveillance is required due to the unpredictability of growth patterns for CCAM lesions [7].

In the case of lung malformations, associated anomalies and chromosomal aberrations are rare. The rate of associated anomalies is given in the literature as 11% [1]. When other structural anomalies are recognized, a karyotyping analysis should be performed. Organs that may be affected are the kidneys (renal agenesis), the heart (truncus arteriosus communis, tetralogy of Fallot) and the gastrointestinal tract (atriesia, diaphragmatic hernia). Hydrocephalus and skeletal malformations may also be found [1].

Pulmonary rhabdomyosarcoma (RMS) and bronchoalveolar carcinoma (BAC) are reported complications of CCAM [10]. Increased cell proliferation, decreased apoptosis and malignant transformation of the glandular component are considered to be carcinogenic mechanisms in CCAM. RMS occurs early in childhood (about 3 years) and should be treated by lobectomy and combination cytotoxic chemotherapy. In contrast, BAC accounts for about 15% to 20% of all lung cancers and its incidence appears to increase. The mean age that this carcinoma occurs is about 50 years; however, in those cases related to CCAM, there is an earlier presentation (about 20 years). In these tumors a prominent mucinous component can be found, and this seems to be particularly prevalent in associated cysts.

Newborn infants with congenital cyst malformations of the lung present varying degrees of respiratory difficulty [1]. Respiratory distress can develop not only from the lung hypoplasia or agenesis, but also because the abnormal cysts can fill with air and compress the adjacent healthy lung tissue after an infant takes its first breaths [6].

Current neonatal and pediatric management involves constant observation and stabilization within the neonatal unit. If respiratory distress is present then a computed tomography (CT) examination is performed and surgery is undertaken immediately. Otherwise, the CT examination is performed with the patient under general anesthesia at four to six months of age, and surgery is postponed until the patient is between six and 12 months old. Ten percent of the cases with congenital cystic adenomatoid malformations of the lung present with problems after the first year of life and they do so because of recurrent respiratory tract infections [1]. Thoracotomy with lobectomy is the treatment of choice. If the lesion is more extensive, further limited partial resection may have to be performed to avoid chest wall deformation.

Surgical operations have been performed for the correction of such fetal malformations, even on the fetus in utero [11]. However, if the malformation appears major and ultrasound indicates other associated problems such as hypoplasia of the remaining lung, then a poor outcome is to be expected [1]. In our cases the ultrasound scan that was performed on the first patient detected areas with small cystic lesions that were classified as a type-II congenital cystic adenomatoid malformation of the lung. No cystic lesions or other abnormal ultrasound findings were observed in the second patient. Both patients had to terminate the pregnancy because of spontaneous rupture of the membranes.

In conclusion, we have presented two rare cases of type-II congenital cystic adenomatoid malformations of the fetal lung and described the ultrasonographic and pathologic findings of this entity.

References


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Spontaneous heterotopic pregnancy leading to intrauterine abortion and subsequent ruptured ectopic pregnancy with a βhCG of 125 mIU/ml: a case report

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Summary
A case of heterotopic pregnancy after spontaneous conception with abortion of the intrauterine pregnancy and subsequent rupture of the ectopic pregnancy is presented. A 34-year-old woman at five weeks of gestation presented with a ruptured ectopic pregnancy after spontaneous abortion of an intrauterine pregnancy with mIU/ml βhCG as low as 125 mIU/ml. Close monitoring of βhCG and careful ultrasound examination together with patient consultation are extremely important in the management of heterotopic pregnancy, especially in cases of diagnostic uncertainty.

Key words: Heterotopic pregnancy; βhCG; Spontaneous pregnancy; Combined ectopic pregnancy; Simultaneous intra- and extrauterine pregnancy.

Introduction
The definition of heterotopic pregnancy is the simultaneous development of a gestation within the uterine cavity and a gestation outside the uterine cavity. In natural conception cycles it is a rare event occurring less than 1:30,000 pregnancies [1]. With assisted reproduction techniques (ART) this incidence rises up to between 1:300 and 1:500 [2, 3]. The etiology is obviously normal implantation of a fertilized ovum within the uterine cavity and an abnormal implantation of a fertilized uterus outside the uterine cavity.

In the general population the major risk factors for heterotopic pregnancy are the same as those for ectopic pregnancy. For women in an assisted reproductive program there are additional factors: a higher incidence of multiple ovulation, a higher incidence of tubal malformation and/or tubal damage, and technical factors in embryo transfer which may increase the risk for ectopic and heterotopic pregnancy [4].

The differential diagnosis in a patient with heterotopic pregnancy is a normal intrauterine pregnancy, a normal intrauterine pregnancy and a ruptured ovarian cyst, a corpus luteum, or an appendicitis.

The prognosis for the extrauterine fetus is very poor, having an estimated 90-95% mortality rate. The mortality rate for intrauterine pregnancy is approximately 35% [4].

Case Report
We present a case of a pregnancy after natural conception in a women who first visited our department at five weeks of gestation with a βhCG of 689 mIU/ml and an endometrial sac of 4.6 mm during ultrasound examination. Three days later she presented with bleeding per vaginum and a βhCG of 250 mIU/ml. During the following days the clinical signs and symptoms were of inevitable abortion, so an evacuation of retained products of conception (ERPC) was performed and the patient was discharged the next day. The histological examination confirmed the diagnosis of abortion.

Three days after the ERPC she returned complaining of severe lower abdominal pain. An ultrasound examination reported a mass of mixed echotexture measuring 23 x 19 mm next to the left ovary, together with a large amount of free fluid and clots in the pouch of Douglas. The blood βhCG levels were only 125 mIU/ml at that time. Emergency laparotomy was performed and a left salpingo-oophorectomy was carried out. The histological report confirmed the presence of an ectopic pregnancy inside the left fallopian tube.

Discussion
This case is an extremely rare situation in which natural conception led to heterotopic pregnancy. In addition, a ruptured ectopic pregnancy took place with very low βhCG blood levels. This raises many concerns about extra-cautionary measures that need to be taken in cases of intrauterine pregnancy abortion, as well as the importance of performing a very precise ultrasound pelvic scan.

On the other hand the βhCG blood levels should probably be measured on at least two consecutive occasions to detect any falling pattern, and also to closely observe the patient, even with low levels of βhCG, until the level is undetectable. It should always be kept in mind that these values may be misleading in heterotopic pregnan-
cies; subnormal hormone production from ectopic gestation may be masked by the higher placental production from intrauterine pregnancy [5]. In this case the patient should be consulted and remain close to medical care.

The diagnosis of heterotopic pregnancy is often difficult as the symptomatology can often be misleading. Maternal and intrauterine fetal prognosis depends on early diagnosis which should be made, if possible, prior to termination of the extra-uterine pregnancy. Lower quadrant pain is the most common clinical sign of emergency patients admitted to hospital because of acute abdominal pain [6]. Cases have been reported, where the clinical signs were minimal i.e., right lower quadrant pain with mild cramping. In these cases heterotopic pregnancy was not suspected [7, 8].

Conclusion

During the last decade a remarkable increase in the rate of heterotopic pregnancy has been observed, especially with the use of ART e.g., the induction of ovulation, in vitro fertilization and embryo transfers in infertile women [9]. Heterotopic pregnancy is rare in spontaneous conception.

Nonetheless we should always be cautious about this rare, but life-threatening condition. Diagnosis is based on a precise ultrasound examination and serial βhCG measurements. In our patient, even with low βhCG levels, there was a risk of an emergency situation. As a matter of fact we should have kept the patient under close observation even after hospital discharge i.e., advised her to be aware of any clinical signs and symptoms, and to stay in close proximity of medical care.

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Tubal ectopic pregnancy associated with an extraskeletal chondroma of the fallopian tube: case report


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Summary
Extraskeletal chondroma is a relatively uncommon benign soft tissue tumor, which usually occurs in the hands and feet. The tumor may also occur around the tendon, synovium, or joint capsule. Rare sites are the tongue, testes and liver. Chondroma of the fallopian tube is extremely rare, with only two reports in the English literature. We present the first reported case of extraskeletal chondroma of the fallopian tube causing transportation impairment of the fertilized ovum in a 32-year-old gravida 1, para 1 woman.

Key words: Extraskeletal tumor; Chondroma; Osteochondroma; Fallopian tube; Soft tissue neoplasms; Cartilaginous tumor; Benign tumor.

Introduction
Extraskeletal chondroma is a relatively uncommon benign soft tissue tumor [1]. It is a small, slow growing and usually a well-defined nodule of cartilage that is not attached to bone [2, 3]. Other terms used for this lesion are soft-tissue chondroma or osteochondroma and pararticular or intracapsular chondroma [1]. The most common affected sites are the hands and feet (in about 96% of cases) [4]. The mass may also occur around the tendon, synovium, or joint capsule. Rare sites such as the tongue, testes and liver have been documented [1, 3, 4, 5]. The occurrence of extraskeletal chondroma in the fallopian tube is extremely rare. To our knowledge there have been only two previous reports of chondroma at this site [3, 6].

The present case illustrates the rare coexistence of an ectopic pregnancy and an extraskeletal chondroma arising from the fallopian tube in a 32-year-old woman. To our knowledge this is the first reported case of extraskeletal chondroma of the fallopian tube causing transportation impairment of the fertilized ovum and consequent ectopic pregnancy.

Case Report
A 32-year-old Albanian female, gravida 1, para 1, was referred to the Department of Obstetrics and Gynecology, “Tzaneion” General State Hospital, Piraeus, because of abnormal vaginal bleeding and lower abdominal pain six weeks after her last menstruation. A pregnancy test was positive. Pelvic examination revealed an anteverted, uterus; the right adnexa was tender and palpable. Transvaginal sonography showed the absence of an intrauterine gestational sac and endometrium of normal thickness. Also, the presence of an ectopic pregnancy in the right fallopian tube was suspected. No intraperitoneal fluid was reported. Her serial serum beta-hCG titers were 3700 mIU/ml and 5600 mIU/ml the first and third preoperative days, respectively. The preoperative hematological date showed: hemoglobin 13.1 g/dl, hematocrit 39%, platelet count 269 x 10^9/l and leukocyte count 6.26 x 10^9/l. Preoperative biochemical tests were within normal rates. Under the diagnosis of ectopic pregnancy, a laparotomy was performed. The uterus and left adnexa looked normal, however the right fallopian tube was enlarged, suggesting a right tubal pregnancy (Figure 1). Salpingotomy was performed making a longitudinal incision on the anterior mesosalpinx of the tube and the products of conception were seen inside the tube (Figure 2). Also, a whitish mass measuring 1.5 cm in the greatest dimension was found within the right fallopian tube (Figures 3-5). The mass was firmly attached to endosalpinx (Figure 6) and we removed it very carefully. Finally, the products of conception were extracted and repeated washing of the pregnancy bed resulted in complete removal of all trophoblastic tissue. Once the ectopic material was extracted, meticulous hemostasis was carried out and the incision was left open (Figure 7). The postoperative recovery was unremarkable and the patient was discharged on the fourth postoperative day. The mass was smooth and ovoid with a nodular surface and the histopathology confirmed the presence of an extraskeletal chondroma.

Discussion
Extraskeletal chondroma constitutes approximately 1.5% of benign soft tissue tumors [3]. It occurs predominantly in people of either sex, who are between the fourth and sixth decades of life. However, there is very wide age range, with lesions presenting in patients from one to 85 years [3, 4, 7]. Grossly, these tumors are firm, well circumscribed, lobulated and often encapsulated and have a glassy, myxoid or calcified cut surface. The lesions rarely exceed 3 cm in their maximum diameter [3, 8]. On light microscopic findings, the tumors are composed of mature hyaline cartilage [3]. Areas of calcifica-
Figure 1. — The right fallopian tube is enlarged suggesting a tubal pregnancy.

Figure 2. — Salpingotomy is performed making a longitudinal incision on the anterior mesosalpinx of the right fallopian tube and the products of conception are recognized inside the tube.

Figures 3-5. — A whitish mass measuring 1.5 cm in the greatest dimension is found within the right fallopian tube at the position of implantation of trophoblastic tissue.

Figure 6. — The mass is firmly attached to the endosalpinx.

Figure 7. — The incision is allowed to heal without primary closure.
tion are identified within the hyaline cartilage and some of the tumors show ossification, fibrosis and myxoid changes. Cellularity of the tumor is quite variable [1, 8, 9]. In addition, granulomatus proliferation consisting of multinucleated giant cells and epithelioid cells is sometimes observed [10]. Cellular atypia may be seen histologically, but no malignant transformation or metastatic lesions have been demonstrated [8, 9]. Lesions appear to arise de novo without any apparent precursor [8]. The differential diagnosis includes tumoral calcinosis, juxtacortical chondromyxoid fibroma, Hoffa’s disease, mesenchymoma, synovial chondromatosis, myositis ossificans, periosteal desmoid tumor and soft-tissue chondrosarcoma [2, 3, 4]. Treatment of choice is local excision. Of importance, the tumor should be removed completely, due to the high recurrence rate of 10-15% [3].

We have presented a case of an extraskeletal chondroma of the right fallopian tube as the cause of an ectopic tubal pregnancy in a 32-year-old woman. In general, any factor which impairs the ability of the tube to transport the fertilized ovum predisposes to tubal implantation. Hence, congenital tubal abnormalities, failed tubal sterilization, reconstructive tubal surgery, salpingitis isthmica nodosa, post-inflammatory tubal damage and primary neoplasms of the fallopian tube are all associated with an increased incidence of tubal pregnancies [11]. However, an extraskeletal chondroma arising in the fallopian tube is the most unusual predisposing factor for tubal pregnancies.

References


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Leiomyomatosis with multiple extrauterine pulmonary sites: an unusual case report

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Summary
The objective of the present study is to present a case of a 48-year-old woman with leiomyomatosis and multiple pulmonary metastases. The classification, pathophysiology, clinical signs, treatment and prognosis of this rare case are discussed. Leiomyomatosis is potentially life-threatening while patients with pulmonary metastases are usually asymptomatic and the condition is incidentally discovered. The treatment of leiomyomatosis is not standardized and many possible variations are under investigation. Still the prognosis is usually excellent.

Key words: Leiomyomatosis; Pulmonary masses.

Introduction
Leiomyoma or fibroid [1] is a growth of the muscular wall of the uterus which is benign most of the time (> 99%). Uterine leiomyomas are the most common gynecological tumors especially in the fourth and fifth decades of life. They are composed of smooth muscle cells with varying amounts of fibrous connective tissue. Leiomyomas occur in 20% to 30% of women of reproductive age. They are thought to arise from a somatic mutation of a monoclonal myometrial cell line. Myomas are sensitive to estrogen levels as they contain both progesterone and estrogen receptors. They usually grow during a woman’s reproductive period and frequently shrink after menopause.

Metastatic leiomyomatosis is a rare but potentially life-threatening situation. It presents post-hysterectomy with multiple extrauterine metastatic sites, most commonly pulmonary [2-5], but also the inferior vena cava and right heart can be affected [6]. Other possible metastatic sites are the lymph nodes, peritoneum and retroperitoneum [7].

Case Report
We present a case of a 48-year-old woman (gravida 2, para 2) who presented at our gynecological clinic with the suspicion of leiomyomatosis with multiple pulmonary sites. The patient had a non-productive cough. Her previous medical history included the removal of a leiomyoma of the uterus (5 cm) two years prior to presentation. Vital signs were within normal limits. Gynecological examination revealed a pelvic tumor 6 cm in diameter. Chest X-ray showed multiple bilateral pulmonary nodules. Ultrasonographic examination revealed a pelvic tumor 7 cm in diameter. The chest and abdominal computed tomography confirmed the aforementioned findings.

The patient underwent an exploratory laparotomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. The postoperative period was uneventful.

Pathologic examination revealed that the tumors were composed of smooth muscle cells without mitotic activity. Histology confirmed metastatic leiomyomatosis (Figure 1). A decrease in hormone levels led to stable pulmonary lesions with an excellent prognosis after three years of follow-up.

Discussion
Our patient had leiomyomatosis in combination with multiple extrauterine pulmonary metastatic sites. According to Martin’s classification system three types of smooth muscle tumors exist [8]: leiomyomatosis, metastatic leiomyoma, and multiple fibroleiomyomatous hamartomas. Leiomyomatosis occurs exclusively in women with uterine leiomyomas and is further subdivided into benign metastasizing leiomyoma, lymphangiomyomatosis (lymphangioleiomyomatosis), disseminated peritoneal leiomyomatosis, and intravenous leiomyomatosis.

There is a proposed classification system for multiple lung smooth muscle lesions:

a) benign metastasizing leiomyoma: uterine source in mature women;

Figure 1. — Leiomyomatosis of the uterus.
b) metastatic leiomyoma: extraterine source in children and men;

c) multiple fibroleiomyomatous hamartoma: no extrapulmonary source.

Birch-Hirschfield [9] described intravenous leiomyomatosis as a uterine tumor with benign-appearing smooth muscle within the veins or lymphatics which can enter the inferior vena cava, heart, and lung. Benign metastasizing leiomyoma (BML) is described by Steiner et al. [10] and others as a well-differentiated tumor composed of smooth muscle cells and dense connective tissue which can also travel to the lung. Canzonieri et al. [11] believed that the two are “the same pathological entity with different clinical features”.

The lesions have specific microscopic features characterized by smooth muscle cells without aplasia or vascular invasion and rare mitosis. Some lesions are less cellular with moderate amounts of collagen. After immunochemistry assays, strong reactivity for desmin and muscle specific actin is found as well as estrogen and progesterone receptors.

The mechanism of the tumor diffusion is not clear. Intravascular tumor dissemination from surgical trauma is a commonly postulated mechanism as many of the reported cases of pulmonary metastasis occur in patients with a history of previous hysterectomy [12, 13]. Others believe pulmonary metastasis is from microscopic vascular invasion of the leiomyoma into the venous system (intravenous leiomyomatosis). This could explain the concurrence of pulmonary nodules and a uterine tumor before surgery in some cases [14, 15].

Metastatic leiomyomatosis occurs through hematogenous metastases from benign uterine leiomyomas. The metastatic cells spread throughout the uterus into pelvic venous channels [5]. Even though many authors assume that multiple pulmonary leiomyomas (MPL) is a lung metastasis of benign tumors, the pathogenesis is still hypothetical. Supporting this theory is the hormone dependence of both the uterus and the pulmonary tumors; in contradiction is the fact that extrapulmonary metastases from benign uterine leiomyomas. The lesions have specific microscopic features characterized by smooth muscle cells without aplasia or vascular invasion.

The presenting symptoms are non-specific and leiomyomatosis has a broad differential diagnosis, including malignant metastases and infectious inflammatory granulomas. Other possibilities include sarcoidosis, rheumatoid nodules, amyloidosis, and arteriovenous malformations. Percutaneous or open biopsy could be used to confirm the diagnosis.

There is no standardized treatment for leiomyomatosis. Whenever technically possible, a radical parenchymasaving surgical therapy should be the first choice, and thus hysterectomy with bilateral salpingo-oophorectomy is performed to remove the primary tumor and decrease estrogen and progesterone levels [12, 13]. Martin [8] and Matsumoto et al. [20] found that pulmonary lesions remained stable in size after hysterectomy/bilateral salpingo-oophorectomy. Kullo et al. [21] reported using megestrol as a hormonal agent to treat these hormonesensitive tumors. Surgical resection is feasible if the pulmonary lesions are localized.

Prognosis is excellent and affected women usually die from other causes rather than leiomyomatosis. Hormonal manipulation (surgical or medical) is central to disease management. The clinical course of patients with pulmonary BML is usually indolent. Abramson et al. reviewed seven patients with BML in the lungs and found no significant morbidity or mortality on long-term follow-up. They also did not find much correlation between the patients’ respiratory symptoms and the radiologically assessed disease extent [14]. The disease course depends on the estrogen and progesterone status of the patients. In postmenopausal women most of the pulmonary nodules will either regress or remain static, whereas in premenopausal women disease progression has been reported.

**Conclusion**

Leiomyomatosis is a rare situation and the co-existence of pulmonary metastases is even rarer. However, the prognosis after careful management is excellent.

**References**


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