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Contents

Clinical and Experimental Obstetrics & Gynecology - Vol. XXXVI, no. 3, 2009

ORIGINAL ARTICLES

Reproductive Biology Section

CASE REPORTS

Original Articles

Reproductive Biology Section

Failure to have menses following progesterone withdrawal in a normal estrogenic woman with polycystic ovarian syndrome who menstruates with oral contraceptives

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Summary

Purpose: To evaluate a case of a normal estrogenic woman with amenorrhea and polycystic ovarian syndrome who fails to get menses after progesterone withdrawal but who menstruates with oral contraceptives. *Methods:* The following sera assays were obtained: total testosterone (T), free T, weakly bound T, dehydroepiandrosterone sulfate, 17 hydroxyprogesterone, estradiol, free thyroxin, thyroid stimulating hormone, prolactin, evening cortisol, LH and FSH. *Results:* The total testosterone was markedly elevated but the free testosterone was normal and the free and weakly bound testosterone was the high end of normal. The LH/FSH ratio was markedly increased consistent with the ultrasound findings of polycystic ovarian syndrome. Vaginal cytology showed a mixed high estrogen/high androgen effect and the endometrial thickness was only 5 mm. Twice she failed to have menses following progesterone withdrawal. *Conclusions:* One hypothesized mechanism is that the high testosterone levels even though mostly in the bound form inhibited estrogen from causing adequate endometrial development.

Key words: Progesterone withdrawal; Amenorrhea; Endometrial thickness; Polycystic ovarian syndrome; Testosterone.

Introduction

The classic dogma concerning polycystic ovarian syndrome (POS) is that women with POS are hyperestrous, tend to form thicker endometria because of lack of progesterone opposition and are more prone to endometrial hyperplasia. Some clinicians suggest that when faced with a woman with amenorrhea and clinical symptoms and signs of androgen excess a progesterone withdrawal test should be performed and if menses ensue the woman probably has POS. To be sure that a 21 hydroxylase type of congenital adrenal hyperplasia does not exist, a serum 17 hydroxyprogesterone level could be drawn and if normal the diagnosis would be POS.

If a woman with apparent polycystic ovaries does not achieve menses following progesterone withdrawal then she could be pregnant or have some problem with the endometrium, e.g., intrauterine adhesions (Asherman's syndrome).

A case is described of a woman with normal estrogen who was not pregnant, never had an intrauterine procedure, and did show a normal uterine component by having menses while using oral contraceptives, and yet failed to get menses after progesterone withdrawal. A theory will be presented to explain this apparent paradox.

Case Report

A 30-year-old woman who was five feet tall and weighed 112 pounds presented with secondary amenorrhea. She was diagnosed as having POS based on the classic appearance on pelvic sonography and increased serum androgen levels. Her referring physician had obtained the following serum levels: serum testosterone 137 ng/dl (nl 20-76 ng/dl) and serum estradiol 105 pg/ml. Furthermore, she did not have insulin resistance as evidenced by her glucose level of 85 mg/dl with a serum insulin level of < 2 uIU/ml) (nl = 0-29.1 uIU/ml). She had the classic increased LH/FSH ratio with LH = 15.8 mIU/ml and the serum FSH was 2.9 mIU/ml. Serum prolactin was normal at 5.6 ng/ml.

Clinically, besides the amenorrhea for one and a half years, she only had mild hirsutism of the upper lips with no other androgen excess symptoms or signs.

The woman had failed to have withdrawal menses two times with 10 mg medroxyprogesterone acetate for 12 days. Repeat testing revealed a total serum testosterone (T) of 141 ng/dl, sex hormone binding globulin of 85 nmol/l (nl - 14 to 102 nmol/l, serum-free testosterone of 14 pg/ml (nl - 1-21pg/ml), serum testosterone free and weakly bound of 29 ng/dl (nl = 3-29 ng/dl), serum LH of 22.3 mIU/ml and serum FSH of 4.4 mIU/ml, a serum 17 hydroxyprogesterone level of 189 ng/dl (normal follicular phase 185 or less), dehydroepiandrosterone (DHEA) sulfate level of 131 mcg/dl (nl - 40-325 mcg/dl), a serum beta hCG level of < 2 mIU/ml, and a pm cortisol of 5.0 mcg/dl (normal for time taken 3.0-17 mcg/dl). Her free thyroxin and thyroid stimulating hormone levels were normal.

The woman was not trying to conceive and previously had stopped oral contraceptives because of side-effects. Since she had only minimal clinical manifestations of her markedly elevated serum testosterone (T) she elected not to do anything

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about the elevated level. She was advised to recheck the T level in four months since a rapidly rising level could increase suspicion of a T-secreting ovarian or adrenal neoplasm possibly causing a polycystic ovarian state [1, 2]. Since she was producing adequate estrogen she was advised not to take estrogen replacement. Furthermore since the ultrasound showed in addition to the classic polycystic ovary appearance (right ovary measured 33 x 42 x 37 mm and left ovary 53 x 78 x 56 mm with multiple follicles about 6 mm in a pearl necklace pattern) that she only had a 5 mm endometrium, she was advised not to take supplemental progesterone for unopposed estrogen as is the typical suggestion for POS.

Her vaginal cytology showed the classic mixed hormonal effect, i.e., superficial cells and parabasal cells seen together on the same slide, thus showing a high estrogen effect and high androgen effect.

Discussion

It is not clear why despite the very high serum testosterone (higher than most women with POS) the serum free testosterone was quite normal. The active hormones are considered the free and weakly bound T and that level was the high end of normal.

The normal free and the top normal free and weakly bound T could explain the lack of clinical androgen clinical manifestation other than very mild hirsutism of the upper lip but does not explain the reason for the high total T since the sex hormone binding globulin level was normal.

If there was a high level of active T it could be hypothesized that testosterone competes with estrogen in stimulating the growth of the endometrium. However the free T was completely normal. The possibility exists that although the bound T is not considered to be a major factor in hirsutism, acne and alopecia, it may still be very active in acting to compete with estrogen in the genitourinary tract. This would also explain why despite the absence of hyperandrogen characteristics there was a marked androgen effect seen on vaginal cytology. The mixed hormonal effect seen on vaginal cytology is usually only found with severe hyperandrogen states.

Another possible explanation is that this woman fortuitously had a paucity of receptors in the hair follicles and skin for dihydrotestosterone to explain the absence of hirsutism, acne or alopecia. The explanation for the normal free T level could be laboratory error for the free T assay but not for the total T assay.

Whichever theory is operational in this woman, this case demonstrates that one cause of failure to have menses following a challenge with progesterone withdrawal in a woman with normal estrogen could be high levels of testosterone competing with estrogen leading to a thinned endometrial lining. The analogy is similar to the inhibition of menses by combining daily conjugated estrogen replacement in menopausal women with a small daily dosage of medroxyprogesteorne acetate or newly developed oral contraceptives that lead to poor endometrial development and lack of menstrual shedding by daily consumption of a pharmacologic higher level of estrogen than is normally made with a potent 19-nor testosterone derived progestin.

The question arises that if this hypothesis of high androgen levels interfering with endometrial development is correct why did this woman have adequate menses while on the oral contraceptives? The possibility exists that by the oral contraceptive suppressing pituitary LH the testosterone levels were suppressed while taking the oral contraceptive and thus did not compete with estrogen in causing endometrial proliferation.

Based on these observations and hypothesis the woman was advised that when she is ready to conceive it may be necessary to find an oral contraceptive that she can tolerate to lower the androgen levels before starting follicular maturation drugs to induce ovulation to allow adequate endometrial development. Alternatively, she could be pretreated with a GnRH agonist with replacement estrogen therapy.

Generally, when such high levels of total T are generated with polycystic ovaries, hyperthecosis and marked insulin resistance are present. This patient clearly did not even have a trend for insulin resistance. Though this very high testosterone level was obtained twice two months apart, drawn from two different offices, the blood was sent to the same commercial laboratory. Thus the possibility exists that the free and weakly bound T levels were accurate but the total T was falsely high. In this case it could be hypothesized that the endometrium of some women may be markedly sensitive to even top normal free plus loosely bound testosterone thus inhibiting endometrial development.

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Donor-recipient pairs to evaluate the effect of day 3 embryos having at least six blastomeres on pregnancy outcome

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Summary

Purpose: To determine if having all embryos transferred with at least six blastomeres improves pregnancy rates compared to women having an embryo transfer with at least one embryo with less than six cells. *Methods:* Donor-recipient pairs were used to help remove the confounding effect of egg quality. Four donor-recipient pair types were evaluated: 1) both donor and recipient had all embryos with at least six cells, 2) neither donor nor recipient had all embryos with ≥ 6 cells, 3) donor but not recipient had all ≥ six cell embryos, 4) recipient but not donor had all embryos with ≥ six cells. Combining donor and recipients there was a significantly higher pregnancy rate per transfer when all embryos had at least six blastomeres (50/92 or 54.3%) vs the group with at least one embryo with < 6 cells (46/121 or 38.8%). Similarly the implantation rate was significantly higher (37.8% vs 20.3%). *Conclusions:* These data corroborate conclusions made by evaluating single embryo transfer in women with diminished egg reserve that the presence of at least six blastomeres is associated with a better chance of a given embryo to implant

Key words: Blastomere number; Implantation rate; Donor egg.

Introduction

Previous studies found improved outcome when at least one embryo in a multiple embryo transfer (ET) had six to eight blastomeres [1, 2]. Single ET may be the best way to determine which embryos have the highest implantation potential. Studies of the outcome of single ET have demonstrated that embryos with six to eight blastomeres on day 3 are more likely to implant compared to embryos with four to five blastomeres [3].

The objective of the present study was to determine if having 100% of the embryos transferred with at least six blastomeres vs at least one embryo with less than six cells has any impact on delivered pregnancy and implantation rates by comparing donor recipient pairs. The source of eggs from donors was chosen to eliminate the potential for egg quality to be a confounding variable.

Materials and Methods

A retrospective review from 1/1/97 to 7/31/06 was performed on all fresh ET cycles in our shared donor program in which both the donor and oocyte recipients were trying to conceive. Donors and recipients were each divided into four groups according to whether all embryos transferred had at least six blastomeres (Type I) vs at least one embryo with less than six cells (Type II). There were four pair groups established: Group 1 – both donors and recipients had Type I embryos transferred, Group 2 – both donors and recipients had Type II embryos transferred, Group 3 – donors had Type I, recipients had Type II, Group 4 – donors had Type II, recipients had Type I.

All women had a normal uterine cavity by hysterosalpingogram or saline infusion sonography All pairs had ET on the same calendar date and by the same physician. All embryos were three days old at the time of ET. Luteal phase progesterone support was given to all women.

Clinical (ultrasound evidence of pregnancy at 8 weeks), and live delivery rates and implantation rates were compared in the four groups. Chi-square analysis was used to assess the comparisons with a p value of .05 to determine significance.

Results

There were 151 donor-recipient pairs who fulfilled the criteria. Distributions by group, pregnancy and implantation rates are seen in Table 1.

More women in the study (92/151 (60.9%) for donors and 89/151 (58.9%) for recipients) had ETs with all embryos having six or more blastomeres. There was no difference in delivered pregnancy rates (PR) for donors, 47.7% (72/151) and recipients, 48.3% (73/151).

No differences in PR were observed when both donor and recipient had the same Type ET; Type I – donor PR 54.3% (50/92) vs recipient PR 55.1% (49/89) and Type II – donor PR 37.2% (22/59) vs recipient 38.7% (24/92). The implantation rate was higher in recipients at 33.4% (154/461) than in donors at 27.3% (116/424) but the difference was not significant.

The PR and implantation rates for donors that had Type I embryo transfers showed a trend for higher pregnancy rates than those for recipients with Type II embryos but the difference was not significant. Statistical differences for PR and implantation rates were observed when donors had Type II ET and recipients had Type I ET.

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Table 1. — *Comparison of pregnancy rates (PR) and implantation rates (IR) in donors vs recipients according to whether all embryos transferred had at least six blastomeres (Type I) or not (Type II).*

Group	Variable	Donor	Recipient
Both Type I	Average no. of blastomeres	7.76 ± .81	7.87 ± .82
(n = 68 pairs)	Deliveries	52.5% (36/68)	50.0% (34/68)
	Implantation rate	31.5% (59/187)	38.0% (73/192)
		p = NS, donors vs recipients in group 1	
Both Type II	Average no. of blastomeres	5.10 ± 1.1	5.16 ± .97
(n = 38 pairs)	Deliveries	36.8% (14/38)	34.2% (13/38)
	Implantation rate	18.3% (21/115)	20.1% (26/129)
		p = NS, donors vs recipients in group 2	
Donor Type I	Average no. of blastomeres	7.48 ± .96	5.89 ± .66
Recipient Type II	Deliveries	58.3% (14/24)	45.8% (11/24)
(n = 24 pairs)	Implantation rate	36.5% (23/63)	22.5% (18/80)
		p = NS for PR and $p < .07$ for IR	
Donor Type II	Average no. of blastomeres	5.89 ± 1.07	7.38 ± .84
Recipient Type I	Deliveries	38.1% (8/21)	71.4% (15/21)
(n = 21 pairs)	Implantation rate	22.0% (13/59)	45.0% (27/60)
		p = .03 for PR and p = .008 for IR	

NS = non significant.

Overall, when combining donors and recipients, the pregnancy rate was 54.7% (99/181) in Type I ET and 38.0% in Type II ET (46/121) (p = .0049). The overall implantation rate was 37.8% (182/320) for Type I ET and 20.3% (78/385) for Type II ET (p = .0001).

Conclusions

PRs are lowered when not all of the embryos transferred have six or more blastomeres even though there is a least one with six blastomeres. There is a greater impact on implantation rates than on PRs when lesser quality embryos are transferred. These data support conclusions reached by the evaluation of single ET embryo transfers in women with diminished egg reserve [3].

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Effects of endometrial thickness and echogenic pattern on assisted reproductive treatment outcome

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Summary

Purpose: To assess the effects of endometrial thickness and echogenicity on pregnancy and implantation rates in cases using assisted reproductive technology (ART). *Methods:* We retrospectively analyzed the data of 241 ART cycles performed at Istanbul Medical Faculty, Reproductive Endocrinology Unit. The cycles were classified into three groups according to ultrasonographic endometrial thickness measurements on the day of hCG application; 51 cases (group 1) ≤ 8 mm, 182 cases (group 2) between 8-14 mm, and eight cases (group 3) ≥ 14 mm. Also the cycles were grouped according to endometrial echogenicity as trilaminar, isoechogenic and hyperechogenic pattern. *Results:* There was no significant difference in pregnancy rates between the three endometrial thickness groups and echogenic patterns. When conception and non-conception cycles were compared, no significant difference in endometrial thickness was observed (9.88 ± 1.83 mm vs 9.84 ± 1.89 mm). *Conclusion:* Ultrasonographic evaluation of endometrial thickness and pattern is not useful in predicting implantation and conception rates in ART cycles.

Key words: Endometrial thickness; Endometrial pattern; Pregnancy outcomes; ART.

Introduction

Endometrial receptivity is one of the most important factors in the implantation process. However the optimal method for endometrial receptivity has not been found yet. Although ultrasound (US) has allowed endometrial thickness and echogenic pattern to be evaluated during controlled ovarian hyperstimulation, their effects on predicting implantation remain controversial. Several studies have shown that endometrial thickness lower or higher than a definite range affects pregnancy rates negatively [1, 2]. Others, on the contrary, have failed to find any relation between edometrial thickness and implantation rates [3, 4]. Furthermore, some studies have suggested that a trilaminar pattern is a good prognostic factor for achieving pregnancy [5]. However, other authors do not accept endometrial echogenicity as a predictive factor for implantation [6]. The clinical significance of sonographic features remains unclear.

Materials and Methods

We have retrospectively analyzed the data of 241 cases using assisted reproductive technology (ART) performed at the Reproductive Endocrinology Unit of Istanbul Medical Faculty, during the period from February 2005 to February 2007. Long and antagonist protocols were performed for the controlled ovarian hyperstimulation according to the patient's age, ovarian reserve and previous response to ovarian stimulation. In the long protocol with GnRH agonist, 1 mg of leuprolide acetate (Lucrin) s.c. was started on the 21st day of the previous cycle. After the baseline ultrasonographic evaluation of the endometrium and ovaries on the third day of the cycle, either recombinant FSH (Puregon, follitropin beta or Gonal-F - follitropin alfa) or human menopausal gonadotrophin (hMG) was started for ovarian stimulation with an appropriate dosage; GnRH agonist dosage was reduced to 0.5 mg daily. In the antagonist protocol, ovarian stimulation was started on the third day of the cycle and GnRH antagonist of 0.25 mg cetrorelix (Cetrotide) s.c. was applied when the leading follicle became 13-14 mm in diameter throughout the stimulation. The response to treatment was monitored daily by transvaginal ultrasound (TVS) measurements of endometrial thickness – the greatest anteroposterior dimension in a longitudinal section – and follicular diameters. Human chorionic gonadotropin (10000 IU; Profasi or Pregnyl) was administered IM when there were two or more follicles > 18 mm and several follicles ≥ 14 mm. Oocyte retrieval was performed approximately 36 hours after hCG administration by TVS-guided follicular aspiration. Three days after oocyte retrieval usually three but occasionally one or two embryos of grade 1 and 2 were replaced. Pregnancy was diagnosed by serum concentration of β-hCG on the 12th day of embryo transfer.

The cycles were classified into three groups according to ultrasonographic endometrial thickness measurements on the day of hCG application; 51 cases (group 1) ≤ 8 mm, 182 cases (group 2) between 8-14 mm, 8 cases (group 3) ≥ 14 mm. The cycles were grouped according to echogenicity as trilaminar (central and outer echogenic lines with hypoechogenic areas between them), isoechogenic (same reflectivity compared to myometrium) and hyperechogenic (increased reflectivity compared to myometrium) pattern. The pregnancy rates of these groups were compared. Conception and non-conception cycles were compared according to treatment characteristics and ovarian response.

Data were analyzed with the Statistics Package for Social Sciences (SPSS). The level of statistical significance was defined as $p < 0.05$. Statistical tests included χ^2, one-way ANOVA and Student's t test as appropriate.

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Results

The demographic characteristics of patients are summarized in Table 1. Among the 241 ART-embryo transfer cycles the total pregnancy rate was 26.6% (64 cycles).

Table 1. — *Summary of demographic data (values are mean ± SD).*

Total number of ART cycles	241
Age (years)	31.3 ± 5.4
Duration of infertility (years)	7.3 ± 4.5
Diagnosis (%)	
Male factor	45.6
Tuboperitoneal factor	17
Ovarian factor	5
Endometriosis	2.5
Unexplained	26.1
Multiple	3.7
Number of ART attempts	1.5 ± 1
Stimulation protocols (%)	
Long protocol	61
Antagonist protocol	39

Endometrial thickness measurements ranged from 6.5 to 16 mm with a mean of 9.85 mm. Table 2 shows the comparisons of the three groups according to the age, the day of hCG application, the total dose of gonadotrophin, number of oocytes retrieved and the number of embryos per transfer. None was significantly different. Pregnancy rates were 29.4% (15 cycles), 26.4% (48 cycles), 12.5% (1 cycle) respectively.

Table 2. — *Comparisons of variables between the groups according to endometrial thickness (values are mean ± SD).*

Variables	Group 1 (n = 51)	Group 2 (n = 182)	Group 3 (n = 8)	*p*
Age (years)	31.3 ± 5.4	31.3 ± 5.5	31.5 ± 5.8	n.s.
Day of hCG application	12.1 ± 1.8	12.6 ± 1.3	12.6 ± 1.4	n.s.
Total dose of gonadotrophins (IU)	3025.3 ± 1379.5	3308.5 ±1329.4	3309.3 ±2031.3	n.s.
Oocyte number	13.4 ± 7.8	12.7 ± 7	12 ± 8.7	n.s.
Embryo/transfer	2.7 ± 0.6	2.8 ± 0.5	2.6 ± 0.5	n.s.
Pregnancy rate (%)	29.4	26.4	12.5	n.s.

n.s. = not significant.

The trilaminar pattern was detected in 184 cycles, the isoechogenic pattern in 24 cycles and the hyperechogenic pattern in 33 cycles (Table 3). The pregnancy rates were 26.6% (49 cycles), 20.8% (5 cycles), 30.3% (10 cycles) respectively. There were statistically significant differences between the average ages ($p = 0.01$), the number of oocytes retrieved ($p = 0.01$) and embryos per transfer ($p = 0.05$).

The age distribution of patients was significantly different between conception and non-conception cycles (30.1 ± 5.1 vs 31.8 ± 5.5, $p = 0.05$). Day 3 E_2 levels, day 3 FSH levels, day of hCG application, total dose of gonadotrophin and number of oocytes retrieved were not significantly different in conception and non-conception cycles (Table 4). However the number of embryos per transfer was 2.9 ± 0.2 vs 2.7 ± 0.5 ($p < 0.005$). For those who conceived the mean thickness was 9.88 ± 1.8 mm as compared to 9.84 ± 1.8 mm for those that did not conceive.

Table 3. — *Comparisons of variables between the groups according to endometrial echogenicity (values are mean ± SD).*

	Trilaminar n = 184	Isoechogen n = 24	Hyperechogen n = 33	*p*
Age (years)	30.82 ± 5.33	33.04 ± 5.46	33.27 ± 5.57	< 0.05
Total dose of gonadotropin	3133.32	3469.79	3731.06	< 0.05
Endometrial thickness (mm)	9.79 ± 1.73	9.52 ± 2.07	10.45 ± 2.32	n.s.
Oocyte number	13.54 ± 7.37	11.79 ± 5.62	9.70 ± 6.72	< 0.05
Embryo/transfer	2.81 ± 0.49	2.83 ± 0.48	2.55 ± 0.71	< 0.05
Pregnancy rate (%)	49 (26.6%)	5 (20.8%)	10 (30.3%)	n.s.

n.s. = not significant.

Table 4. — *Comparisons of variables between the conception and non-conception cycles (values are mean ± SD).*

Variable	Conception (n = 64)	Non-conception (n = 177)	*p*
Age (years)	30.1 ± 5.1	31.8 ± 5.5	< 0.05
Day 3 FSH levels (IU/l)	6.5 ±1.9	7.1 ± 2.7	n.s.
Day 3 E2 levels (pg/ml)	49.1 ± 26.2	49.1 ± 29.6	n.s.
Day of hCG application	12.5 ± 1.5	12.5 ± 1.4	n.s.
Total dose of gonadotrophin(IU)	3092.5 ± 1206	3305.1 ± 1417	n.s.
Oocyte number	13 ± 6	12.7 ± 7.6	n.s.
Embryos/transfer	2.9 ± 0.2	2.7 ± 0.5	< 0.005
Endometrial thickness (mm)	9.88 ± 1.8	9.84 ± 1.8	n.s.

n.s. = not significant.

Discussion

As a result of non-invasive and easy evaluation of the endometrium by TVS, endometrial thickness and pattern have been one of the most commonly investigated issues as a prognostic factor of ART cycles. In the past many authors suggested that a favorable endometrial thickness can be used as an indicator of conception. However, recently most studies conclude that endometrial thickness at the time of hCG has only marginal prognostic value when extremes of poor growth are seen [7, 8].

This study indicates that there is no relationship between pregnancy rates and endometrial sonographic features. The absence of marginal values of endometrial thickness may be one of the reasons for this result. Although the pregnancy rate of group 3 was as low as 12.5%, the number of cycles was not sufficiently high enough to cause a significant difference. In contrast other to studies, the hyperechogenic pattern had a higher pregnancy rate despite the poor prognostic factors like older age, low number of oocytes retrieved and embryos per transfer. This may be because of the limited number of cycles with the hyperechogenic pattern which is only 33, since most of the cycles appeared to cluster in a trilaminar pattern.

The endometrium can be evaluated on the day of oocyte retrieval or embryo transfer as well as the day of hCG application. Since high levels of progesterone in the luteal phase have some effect on the endometrium, the day of evaluation may change the results of studies. In our study we preferred to measure the endometrium on the day of hCG application. Early evaluation also gives us the opportunity to cryopreserve embryos or postpone hCG in case of an unfavorable endometrium.

In summary, the study presented here shows that endometrial sonographic features have no significant effect on predicting pregnancy rates. On the contrary, age and number of embryos per transfer are the major prognostic factors for ART cycles.

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The effect of cetrorelix vs ganirelix on pregnancy outcome using minimal gonadotropin stimulation in women with elevated day 3 serum follicle stimulating hormone levels

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Summary

Purpose: To determine if the choice of gonadotropin releasing hormone antagonist influences subsequent pregnancy rates in women with diminished egg reserve. *Method:* Retrospective determination of pregnancy rates following embryo transfer in women with day 3 FSH > 12 mIU/ml using lower dose gonadotropin stimulation regimen. *Results:* Though no significant differences were found there was a trend for lower pregnancy rates with ganirelix vs cetrorelix. *Conclusions:* The trend for lower pregnancy rates with ganirelix vs cetrorelix seen in women with diminished egg reserve is consistent with the findings of a study performed in women with normal egg reserve using a normal gonadotropin stimulation regimen. It is not clear if the adverse effect is on the endometrium or the embryo.

Key words: Decreased egg reserve; Ganirelix; Cetrorelix; IVF-ET.

Introduction

Despite elevated day 3 serum follicle stimulating hormones (FSH), pregnancies following in vitro fertilization-embryo transfer (IVF-ET) have still been recorded following the administration of minimal gonadotropins to prepare for oocyte retrieval [1, 2].

To prevent premature luetinizing hormone (LH) surge, a gonadotropin releasing hormone (GnRH) antagonist can be used.

The current study was conducted to evaluate pregnancy rates following IVF-ET in women with decrease ovarian egg reserve based upon which GnRH antagonist was given.

Materials and Methods

A retrospective cohort analysis was performed on all women undergoing minimal gonadotropin stimulation where day 3 serum FSH was ≥ 12 mIU/ml. Women were categorized according to three age groups ≤ 39, 40-42, ≥ 43. The women were further stratified according to type of GnRH antagonist used.

Both cetrorelix and ganirelix dosages were started at 250 mcg daily with a follicle of 14 mm average diameter as long as the serum estradiol (E2) remained > 135 pg/ml.

The clinical pregnancy rate, as determined by an ultrasound at eight weeks, the ongoing/delivered pregnancy rate (defined as viable past 12 weeks), and the implantation rates were all evaluated. Those women having completely natural cycles were excluded from the study.

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Results

Pregnancy rate (PR) and implantation rate according to age and type of GnRH antagonist are shown in Table 1.

An apparent trend for at least a 20% lower PR when using ganirelix as compared to cetrorelix is seen with women with a decreased ovarian reserve. This is consistent with previous findings in women having a normal ovarian egg reserve [3].

Both the clinical and the ongoing/delivered PRs were significantly higher in women aged ≤ 39 compared to women 40-42 years of age. Despite 68 transfers, no live pregnancies were seen in women aged 43 or older with elevated day 3 serum FSH.

Discussion

These data concerning use of GnRH antagonists in women with elevated day 3 FSH having IVF-ET confirm previous conclusions that advanced reproductive age is a much greater determinant for poor pregnancy rates than elevated day 3 serum FSH levels [4, 5].

It is not clear why there should be a trend for lower pregnancy and implantation rates with ganirelix vs cetorelix. Since the differences were not significant it is possible that there is no difference in outcome with the use of ganirelix vs cetrorelix. However, since these data were consistent with a previous study in women with normal egg reserve also showing a trend for lower pregnancy rates with ganirelix vs cetrorelix the possibility exists that for some reason the use of ganirelix does lead to lower pregnancy rates. Thus since this group of woman

Table 1. — *Clinical and live delivered pregnancy and implantation rates according to age and type of gonadotropin releasing hormone agonists*.

		Antagonist		
Age group		Ganirelix	Cetrorelix	*p* value
≤ 39	% transfers with 1 ET	46.1%(24/52)	56.7% (55/97)	.219
	Clinical PR/transfer	28.8% (15/52)	37.1% (36/97)	.311
	Live/delivered pregnancy rate/transfer	26.9% (14/52)	34.0% (33/97)	.374
	Implantation rate	21.2% (21/99)	24.0% (40/167)	.607
40-42	% transfers with 1 ET	50.0% (17/34)	50% (26/52)	1.0
	Clinical PR/transfer	11.8% (4/34)	17.3% (9/52)	.482
	Live/delivered pregnancy rate/transfer	8.8% (3/34)	9.6% (5/52)	.902
	Implantation rate	6.5% (4/62)	12.6% (12/95)	.211
≥ 43	% transfers with 1 ET	73.7%(14/19)	77.5%(38/49)	NS
	Clinical PR/transfer	0%	2.0% (1/49)	
	Live/delivered pregnancy rate/transfer	0%		
	Implantation rate	0%	0%	

PR = pregnancy rate.

with diminished egg reserve are already at a disadvantage when undergoing IVF-ET, until it can be determined if ganirelix compared to cetrorelix does lower pregnancy rates, it is probably safter to use cetrorelix as the GnRH antagonist.

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Conventional oocyte insemination may result in a better pregnancy outcome than intracytoplasmic sperm injection (ICSI) for unexplained infertility

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Summary

Purpose: To determine in cases of unexplained infertility whether conventional oocyte insemination vs intracytoplasmic sperm injection results in differences in fertilization rates, frequency of failed fertilization, clinical and live delivered pregnancy rates, and implantation rates. *Methods:* Retrospective evaluation of these parameters in couples undergoing in vitro fertilization embryo transfer (IVF-ET) (minimum 2 embryos) in women with unexplained infertility over a 7-year period. *Results*: There was a significantly higher fertilization rate ($p < .001$) with ICSI vs conventional insemination (73.7% vs 63.7%). However of greater clinical importance, the clinical and live delivered pregnancy rates were significantly higher with conventional insemination (52.7% and 46.2%) than with ICSI 33.6% and 29.0%. The implantation rates were also significantly higher with conventional oocyte insemination (24.9% vs 17.8%). Failed fertilization was low in both groups. *Conclusions:* The process of ICSI, whether it involves possible subtle oocyte damage by the procedure or the andrologist not choosing the ideal sperm, may lead to embryos that are less hearty despite their normal appearance.

Key words: Unexplained infertility; Intracytoplasmic sperm injection; In vitro fertilization; Conventional insemination.

Introduction

One of the reasons for performing in vitro fertilization-embryo transfer (IVF-ET) is unexplained infertility. One theoretical benefit of IVF for unexplained infertility is to bypass possible defective fallopian tubes despite their apparent normal appearance. Another possibility is that somehow despite apparently normal sperm concentration and motility and morphology, sperm do not reach the oocyte for fertilization or for some reason need more sperm than the normal amount to bind to the zona pellucida to allow fertilization.

However, another possible cause of unexplained infertility may be the failure of the sperm to bind to the zona pellucida. For this reason many IVF centers will fertilize the oocytes by intracytoplasmic sperm injection (ICSI) rather than risk failed fertilization. There is a theoretical downside, however, of empirically using ICSI in that it may be that the zona pellucida has the capacity to select a more ideal sperm than the andrologist/embryologist.

The purpose of the present study was to compare pregnancy outcome for cases of unexplained infertility when IVF-ET was performed using conventional insemination of oocytes vs ICSI.

Materials and Methods

A retrospective review over a 7-year period was performed. Couples aged ≤ 43 with unexplained infertility were given the option of performing ICSI or not.

To be considered unexplained infertility, the couple had to have a minimum of one year of infertility, with a semen analysis demonstrating a concentration of $20x10^6$/ml, 40% motility with at least 10% with linear progressive motion, strict morphology > 4%, absence of antisperm antibodies, and a hypo-osmotic swelling test score ≥ 50%. The female partner (with or without corrective measures) had to demonstrate a mature follicle, oocyte release by ultrasound, patent tubes by at least hysterosalpingogram, normal post-coital test an in-phase endometrial biopsy in the late luteal phase.

The main reason for not performing ICSI was to save money on the extra expense from ICSI. Parameters evaluated included fertilization rate and the rate of fertilization failure, clinical and delivered pregnancy rates, and implantation rates according to whether ICSI was performed or not. Only transfers with two or more embryos were evaluated.

Results

There were 107 transfers with ICSI vs 91 without ICSI. Thus 54% chose ICSI. Failed fertilization occurred in three couples in both groups ($p = NS$). The fertilization rate was 73.7% in the ICSI group vs 63.7% in the non-ICSI group ($p < .001$).

The average number of embryos transferred was 3.2 in each group. The clinical and delivered pregnancy rates for those having ICSI was 33.6% and 29.0% vs 52.7% and 46.2% for those having conventional inseminations ($p < .007$, and $p < .02$, respectively). The respective implantation rates were 17.8% and 24.9% ($p < .02$).

The data divided into four age groups are shown in Table 1.

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Table 1. — *Fertilization, pregnancy and implantation rates according to age based on method of oocyte fertilization.*

	Unexplained with ICSI					Unexplained without ICSI				
	Total	≤ 35	36-39	40-42	≥ 43	Total	≤ 35	36-39	40-42	≥ 43
# transfers ≥ 2 ETs	107	52	43	8	4	91	45	40	6	0
# eggs retrieved	1937	1122	641	124	50	1725	945	625	154	1
# fertilized	1123	670	361	69	23	1078	606	373	99	0
% fertilized	73.7	76.2	70.4	74.2	59.0	63.7	64.8	61.2	66.9	0.0
Average # of embryos transferred	3.2	2.8	3.3	4.1	5.3	3.2	2.8	3.6	4.0	0
# implanted	61	35	22	2	2	73	38	27	8	0
% implanted	17.8	23.6	15.6	6.1	9.5	24.9	29.9	19.0	33.3	0
# of clinical pregnancies	36	18	14	2	2	48	26	17	5	0
Clinical pregnancy rate/transfer (%)	33.6	34.6	32.6	25.0	50.0	52.7	57.8	42.5	83.3	0
# live deliveries	31	18	10	2	1	42	23	14	5	0
Live delivery rate/transfer (%)	29.0	34.6	23.3	25.0	25.0	46.2	51.1	35.0	83.3	0

Discussion

Fertilization of eggs by ICSI for unexplained infertility may result in more embryos for transfer as determined by a significantly higher fertilization rate. Nevertheless, the percentage of couples failing to fertilize any embryos was similar and uncommon (2.8% with ICSI vs 3.2% without ICSI).

However this may be at the expense of a decreased implantation potential of these embryos. A similar finding was found when conventional insemination vs ICSI was compared following fertilization with sperm with low quality morphology as determined by strict criteria [1].

These data suggest that the process of ICSI may result in a less hearty embryo than when fertilized with conventional insemination. Though one should be cautious about the conclusions from a retrospective study involving only 198 cases, this information can be provided to a patient and allow them to participate in the decision to perform ICSI or not.

At least the fear that conventional insemination could lead to a greater risk of failed fertilization can be allayed by this study. The process of ICSI increases the expense for the patient and intensifies the work load for the embryologist. If future prospective studies fail to support the conclusion for higher pregnancy and implantation rates with conventional oocyte insemination vs ICSI for unexplained infertility, there is little likelihood that prospective studies will yield opposite results, and therefore will probably show that conventional oocyte insemination is at least as good as ICSI for unexplained infertility. Thus at a minimum the couple could save money.

Should these conclusions about superiority of conventional insemination be confirmed the possibility exists that the zona pellucida can select a sperm that is more likely to produce a better embryo than the andrologist or embryologist.

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Comparison of the efficacy of selecting sperm with normal nuclei by high magnification for intracytoplasmic sperm injection (ICSI) according to age in refractory in vitro fertilization (IVF) cases

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Summary

Purpose: To determine the pregnancy rates according to age in women failing to conceive after three previous embryo transfers or having a husband whose sperm shows a DNA fragmentation index (DFI) > 30% when performing the sperm chromatin structure assay. *Methods:* Women up to age 45 were included and there was no restriction for low egg reserve. Live delivered pregnancy rates were determined according to three age groups: ≤ 34, 35-38, 39-45. The data were also analyzed in a group comparable to previous publications using high magnification ICSI, i.e., younger women with normal egg reserve. Pregnancy rates following frozen embryo transfer were also evaluated. *Results:* Using all 86 in vitro fertilization-embryo transfer (IVF-ET) cycles the live delivered pregnancy rates were 40% (10/25) for women ≤ age 34, 24% (6/25) in women age 35-38, and 13.8% in women aged 39-45. Evaluating the younger group with normal egg reserve with ≥ 3 previous failed IVF-ET cycles the live delivered pregnancy rate per transfer was 38% (16/42). If one adds the additional six live deliveries from subsequent frozen embryo transfer (6 of 17, 35.3%) this group of women had a 52.3% (22/42) live delivered pregnancy rate from one egg retrieval. *Conclusions:* These data were uncontrolled and thus conclusions should be viewed with caution. The results are sufficiently encouraging to warrant a prospective controlled trial and possibly encourage a company to consider commercially manufacturing high magnification microscopes.

Key words: High magnification; Nuclear morphology; DNA fragmentation index; Intracytoplasmic Sperm Injection.

Introduction

A manuscript published in December, 2003 in *Fertility and Sterility* found that in couples failing to conceive despite at least two previous cycles of in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI), very high pregnancy rates of 66% per transfer could be achieved by designing a special microscope set-up so that there could be sufficiently high magnification to allow viewing nuclear details and injecting into the oocytes only those sperm with normal nuclei [1]. In fact, the couples had failed to conceive after a mean of 4.1 previous IVF-ICSI attempts [1].

These findings were corroborated by a different group in which a 43.5% clinical pregnancy rate/transfer was achieved despite several previous ICSI failures even when the male partner had a high level of DNA fragmentation as determined by TUNEL assay (2).

Materials and methods

The criteria for selection was a minimum of at least three previous IVF cycles or a DNA fragmentation index (DFI) > 30% on the sperm chromatin structure assay.

Pregnancy outcome was evaluated according to the reason for high magnification ICSI performed, i.e., multiple failed cycles vs high DNA fragmentation score.

After oocyte retrieval, sperm were selected with the aid of a specially designed microscope that magnifies sufficiently to observe nuclear detail. Sperm were immobilized by polyvinylpyrrolidone (PVP) and then selected according to the criteria of normal established by Bartoov *et al.* (1).

Results

There were a total of 86 IVF-ET cycles evaluated. Only one cycle per couple was evaluated. There were 54 women failing at least three IVF-ET cycles (mean 3.2 ± 0.9) and 32 women whose male partners had DFI scores > 30%.

The live delivery rates according to age combining refractory IVF cases with previous three or more failures and couples with male partners with high DFI scores are shown in Table 1.

If one evaluates women more comparable to those in the reports by Bartoov *et al.* [1] and Hazout *et al.* [2] i.e., women with sufficient egg reserve having three or more previous embryo transfers (ETs) that failed to achieve a live pregnancy, there were 42 ETs. The clinical pregnancy rate per transfer was 42.8% (18/42) and the live delivered pregnancy rate/transfer was 38.0% (16/42).

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Table 1. — *Live delivery rates following IVF-ET according to age using high magnification ICSI (using all patients, i.e., multiple failed IVF cycles or high DFI scores).*

Age	Number transfers	Live deliveries	% live deliveries/transfer
< 34	25	10	40
35-38	25	6	24
39-45	36	5	13.8

These data include women with poor egg reserve and even only one embryo transferred.

There were 17 frozen ETs (all ages) resulting in six (35.3%) live deliveries in women who were good responders. Thus if one adds these six cases to other 16 live deliveries from fresh transfers the overall live delivered pregnancy rates per retrieval in this group of refractory cases using high magnification ICSI was 52.3% (22/42).

Conclusions

The study by Bartoov *et al.* evaluated women age 36 and under and the 66% quoted rate was close to the delivery rate [1]. The study by Hazout *et al.* [2] did not specify the age studied or the live delivered pregnancy rate. At least in the younger group that we studied (age ≤ 34) the present data would be consistent with the Hazout *et al*. study since it would be safe to assume at least a 10% miscarriage rate.

The present data found a significantly lower live delivery rate ($p < .01$) in women 35-40 compared to 34 and under. This contrasts with our normal IVF statistics where the 35-40 year-old group only has a non-significant trend for lower live delivery rates compared to the younger group.

The possibility still exists that similar delivery rates could have been achieved by performing ICSI without high magnification since there were no controls. The cost for building the microscope was over 55 thousand dollars. Furthermore it takes much longer to perform ICSI using this technique and there is much greater exposure of the sperm to PVP and possible increased exposure to reactive oxygen species. A prospective controlled study is greatly needed before the true benefit of this new sperm selection technique can be determined.

These data do support that in multiple failed cycles of IVF a sperm factor may be the more likely etiologic factor in younger women but possibly the oocyte factor may be more important in women aged 35-45. Despite live delivery rates less than half compared to the younger group, the possibility exists that prospective studies could still demonstrate some benefit for selecting sperm by nuclear characteristics using high magnification even in somewhat older patients.

When we first built the microscope there had been reports of practically no pregnancies even with ICSI when the DFI score was > 30% [3]. Subsequently several articles refuted this claim [4-8]. At present it is not clear whether high DFI scores are associated with a higher miscarriage rate [4, 5] or not [6, 7] when performing ICSI.

Initially thinking that the live pregnancy rate was zero, it was exciting to find ongoing pregnancies by performing ICSI with selection of sperm by nuclear characteristics. Thus a prospective controlled study would be needed to determine if high magnification ICSI improves outcome when the male partner has a high DFI score. Nevertheless, we frequently did not perform the SCSA test unless there had been previous IVF failures. Though having three previous failures was not a prerequisite for obtaining a SCSA assay, it should be noted that the mean number of previous IVF cycles with failure to have a successful pregnancy was 2.7 ± 8 in those with high DFI scores.

These data despite the caveats are sufficiently adequate to possibly encourage a company to commercially manufacture these high magnification microscopes.

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Successful pregnancy with frozen embryo transfer into a gestational carrier from eggs obtained from a woman in premature menopause

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Summary

Purpose: To describe a unique case of a successful gestational carrier pregnancy in a woman with premature ovarian failure using her own oocyte. *Methods:* Despite amenorrhea, failure to have menses to progesterone withdrawal and resistance to gonadotropin stimulation, ovulation induction was attempted by restoring down-regulated follicle stimulating hormone (FSH) receptors by lowering the elevated serum FSH and allowing stimulation by endogenous or exogenous gonadotropins. Oocyte retrieval was attempted if a mature follicle was obtained. GnRH antagonist was used to prevent premature oocyte release. Tapering prednisone was used for the first five days of the cycle due to patient's history of autoimmune disease (vasculitis and Crohn's disease). IVIG was given 8/2003 for vasculitis. *Results:* The patient underwent a total of 19 attempted retrievals during continuous natural cycles from 3/2003 to 2/2007. Oocyte retrieval required traversing the uterus with the retrieval needle because of ovarian position after multiple surgeries for bilateral endometriomas and Crohn's disease. Empty follicle syndrome was encountered in four retrieval attempts. In 15 attempts, an oocyte was obtained. The sole attempt at natural fertilization failed. ICSI and assisted hatching were used in all subsequent attempts, and were successful in all but one attempt which led to a 3 pronuclei embryo which was discarded. The first four single embryos retrieved (7, 4, 6 cells and morula) were all A1 or A2 and transferred fresh to the patient, but no pregnancy resulted. All subsequent embryos were cryopreserved. The transfer of four embryos (6-cell and 7-cell and 3-cell and 8-cell) in two cycles to two different gestational carriers resulted in a successful delivery of a full-term healthy female infant 3.3 kg. Genetic testing confirmed maternal identity to be the patient, not the carrier. *Conclusions:* This is the first reported case of a successful gestational carrier pregnancy after reversing ovarian failure, inducing ovulation, and transferring a frozen-thawed embryo.

Key words: Frozen embryo; Ovarian failure; Gestational carrier.

Introduction

There are studies suggesting that even if normal embryos are transferred as a result of in vitro fertilization (IVF) in regularly menstruating women of any age, the prognosis for pregnancy is extremely poor, if day 3 follicle stimulating hormone (FSH) is elevated [1-7]. This opinion is markedly intensified if the woman is in apparent menopause as evidenced by amenorrhea, estrogen deficiency, and elevated serum FSH.

Recently an editorial was published entitled "A 59-year-old woman gives birth to twins - when should a fertility specialist refuse treatment?". The editorial described several cases of infertility in which women were willing to take significant health risks to achieve pregnancy against great odds and where the infertility specialist was willing to try to help the women [8]. Another editorial article described IVF in women who were willing to undergo great expense to fulfill their dreams [9].

The present case report describes a woman who was advised that the odds of her conceiving (and for that matter even ovulating) were extremely remote and that the mode of treatment would be extremely risky and yet she, a very intelligent physician, wanted to take her chances to fulfill her dream of having a child with her genetic material.

Case Report

A 34-year-old physician consulted us for primary infertility and premature ovarian failure in January, 2003. She had a history of severe endometriosis and fistulizing Crohn's disease, including a rectovaginal fistula. In 1989 she had a left oophorectomy for a 12 cm endometrioma with associated extremely elevated CA-125 level (1243 units/ml) and in 2002 had an 8 cm right ovarian endometrioma removed leaving very little ovarian tissue. Her serum FSH following surgery was increased to 38.6 mIU/ml.

She also had other surgical procedures. In 1989 she had a total colectomy/ileostomy and a Hartmann pouch for her Crohn's disease. In 1990 she had to redo the ileostomy because of a stricture and she also had adhesiolysis related to her Crohn's disease.

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Her medical history included a grand mal seizure as a result of an allergic reaction and vasculitis as a side-effect of Infliximab. Her medications included prednisone 10 mg daily, ranitidine 150 mg twice daily, loperamide 2-4 mg daily, metronidazole 250 mg 3x/day, folic acid 1 mg daily, various vitamins including vitamin B12 (1000 U) s.c. monthly and TPN 2x/week.

Related to her various surgeries her right fallopian tube was occluded and she was told if she wanted to conceive that it would not be possible through artificial insemination with donor sperm (she was single and did not have a male partner) and that she would need IVF.

She attempted IVF in another institution and they started her on leuprolide acetate 20 units daily followed by 300 units once daily of recombinant FSH and 300 units of human menopausal gonadotropin. At this time despite her day 3 serum FSH of 38.6 mIU/ml she was still menstruating approximately every 28-35 days (but did occasionally skip menses). Nevertheless after a week's worth of 600 units daily of FSH her serum estradiol (E2) dropped from 28.5 pg/ml to zero and her IVF cycle was cancelled. This was in November, 2002.

She had a spontaneous menstrual cycle the end of December, 2002 but had very few spontaneous menstrual cycles over the next five years.

From doing a computer search on premature ovarian failure (PubMED 1966-2002) the patient was aware that we had published a technique for inducing ovulation even in women in apparent premature ovarian failure who were unresponsive to gonadotropins [10-16]. She was also aware that we had published case reports of successful pregnancies following in vitro fertilization-embryo transfer in two women with premature ovarian failure with tubal factor [17, 18].

Pelvic sonography however found the right ovary to be located very high in the pelvis and the ovary was inaccessible by transvaginal needle. Abdominal ultrasound (US) suggested that the ovary was in a deep location and was covered by bowel thus it did not seem accessible by abdominal guided US either.

The woman was willing to have general anesthesia and an abdominal laparotomy if we could induce her to mature a follicle but our IVF center, though university and hospital based, is a free standing IVF center not physically connected to an operating room. We suggested that we could monitor her cycle and she could request the retrieval with laparotomy be performed at the facility that attempted her first IVF cycle since they were hospital based. However they rejected the proposal. The patient then had a failed attempt at J-pouch and simultaneous attempt to move the ovary to a more accessible location (4/2003) by expert colorectal surgeons.

Our IVF group then concluded that it would be possible to retrieve an egg if there was a transuterine approach but we explained this could be risky because we could puncture her bowel. As a gastroenterologist she believed that the needle was too thin to cause any serious damage even if it did hit the bowel. She would also take extra IV antibiotics for the egg retrievals.

Four of the five physicians in our facility agreed to do her egg retrievals and one physician declined. However, that physician subsequently agreed to do two of the 19 egg retrievals she had when it fell on the weekend in which that doctor was on call. The only time the woman did not take her IV antibiotics for seven days (the medication never arrived from the pharmacy), and instead took PO antibiotics, she developed a pelvic abscess (this was after her 6th retrieval attempt) requiring hospital admission and six weeks of IV zosyn; she never had another episode. Also, during stimulation a 3.5 cm ovarian cyst developed 12/2006 and resulted in acute hydronephrosis of the right kidney with resulting severe pain. This resolved without complications after cyst drainage via the same transuterine approach.

The woman had follicular maturation using ethinyl estradiol to lower elevated serum FSH levels associated with low E2 levels (E2 < 20 pg/ml). When a follicle was finally recruited as evidenced by a rise in serum estradiol, the follicle was allowed to develop naturally and when an 18 mm diameter follicle associated with a serum E2 of 200 pg/ml or more was reached, 10,000 IU of human chorionic gonadotropin (hCG) was given. The attempted egg retrieval was performed 34 hours later. In addition, when she was able to be off prednisone for her Crohn's disease, a prednisone taper (40, 30, 20, 10, 5 mg) was given for the first five days of the cycle. A single dose GnRH antagonist 250 mcg s.c. was added to prevent endogenous LH surge and oocyte release.

Alternatively, once the serum E2 began to rise thus helping to keep the FSH from increasing (and thus down regulating FSH receptors), a boost of a low-dose (usually 75-150 IU per day) FSH drug was given and antagon daily was added to keep the LH:FSH ratio low. The woman was single and the eggs were fertilized with donor sperm.

Out of the 15/19 retrievals resulting in an oocyte, three were completely natural cycles with one dose of antagon, or also taking ethinyl estradiol to lower the elevated serum FSH. Intracytoplasmic sperm injection and assisted embryo hatching were performed for 14/15, after the very first successful natural cycle oocyte retrieval resulted in failure of natural fertilization. Minimal stimulation or natural cycles with boost protocols were used for the rest of the IVF cycles (combination of ethinyl estradiol, rhFSH, GnRHa, prednisone as described above). The woman failed to conceive following four single embryo transfers of 4-cell, 6-cell, 7-cell, and 14 cell morula stage (the abscess cycle) embryos on day 3.

The woman decided that any subsequent embryos formed would be frozen for transfers to a gestational carrier that she would obtain in the future since she thought that she may have a compromised uterus or immune system. She was able to fertilize and freeze nine single/2 pronuclear embryos. She thawed two 2 pronuclear embryos that had been frozen for two and a half years (at age 35 and 36 years) and transferred a 6-cell and a 7-cell day 3 embryo with < 25% fragmentation to a gestational carrier. She did not become pregnant (just a chemical pregnancy).

She then thawed two more embryos that had been frozen one and a half years before (at age 37 and 38 years) and transferred a 3-cell and an 8-cell embryo with no fragmentation to another (different) gestational carrier and a singleton pregnancy was conceived. A healthy 3.3 kg baby girl at 38 weeks' gestation was successfully delivered. Because of fear of losing the pregnancy she did not have the gestational carrier undergo chorionic vilus sampling or amniocentesis. However, quadruple screens adjusted for the patient's age (not the carrier's) and high level US for signs of genetic abnormality done at 20 weeks of gestation were normal. The baby underwent maternity testing by the DNA Diagnostic Center, using DNA fingerprinting with the Power Plex 1.2 system by Promega Corp., Madison WI, confirming maternity with 99.99% probability to be our patient.

Other pertinent tests that had been performed on this woman was a chromosome analysis showing a normal 46XX karyotype, and fragile X PCR was negative. Hysteroscopy done 4/2007 for increased CA-125 (> 200), dysmenorrhea, and

menometrorrhagia showed severe uterine adhesions and endometrial polyps. Lysis of the adhesions and polypectomy were successful, with resolution of symptoms and marked reduction in CA-125 to 40 units/ml. The patient is presently well, maintained on hormone replacement therapy with continuous estradiol 20 mcg daily and medroxyprogesterone 10 mg daily for the first two weeks of each month.

Discussion

The cathexis for this extremely intelligent physician was to have a child with her own genetic background. However, she was advised by a reproductive endocrinologist at an academic medical university center that even though she was still menstruating at the time of that appointment it would not possible for her eggs to result in a pregnancy. That reproductive endocrinologist quoted even recent studies claiming extremely poor or no pregnancies even with normal appearing embryos transferred once the serum FSH was elevated let alone a woman in actual ovarian failure [7]. A second opinion from another reproductive endocrinologist at an academic medical university center agreed that pregnancy was highly unlikely but they were willing to attempt the one IVF cycle with extremely high dosage gonadotropins. When she failed to raise her serum E2 at all (it plunged to zero) despite several days of high dose gonadotropin, they too considered that she would need donor eggs to become pregnant. A third reproductive endocrinologist at an academic medical university center with expertise in premature ovarian failure/high FSH cancelled her consultation appointment, refusing even to see her as "nothing could be done". A fourth reproductive endocrinologist, and national expert in premature ovarian failure, expressed sympathy, but agreed it was futile.

The patient did her own computer search and in contrast to the opinions expressed by the previously consulted experts she found many articles concerning not only achieving pregnancies in younger women with high day 3 serum FSH but even live deliveries in women in apparent menopause with the aforementioned techniques.

At her consult at our facility her consulting physician was confident that she could be made to ovulate and that these eggs would probably be of good quality. However, our head surgeon and co-director of the IVF program strongly believed that the safest way to retrieve the eggs would be through a laparotomy. The importance of a pregnancy with her own genetic material was so great that she was willing to go through major surgery. Unfortunately, however, our IVF facility is not in the operating room and she could not find an IVF center that performs retrievals in the operating room willing to take her case, even if she did attain a mature follicle with our technique.

When she returned asking if we could consider another alternative to a laparotomy we said that we could retrieve the eggs by placing the retrieval needle through the uterus but that could be extremely risky. Nevertheless this highly motivated and informed physician was willing to take the risk of puncturing her bowel or other complications.

Thus with the expense of 19 oocyte retrievals and a gestational carrier, the risks that she was willing to take, and the successful outcome that she achieved, her case should be added to the group described willing to risk poverty to attain their dreams and willing to take significant medical risks [8, 9]. This woman was undaunted by the development of an abscess after one cycle and the development of an ovarian cyst which we drained with a retrieval needle that had caused ureteral obstruction and hydronephrosis.

This case report is unique. Although there are two other cases of women in apparent ovarian failure achieving a pregnancy following IVF-ET, this is the first one that was achieved by transferring frozen-thawed embryos from a woman whose apparent ovarian failure was reversed through suppression of elevated serum FSH, with theoretical restoration of down-regulated FSH receptors followed by mild FSH stimulation. This is also the first case of successful pregnancy achieved by a woman in premature ovarian failure using her own eggs but transferring embryos to a gestational carrier.

This case report is not intended to level criticism against the physicians who refused treatment. Physicians devote a great deal of time and money into acquiring their degree and it is not fair to insist that they take risks that could jeopardize their continuance of providing health care. If a complication occurs despite the presence of informed consent, a woman may still litigate. Even in the presence of a complication the individual patient may not sue but the family could litigate or some peer-review board could censure the treating physician stating that the case should have never been tried.

Thus one take-home message from this case is that a highly motivated patient with a dream does not have to accept rejection by the first or second opinion but can continue a search for a physician willing to work with her if that physician thinks that there is a possible chance of the dream being achieved. A careful explanation of the potential complications and the estimate of success must first be provided.

One of the best ways to accomplish this is to do what the patient did and perform a computer search to see if there have been any successful precedents for this type of case. In this circumstance, the patient was not only a physician but she had training in reproductive endocrinology. Even non-physicians however, are very computer savvy today and frequently can gain this information through the internet.

Nevertheless, even though our patient first went to colleagues with whom she had trained, they told her that her eggs were not of good quality and told her point blank she would need donor eggs. I do not believe that they did due diligence by not at least making her aware of contrasting conclusions from the ones they quoted that were the basis of their opinions. The second physician could be criticized for not reviewing the literature sufficiently to realize that the usage of high dosage gonadotropin stimulation is not the best choice for this type of patient but to be fair the emphasis on how important low-dose FSH

regimens are for this type of woman has only recently been emphasized [19, 20].

One of my associates had the right to refuse to perform egg retrieval on this patient for fear of complications and possible jeopardy to her future career. I greatly appreciate my other associates who despite agreeing that risk did exist, but realizing that this patient would not accept donor eggs or donor embryos, were willing to take some personal risks to provide this woman a chance to fulfill her dreams. The one associate never officially changed the refusal to do the egg retrieval, so the other physicians retrieved the eggs when it was the objecting physician's weekly turn for IVF-ET. However that physician was willing to perform the procedure twice on weekends rather than make other associates come in on their weekend off work. It was in fact the physician who had refused to do egg retrievals that did the transfer to the second gestational carrier which proved to be the conception cycle.

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General Section

Patient compliance with colposcopy information leaflets

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Summary

Objective: To investigate patient satisfaction and compliance with recommendations in information leaflets sent to women prior to colposcopy clinic attendance and to establish whether alteration to the leaflet improved compliance. *Study design:* Data was collected prospectively and analysed retrospectively on the first 50 women attending for colposcopy before and after alterations to the information leaflet. *Results:* All the patients received our patient leaflet and over 90% in each group felt that the information was understandable, clear and adequate. This is in complete contrast to overall compliance of less than 40% in both groups of the women. The first language of the patients did not make any major impact on compliance. *Conclusion:* Patients understanding of the information provided in the leaflets was not reflected in compliance. Compliance was no better in repeat attendees. The compliance with the information provided was not affected by the womens first language. Alterations in the leaflet did not improve compliance. Other methods of information provision should be looked at to try to improve compliance.

Key words: Colposcopy; Information leaflets; Language; Patient satisfaction.

Introduction

Studies have shown that patients frequently forget and misunderstand information discussed verbally [1]. Educational information sent to women prior to their attendance at colposcopy clinics improves their understanding of cervical screening and of colposcopy [2, 3]. It has also been shown to reduce women's anxiety [4]. Additional approaches such as video information and telephone communication have been shown to improve follow up attendance [5-7].

However, the timing of provision of information to women attending many UK colposcopy clinics has been shown to be inefficient [8]. This unit mails information leaflets to women prior to their attendance and have found it to be a useful means of providing information about colposcopy. When designing the leaflet we acknowledged that patient compliance has been shown to be increased when the information provided is as simple as possible [9] and that excessive information and poor presentation reduces the overall effectiveness [10].

Developing a patient information leaflet can be a major undertaking in terms of time and resources [11]. There are NHS cost implications involved in running a colposcopy clinic that include leaflet production and distribution, provision of sanitary pads and length of appointment time.

The aim of this study was to investigate patient compliance with the recommendations in our information leaflet sent to women prior to colposcopy clinic attendance and whether alteration to the leaflet improved compliance.

The recommendations were to wear loose fitting clothing to reduce time of consultation and to bring a sanitary pad to help reduce cost. The alterations to the leaflet included highlighting in bold print the instructions to wear loose fitting skirts and to bring a sanitary towel.

The impact of the woman's primary language on compliance was also assessed as this may be particularly important in a trust with a high ethnic population.

Methods

The study was carried out by an analysis of prospectively collected data from the first 50 women attending the colposcopy clinic before (Group A) and after (Group B) changes to the information letter. The women were asked to fill in a questionnaire immediately prior to their consultation about the letter they had received. Compliance with the instructions was recorded by the colposcopist. The questions related to the adequacy and understanding of the material. The compliance related to whether the woman had followed the requests within that material to wear loose fitting dress and bring a panty liner for after the procedure.

Each group was comprised of women between the ages of 25 and 59 years attending for their initial or subsequent visit to the clinic. In Group A 20/50 were attending for the first time, compared to 32/50 in Group B. The remainder 30/50 (Group A) and 18/50 (Group B) were attending for a treatment or follow-up visit. In both groups, 98% (49/50) of the women felt that the information given was understandable and clear. In Group A, 98% (49/50) and 94% (47/50) out of Group B responded that the information was adequate. Despite an overwhelming endorsement of the information provided, compliance with wearing loose fitting clothing and bringing a panty liner suggested a different situation. Table 1 shows the overall poor compliance with requests in the literature sent to all women prior to their colposcopy visit irrespective of whether they had previously attended. Tables 2 and 3 show that there was no statistical difference in compliance between women attending for their first or subsequent visit within the before and after group and when an overall comparison of the groups was undertaken.

Discussion

This study has shown that the alteration of our information leaflets did not significantly alter women's compliance. The giving of information leaflets to patients has become an established part of the medical culture. It is expected by ethics and clinical governance committees

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Table 1. — *Comparison of first and subsequent visit compliance before and after leaflet changes*.

	Compliance with dress	Compliance with panty liner	Compliance with both
Group A 1st visit	12/20 (60%)	13/20 (65%)	7/20 (35%)
Subsequent	16/30 (53%)	20/30 (66%)	12/30 (40%)
Overall	28/50 (56%)	33/50 (66%)	19/50 (38%)
Group B 1st visit	14/32 (44%)	21/32 (66%)	11/32 (34%)
Subsequent	7/18 (39%)	15/18 (66%)	5/18 (36%)
Overall	21/50 (42%)	36/50 (72%)	16/50 (32%)

Table 2. — *Comparison of group A & B's first and subsequent visit compliance*.

	Compliance with dress	Compliance with panty liner	Compliance with both
Group A Odds ratio	1.31	0.93	0.81
1st vs subsequent visit (95% CI)	(0.36-4.86)	(0.24-6.38)	(0.21-3.81)
Group B Odds ratio	1.22	0.38	1.36
1st vs subsequent visit (95% CI)	(0.33-4.75)	(0.06-1.83)	(0.33-6.15)

Table 3. — *Comparison of first and subsequent visit compliance*.

	Compliance with dress	Compliance with panty liner	Compliance with both
1st visit	1.93 (0.54-7.04)	0.97 (0.26-3.77)	1.03 (0.27-3.83)
Subsequent	1.80 (0.47-7.03)	0.40 (0.06-1.97)	1.73 (0.42-7.81)
Overall	1.76 (0.74-4.19)	0.75 (0.29-1.92)	1.30 (0.53-3.23)

Table 4. — *Compliance depending on first language*.

	Compliance with dress	Compliance with panty liner	Compliance with both
Group A English	20/36 (58%)	24/36 (67%)	14/36 (39%)
Other 1st language	8/14 (57%)	9/14 (64%)	5/14 (36%)
Group B English	19/42 (45%)	32/42 (74%)	14/42 (33%)
Other 1st language	2/8 (25%)	4/8 (50%)	2/8 (25%)

alike, as well as of candidates in Objective Structured Clinical Examinations (OSCEs) that leaflets and information will be provided for the patient. Though small, this study would question whether the provision of written instructions in information leaflets is of value for the majority of patients. In each group, all the patients received our patient leaflet and over 90% in each group felt that the information was understandable, clear and adequate. This is in complete contrast to overall compliance of less than 40% in both groups of the women wearing loose fitting clothing and providing their own panty liner. Surprisingly, there was no statistical difference in the compliance between women attending for their first visit and those who had previously undergone colposcopy irrespective of which information they had received. Though the numbers are small, the first language of the patient did not make any major impact on compliance.

Previous studies have looked at the benefit of information sheets for providing women with information related to colposcopy and the related disease processes. However, one could conclude from this study that the patient may answer any questionnaire in manner that they feel will fulfil the doctor's expectations.

In the current target driven culture, the aim of our information leaflet has been to be as cost effective as possible by optimising colposcopy consultation times and placing the onus on women to bring their own sanitary pads. This kind of analysis of patient compliance has not been addressed previously but this study suggests that the impact of information leaflets in this regard is low irrespective of previous attendance experience. It is interesting to consider generally how much money is spent on letters and leaflets to the patients and whether there is any merit in it at all. As most of the women attending for colposcopy are within the working age group, perhaps including a website address on their appointment letter may have more success. Further audits into this aspect of providing information linked with compliance would be beneficial in allowing assessment of the best way of utilising resources. As patients are now contacted by telephone on receipt of their referral, the next stage in trying to address patient compliance is to include appropriate information to the patient at that time.

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Analysis of federal process of care data reported from hospitals in rural westernmost North Carolina

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Summary

Objective: To evaluate standardized process of care data collected on selected hospitals serving a remote, rural section of westernmost North Carolina. *Materials & Methods:* Centers for Medicare & Medicaid Services (CMS) data were retrospectively analyzed for 21 clinical parameters at Fannin Regional Hospital (FRH), Murphy Medical Center (MMC), and Union General Hospital (UGH). A binomial test was used to compare each study site to state (NC) and national (USA) average. *Results:* Summary data showed FRH to have higher scores on a significant number of standardized clinical process of care measures compared to state ($p < 0.05$) and national ($p < 0.005$) averages. Too few process of care measures at UGH were significantly higher than state and national averages to conclude that differences were not due to Type I error. Similarly, at MMC too few process of care measures were significantly higher than national averages to conclude that observed differences were not attributable to Type I error. MMC did not achieve a significantly higher score on any process of care measure when compared to state averages. *Conclusion*: Despite limitations associated with summary data analysis, the CMS "Hospitals Compare" information suggests that process of care scores at FRH are significantly higher than the state and national average. As these hospital quality data are freely available to patients, it remains to be determined what impact this may have on hospital volume and/or market share in this region. Additional research is planned to identify process of care trends in this geographical area.

Key words: Hospital quality; Process of care; Rural health; North Carolina.

Introduction

How patients make decisions about where to obtain medical services has been the focus of considerable study, particularly in the setting of a competitive healthcare marketplace. Some patients appear to base their choices mainly on characteristics of care delivery rather than location of care [1], but hospital quality and/or proximity could also influence this decision.

Beginning in 2004, acute care hospitals in the USA could voluntarily elect to report quality data in order to receive incentive payments established by Section 501(b) of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA). To obtain the increased payment, eligible hospitals were required to report on an initial set of ten quality performance measures and to agree to have their data publicly displayed. Initially, almost all hospitals eligible for the payment incentive provided these data, reflecting care delivered during 2004. Under Section 5001(a) of the Deficit Reduction Act of 2005, the set of measures included in the incentive was expanded, the magnitude of the incentive was increased, and the time-limit for the provision removed.

In the present study, standardized process of care figures derived from this dataset were examined for the hospitals serving westernmost North Carolina. This is a remote area of Appalachia where three independent hospitals of comparable size offer similar coverage for several thousand patients within a shared 30-mile radius. We compared each hospital's performance to state and national averages using the same standardized data publicly available to patients.

Materials and Methods

Data source

This analysis utilized standardized federal data on adult hospital care tabulated by Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services (HHS), along with the Hospital Quality Alliance (HQA). The HQA initiative was launched in December 2002 and resulted from coordinated efforts by the American Hospital Association (AHA), Federation of American Hospitals (FAH), and Association of American Medical Colleges (AAMC). The HQA promotes reporting on hospital quality of care and consists of organizations representing consumers, hospitals, doctors and nurses, employers, accrediting organizations, and U.S. Federal agencies.

Data were collected retrospectively on process of care measures originating from information extracted from the study hospitals' medical records maintained at each facility, in accordance with federal law. The source data are indicative of how often hospitals provide selected care recommended for patients being treated for myocardial infarction, heart failure, pneumonia, or care provided immediately following surgery. These process of care measures have evolved to include eight measures related to myocardial infarction care, four measures related to heart failure care, seven measures related to pneumonia care, and five measures related to surgical infection prevention. Process of care information regarding children's medical serv-

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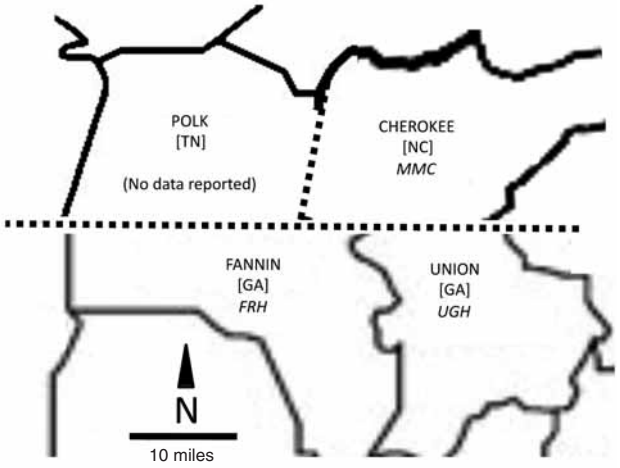

Figure 1. — County geography of Appalachian tri-state region covered in the federal process of care analysis, demonstrating intersections of Tennessee, North Carolina and Georgia (dashed lines), and relative locations of Murphy Medical Center (MMC), Fannin Regional Hospital (FRH) and Union General Hospital (UGH).

ices, psychiatric hospitals, rehabilitation facilities, or long-term care hospitals was excluded. Updated versions of these data are periodically published and are publicly accessible via the HHS website, Hospitals Compare. Data used for this study were reported current to September 2007.

Individual facility performance rate calculations

For this study, denominators were the sum of all eligible cases (as defined in measure specifications) submitted to the QIO Clinical Data Warehouse for the reporting period, while numerators were the sum of all eligible cases submitted for the same reporting period where the recommended care was provided. Performance rates were then calculated by dividing the numerator by the denominator. Hospital sampling methodology was determined by rules established by The Joint Commission and CMS.

Study region and vicinity hospitals

Extreme western North Carolina describes a difficult to access geographical region in rural Appalachia where the state boundaries of Georgia, North Carolina, and Tennessee intersect (Figure 1). While the largest population center over 50,000 is approximately 90 minutes away by car, health care for local residents is available in the three contiguous counties of Union (Georgia), Fannin (Georgia) and Cherokee (North Carolina). Each of these counties has one accredited hospital with a 24-hour emergency department. As these hospitals are situated either in or near western North Carolina (*i.e.*, within 30 miles), the facilities share a common patient service area.

Fannin Regional Hospital (FRH) is a nonprofit community hospital located in Blue Ridge, Georgia. It opened in 1979 and is licensed for 50 beds. The total population of Fannin County, Georgia was 22,319 (est.) in 2006.

Murphy Medical Center (MMC) is a nonprofit community hospital located in Murphy, North Carolina. It opened in 1979 and is licensed for 57 beds. MMC also operates a long-term care/nursing home facility with an additional 106 inpatient beds. The total population of Cherokee County, North Carolina was 26,309 (est.) in 2006.

Union General Hospital (UGH) is a nonprofit community hospital located in Blairsville, Georgia. It opened in 1959 and is licensed for 45 beds. The total population of Union County, Georgia was 20,652 (est.) in 2006.

Residents of westernmost North Carolina also have access to a fourth facility, Copper Basin Medical Center, located immediately west of the study area in Polk County, Tennessee (est. population 15,939 in 2006). However, this small 25-bed hospital did not report any data to CMS and therefore was excluded from study.

Statistical analysis

Process of care measurements were reported from the three study sites in aggregate form and compared to national (USA) and state (North Carolina) averages using the binomial test (R version 2.6.2). A process of care measurement was considered significantly better than average at a 90% confidence level. Due to the large number of comparisons, the fraction of process of care measurements that were significantly better than average was compared to the expected Type I error rate of 10% using a binomial test; a hospital was considered significantly better if this test yielded a p value < 0.05. As patient-level data were not available, multiple regression analysis was not possible.

Results

A summary of CMS data on the three study hospitals is presented in Table 1. Because the study hospitals did not offer the full range of services that were evaluated by the national CMS template, some data cells were intentionally empty. Specifically, FRH reported no data on frequency of administration of fibrinolytics to patients with myocardial infarction within 30 min of arrival, or on the number of patients given percutaneous coronary interventions within 90 min of arrival due to insufficient patient volume. This hospital also reported no data on smoking cessation counseling for myocardial infarction patients. We found process of care determinants at FRH to be significantly higher than state ($p < 0.05$) and national ($p < 0.005$) reference groups.

At MMC, no data were reported on the number of patients given percutaneous coronary interventions within 90 min of arrival. No data was reported from UGH on frequency of administration of fibrinolytics to patients with myocardial infarction within 30 min of arrival, or on the number of patients given percutaneous coronary interventions within 90 min of arrival.

Table 1. — *Summary of process of care measurements (n = 21) at three hospitals serving westernmost North Carolina.*

	Significantly better than national average?			Significantly better than state (NC) average?		
	N	Y	p[1]	N	Y	p[1]
FRH	12	7	< 0.005	14	5	< 0.05
MMC	20	1	ns	21	0	ns
UGH	18	2	ns	19	1	ns

FRH = Fannin Regional Hospital (Georgia), MMC = Murphy Medical Center (North Carolina), UGH = Union General Hospital (Georgia). Some hospitals did not report data for all 21 categories ([1] by binomial test). ns = not significant.

Discussion

This is the first report on process of care data on hospitals available to medical consumers in the mountainous area of extreme westernmost North Carolina. The hospital "report card" used in this analysis is one source of information attracting significant consumer interest [2] particularly when data are considered reliable and collected in a highly standardized format. The present study focused on westernmost North Carolina because this region is remote and represents an essentially captive, rural healthcare market where outside influences are unlikely to play a major role.

It is reassuring that patients in westernmost North Carolina have access to these key medical services at multiple locations; the CMS data do not suggest that any of the study hospitals performed significantly below state (North Carolina) or national (USA) average. Although direct comparisons were not made among the three study hospitals, Fannin Regional Hospital emerged as the institution where process of care measures were significantly better than state and national average. In contrast, this investigation found one study hospital (MMC) that achieved no process of care score above the state average. It was beyond the scope of the current study to identify institutional or administrative factors that may be associated with variable process of care performance.

This descriptive pilot study was limited in several ways. Since CMS information is not provided as patient-level data, it was impossible to undertake a regression analysis for a more detailed assessment of clinical factors. Whether these aggregate data depicted a series of independent observations must also be questioned, since it cannot be confirmed that each patient was counted only once and the treatments assessed were themselves independent. Our analysis depended on hospital self-reported data collected retrospectively by manual tabulation from medical records, although the accuracy and consistency of this methodology have not been rigorously validated. Accordingly, confusion exists in "ranking" hospitals on the basis of CMS data [3] since information available via the Hospitals Compare website does not always agree with other publicly available evaluation instruments [4]. This can present a conflicting picture on hospital performance to patients and their families. Given these limitations, we prefer to advance our conclusions as preliminary (rather than definitive) until further studies with greater robustness are undertaken. Nevertheless, this pilot investigation suggests a methodology for further research on how CMS data may be associated with patient decisions regarding hospital choice in westernmost North Carolina.

CMS data available on the Hospitals Compare website represents a highly accessible tool to empower patients with current and standardized information about hospitals. In other settings, hospital market share has been influenced by factors including population density, number of nearby hospitals, medical school affiliation, percentage of Medicaid admissions, and medical/surgical service offerings [5, 6]. To determine if the CMS Hospitals Compare dataset plays a similar role for medical consumers in westernmost North Carolina, and if this information influences patient choice or contributes in other ways to this market dynamic, represents the aim of ongoing research.

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Role of a non-hormonal oral anti-fibrinolytic hemostatic agent (tranexamic acid) for management of patients with dysfunctional uterine bleeding

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Summary

Objective: Perimenaposal dysfunctional bleeding is a common complaint seen in gynecology clinics. Tranexamic acid is a cheap, over the counter hemostatic agent with antifibrinolytic activity that can be used for management of excessive menstrual bleeding. However, there are few reports analyzing its effectiveness in the management of abnormal menstrual bleeding. This study aimed to evaluate the effectiveness of oral transexamic acid treatment in patients with excessive dysfunctional perimenopausal menorrhagia. *Method:* One hundred and thirty-two consecutive patients with dysfunctional perimenepausal uterine bleeding who were admitted to Cankırı Government Hospital between March 2007 and January 2008 were prospectively enrolled into this one-sided study. All the patients were asked to fill out menstrual diaries and to come to follow-up three months after the initial evaluation. All patients took 500 mg of transexamic acid (Transamine® 3x2) during their menses as the primary treatment and iron preparations if Hb was < 10 g/dl. The paired sample t-test was used for statistical evaluation. *Results:* Mean age of the patients was 42.8 (range 38-46 yrs). Median bleeding time was nine days (range 8-12 days) and median Hb was 10.6 g/dl (range 8.2-11.7) before starting the treatment. During follow-up 45 patients were unresponsive to transamine and needed further treatments (overall response rate was 65.9%). Among responsive patients, after three cycles of transamine usage median bleeding time was five days (range 3-8 days) and median Hb values were 12.1 g/dl. *Conclusion:* Oral tranexamic acid is a reasonable treatment option for patients with excessive dysfunctional perimenopousal bleeding with a 66.0% response rate.

Key words: Transexamic acid; Abnormal uterine bleeding; Abnormal perimenopausal bleeding; Oral antifibrinolytic agent; Homeostasis.

Introduction

One-third of all women experience heavy menstrual bleeding at some point in their life. Menstrual blood loss increases with age. Menorrhagia is usually defined as heavy but regular menstrual bleeding of over 80 ml/cycle [1-8]. Medical therapy, with the avoidance of possibly unnecessary surgery, is an attractive treatment option [8-14]. A wide variety of medications are available to reduce heavy menstrual bleeding but there is considerable variation in practice and uncertainty about the most appropriate therapy [1-14]. The most effective is intrauterine levonorgestrel [4]. Other options are oral progestogens, combined oral contraceptive pills, tranexamic acid, mefenamic acid, danazol and gonadotrophin-releasing hormone (GnRH) analogues [4].

Tranexamic acid is a cheap, over-the-counter homeostatic agent with antifibrinolytic activity that can be used for the management of excessive menstrual bleeding. However, there are few reports analyzing its effectiveness in the management of abnormal menstrual bleeding [1-14]. This study aimed to evaluate the effectiveness of oral transexamic acid treatment in patients with excessive dysfunctional perimenopausal menorrhagia.

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Material and Methods

One hundred and thirty-two consecutive patients with dysfunctional perimenopausal uterine bleeding who were admitted to Cankırı Government Hospital between March 2007 and January 2008 were prospectively enrolled in this one-sided study.

All patients complained of menorrhagia. Each patient was evaluated by pelvic examination, transabdominal ultrasonography, cervical smear and Karman endometrial aspiration. Complete blood counts and blood hormonal profiles (FSH, LH, PRL and TSH) were collected for each patient before starting treatment. Women with postmenopausal bleeding, intermenstrual bleeding, iatrogenic or pathological causes of heavy menstrual bleeding were excluded.

All the patients were asked to fill out menstrual diaries and attend follow-up three months after the initial evaluation. All patients took 500 mg of transexamic acid (Transamine® 3x2) during their menses as the primary treatment and iron preparations if Hb was < 10 g/dl. A paired sample t-test was used for statistical evaluation.

Results

Mean age of the patients was 42.8 (range 38-46 yrs). Median bleeding time was nine days (8-12) and median hgb was 10.6 g/dl (8.2-11.7) before starting treatment. During follow-up 45 patients were unresponsive to transamine and needed further treatments (overall response rate was 65.9%). Among responsive patients, after three cycles of transamine usage, median bleeding time was five days (range 3-8) and median hgb values were 12,1 g/dl ($p < 0.01$).

Table 1. — *Pictorial Blood Assessment Chart*.

	Towels
1 point	For each lightly stained towel
5 points	For each moderately soiled towel
20 points	If the towel was completely saturated with blood
	Tampons
1 point	For each lightly stained tampon
5 points	For each moderately soiled tampon
20 points	If the tampon was completely saturated with blood
	Clots
1 point	For a small clot
5 points	For a large clot

Discussion

An increase in the levels of plasminogen activators has been found in the endometrium of women with heavy menstrual bleeding compared to those with normal menstrual loss [10-12]. Plasminogen activator inhibitors (antifibrinolytic agents) have therefore been promoted as a treatment for heavy menstrual bleeding. The effect of tranexamic acid on the fibrinolytic enzymes at the local endometrial level may be responsible for its success in the treatment of menorrhagia [10-12]. Tranexamic acid is a synthetic lysine derivative that exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation.

There are few studies evaluating the role of tranexamic acid in abnormal uterine bleeding in the published English literature [1-14]. Some of these studies are related with the usage in postpartum bleeding and some studies have evaluated its effectiveness in the management of uterine bleeding associated with intrauterine device usage [2, 13, 17]. What about its use in dysfunctional uterine bleeding?

Sirinil *et al*. found a 49% decrease (from 350.5 to 178.6) in menstrual blood loss using the pictorial blood loss assessment chart (PBAC, Table 1) in a small number of patients (n = 40) with idiopathic menorrhagia [1]. They used 1 g of tranexamic acid orally three times daily for five days from day 1 of menstruation for two consecutive menstrual periods. They also noted an increase in quality of life by using tranexamic acid in patients with menorrhagia.

In another study by Kriplani et al. the authors compared tranexamic acid (4 g/day) and medroxyprogesterone acetate (MPA, cyclical 10 mg twice-daily) for three cycles in patients with dysfunctional menorrhagia [6]. Mean reduction in PBAC score was 60.3% (from 356.9 to 141.6) in tranexamic acid users and 57.7% in MPA users (from 370.9 to 156.6). Lack of response was seen in 6.1% of patients using tranexamic acid (TXA) and 28.9% of MPA users ($p < 0.005$). In patients who reported three months after stopping the treatment, 66.7% in the TXA group and 50% in the MPA group had recurrence of menorrhagia, ($p = 0.155$). During the six-month study period more hysterectomies were performed in the MPA than in the TXA group (17.8% vs 4%; $p < 0.005$).

Wellington et al. reviewed studies on available medical treatments of dysfunctional uterine bleeding (mefenamic acid, flurbiprofen, etamsylate and oral luteal phase norethisterone and intrauterine administration of levonorgestrel) [8]. They found the greatest reduction (96% after 12 months) in blood loss with the use of intrauterine levonorgestrel. However, 44% of patients treated with levonorgestrel developed amenorrhea. Tranexamic acid 2-4.5 g/day for four to seven days reduced menstrual blood loss by 34-59% over two to three cycles, significantly more so than placebo, mefenamic acid, flurbiprofen, etamsylate and oral luteal phase norethisterone. They nevertheless concluded that TXA might be considered as a first-line treatment for the initial management of idiopathic menorrhagia, especially for patients in whom hormonal treatment is either not recommended or unwanted [8].

Another review meta-analysis was published in the Cochrane Database Systems [10-11]. The authors analyzed four of the 15 available randomized controlled trials with antifibrinolytic agents versus placebo, no treatment or any other medical (non-surgical) therapy for regular heavy menstrual bleeding [10, 11]. They found that antifibrinolytic therapy causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestagens and ethamsylate). This treatment is not associated with an increase in side-effects compared to placebo, NSAIDS, oral luteal phase progestagens or ethamsylate. Flooding and leakage and sex life is significantly improved after TXA therapy when compared with oral luteal progestogens.

The PBAC (Table 1) is one of the best known and most frequent methods to assess the amount of blood lost during menstruation. It is a simple non-laboratory method for semi-objective diagnosis of menorrhagia, using scores recorded by women themselves [15]. It was first described by Higham *et al*. in 1990 [15]. A score of 100 was used to define menorrhagia in its originally described form. However validity of this chart has been debated [16]. The method has been reported to have a sensitivity of 86% and a specificity of 89% [15]. We think that PBAC is one of the best available methods to assess blood loss; however it is still not free of patient subjectivity.

In this study, unlike others, we did not use the PBAC system but instead, we preferred to use subjective patient complaints about menorraghia by using their menstrual diaries (either decreased blood loss or no response). Moreover, we preferred to use the Hb value of the patients after three cycles of therapy, which is the most objective assessment of the role of tranexamic acid in reducing dysfunctional uterine bleeding. Our results were also in accord with previous studies [5-8]. There was a high response rate to tranexamic acid (65.9%) and the response was also very quick. Among the responders, Hb values and total menstruation duration were significantly improved within three months of treatment. There were no side-effects reported by the patients (neither mild nor moderate-severe side-effects) attributable to TXA during the three months of medication.

As a conclusion, this one-sided descriptive analysis indicates that tranexamic acid is a safe and cheap, over-the-counter non-hormonal medication which can be used for the management of patients with dysfunctional uterine bleeding. Tranexamic acid might be considered as a first-line treatment for the initial management of idiopathic menorrhagia, especially for patients in whom hormonal treatment is either not recommended or unwanted.

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Disturbed sleep and preterm birth: A potential relationship?

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Summary

Purpose: Many women report disturbed sleep during pregnancy, but its impact on clinical outcomes remains unknown. This study examined subjective sleep quality and daytime sleepiness in relation to preterm birth. *Methods:* A convenience sample of 220 pregnant women completed the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the Perceived Stress Scale (PSS) during the second trimester. Women who had preterm and full-term births were compared on these measures. *Results:* The preterm birth rate of the sample was 14.6 %. Sleep latency, the period from lights out to sleep onset, was significantly longer in the preterm group, which also reported a tendency to use more sleep medications, but had lower PSQI daytime dysfunction scores. Perceived stress did not differentiate preterm and full-term groups. *Conclusion:* Disturbed sleep in pregnancy may be associated with preterm birth. Future studies should examine specific physiological factors that underlie this increased vulnerability.

Key words: Pregnancy; Preterm birth; Sleep; Psychological stress.

Introduction

Prematurity, birth prior to 37 weeks of gestation, occurs in 12.7% of all births in the United States and is the primary cause of neonatal death and morbidity, accounting for over one-third (10,364) of infant deaths in 2005 [1, 2]. Associated morbidity includes a high prevalence of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage which often result in permanent neurological disabilities [3]. The economic costs of prematurity are significant. Estimates from the Institute of Medicine [3] place the 2005 annual expense associated with preterm birth in excess of $26.2 billion. Given the widespread prevalence of this problem and the high human and economic costs, research increasing the elucidation of the factors that contribute to the development of preterm birth is an important public health priority.

Numerous physiological and psychosocial risk factors associated with preterm birth have been identified. Infection, a history of prior preterm birth, and Black race appear to be major determining factors. Other known risks include smoking, low socioeconomic status, multiple gestations, inadequate maternal weight gain, substance abuse, uterine anomalies, shortened cervix, short inter-pregnancy interval, and psychosocial stress. Such physiological and psychological stressors associated with preterm birth are believed to activate the maternal/fetal hypothalamic pituitary adrenal (HPA) axis and immune/inflammatory processes, ultimately triggering the uterine and cervical changes that result in preterm labor and, ultimately, preterm birth [4]. Since the neurochemical responses of these pathways are also known to adversely affect normal sleep [5], we hypothesized that disturbed sleep might be a significant summary indicator of the risk for preterm birth.

Materials and Methods

The study was IRB approved. A convenience sample of 220 pregnant women, between 20-29 weeks gestation, was recruited from 15 obstetrical practices during routine office visits. Inclusion criteria included women between 20 and 29 weeks gestation, ages 20 to 40 inclusive, who intended to deliver at one of the study-site hospitals. The ability to read and understand English was also necessary in order to complete the consent form and questionnaires. Exclusion criteria included a history of drug/alcohol abuse, previously diagnosed sleep disorders, a psychiatric diagnosis, and/or a debilitating acute or chronic illness. During routine office visits, after providing informed consent, subjects completed questionnaires that measured quality of nocturnal sleep (the Pittsburgh Sleep Quality Index [PSQI]) [6], daytime sleepiness (the Epworth Sleepiness Scale [ESS]) [7], and perceived psychosocial stress (Cohen's Perceived Stress Scale [PSS]) [8]. The PSQI also generated data on subjective sleep variables, including sleep latency (in minutes), sleep efficiency (time in bed spent asleep, expressed as percentage) and total sleep time (in minutes). Data were also obtained from subjects' antenatal medical records to ensure study eligibility and to obtain demographic and clinical data. After delivery, data were obtained from the subjects' medical records to determine gestational age at delivery.

Due to lack of normally distributed data, we employed chi-square and Mann-Whitney U tests for comparisons between women with full-term and preterm births. Logistic regression was used to determine whether variables that discriminated between the groups on univariate analyses also differentiated the groups using multivariant models.

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Table 1. — *Comparison of sleep measures during the second trimester of women with preterm vs term deliveries.*

	Preterm (< 37 wks) n (%) 32 (14.55) mean (SD)	Term (≥ 37 wks) n (%) 188 (85.5) mean (SD)	Sample N = 220 mean (SD)	Test Statistic[1]	*p* value[1]
PSQI Global Score	6.81 (2.50)	6.71 (3.22)	6.72 (3.13)	2846.00	0.63
Sleep efficiency (%)	85.16 (13.28)	86.32 (12.45)	86.15 (12.55)	2853.00	0.64
Sleep latency (min)	26.09 (19.91)	18.53 (14.94)	19.63 (15.94)	2370.50	0.03*
ESS	8.94 (4.0)	8.95 (4.12)	8.95 (4.10)	2964.50	0.45
PSQI Sleep quality	1.19 (0.74)	1.20 (0.72)	1.20 (0.72)	2999.00	0.49
PSQI Sleep latency	1.28 (1.11)	1.05 (0.96)	1.08 (0.99)	2687.00	0.16
PSQI Sleep duration	0.81 (0.74)	0.89 (0.87)	0.88 (0.85)	2908.00	0.37
PSQI Habitual sleep efficiency	0.66 (0.83)	0.62 (0.91)	0.63 (0.90)	2844.00	0.29
PSQI Sleep disturbances	1.63 (0.55)	1.63 (0.59)	1.63 (0.58)	3006.00	0.50
PSQI Use of sleeping medications	0.28 (0.68)	0.17 (0.60)	0.19 (0.61)	2718.00	0.05
PSQI Daytime dysfunction	0.91 (0.64)	1.16 (0.68)	1.13 (0.68)	2447.00	0.03*

SD = Standard Deviation; PSQI = Pittsburgh Sleep Quality Index (Scores are based on 0-3 scale with 3 indicating worse problem); ESS = Epworth Sleepiness Scale; [1] Mann Whitney U Test; *$p < 0.05$.

Results

The overall rate of preterm birth in this cohort was 14.6%. However, when prior twin deliveries were excluded the rate dropped to 9.55%. There were no differences in women carrying to full term versus preterm in maternal age, gestational age when the PSQI and the other instruments were completed, race, education, marital status, PSS score, smoking, alcohol use, and infection during pregnancy. Women with preterm births were more likely to have had a previous preterm birth (41.2% vs 12.1%; chi-square = 1002.5, $p < 0.01$) or twin births (34.4% vs 2.1%; chi-square = 44.76, $p < 0.01$) but were no more likely to be primiparous (46.9% vs 34.0%; chi-square = 1.96, $p = 0.16$) than women with full-term births.

Sleep measures are shown in Table 1 and indicate that women carrying to full term reported a shorter time to fall asleep, less use of sleep medication but had a higher daytime dysfunction score. Pre-pregnancy sleep quality did not differentiate women with full-term versus preterm births. Multiple logistic regression analyses designed to predict full-term versus preterm status based on PSQI Global score, PSS score, sleep latency, total sleep time, sleep efficiency, race, infection and previous preterm birth status indicated that both longer sleep latency (OR = 1.04; 95% CI 1.01 - 1.07) and previous pre-term birth history (OR = 0.30; 95% CI 0.10 - 0.92) independently predicted women carrying to full term (cumulative r-squared = .084)

Discussion

Sleep latency, the period from "lights out" until sleep onset, was the only sleep variable that was significantly different in the preterm group. Latencies from the full-term group were similar to the polysomnographic data (19.6 minutes SD 9.1) reported in another group of healthy pregnant women in the second trimester [9]. Despite these findings, mean sleep latency values for both groups in our study were below the 30-minute criterion identified as problematic by the PSQI, which suggested that sleep onset insomnia was not a problem in this sample. Nonetheless, the reason for the somewhat prolonged sleep latency in the preterm group remains unclear, and could hold significance from several perspectives. For example, the longer sleep latency could be a subtle indicator of potential physiologic processes leading to the eventual initiation of pre-term labor. Conversely, the longer sleep latency per se might represent vulnerability or even a potentially modifiable risk for preterm labor. Further research will be necessary to identify sleep latency as a key issue of cause and effect.

Despite the significance of prolonged sleep latency, the more general lack of associations between the other measured variables in this study (PSQI, ESS, sleep efficiency, total sleep time, and PSS) and preterm birth may be explained by limitations in measurement. Measurement of sleep quality was made in the second trimester, the period that is typically associated with the best sleep quality during pregnancy [10]. This period was chosen as a measurement point in order to capture data from those subjects who would potentially deliver a preterm neonate in the late second and early third trimester. However, the mean gestational age for preterm birth was 33.4 weeks (SD 3.2), which resulted in an interval of over seven weeks from the time of measurement. Since sleep quality decreases during the course of pregnancy [11], it is likely that the single assessment made in the second trimester reflected better sleep quality than that experienced in the third trimester when labor onset occurred. Similarly, the single measurement of psychological stress in the second trimester may not have reflected the stress experienced in the third trimester.

A limitation may also exist in the subjective nature of the sleep measurements. While both the PSQI and the ESS provide important dimensions of sleep quality, they are limited by the individual's cognitions and perceptions and may not accurately reflect true sleep characteristics. Studies that evaluated the correlation between subjective and objective assessments, as measured by polysomnography, reveal that subjects frequently underestimated total sleep time. However, outcomes from other research of self-reported "good sleepers" and "bad sleepers" revealed that subjective assessments closely mirrored those

obtained from polysomnography. Further studies conducted with both subjective measures and polysomnography during pregnancy would be required to clarify these issues.

Conclusion

To identify a potential relationship between preterm birth and sleep quality, the sleep quality of a sample of 220 subjects in the second trimester of pregnancy was assessed, using subjective tools. Sleep latency, the period from "lights out" to sleep onset, was statistically longer in the group that delivered preterm and was an independent predictor of preterm birth in a multivariate model that contained other known predictors. Further research is warranted to explore the physiological and psychological factors that may contribute to sleep latency and to identify the quality of sleep near the time of both preterm and term deliveries.

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Albumin/creatinine ratio for prediction of 24-hour albumin excretion of ≥ 2 g in manifest preeclampsia

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Summary

Purpose of investigation: To compare whether albumin/creatinine ratios obtained from random or 8-hour urine collected in different periods of day differ in prediction of albumin excretion ≥ 2 g in 24-hour urine collection in preeclampsia. *Methods:* From a total of 70 women, 24-hour urine collected by three consecutive periods of eight hours and three random urine samples were taken before each period. The variation of albumin-creatinine ratios in samples across the day was analyzed by the Friedman and inter-assay coefficient variation. For each sample, receiver operator characteristic (ROC) curves were constructed to determine an optimal albumin/creatinine ratio value in the prediction of albuminuria ≥ 2 g. *Results:* The albumin/creatinine ratio did not vary significantly over time when all samples pooled. However, there was considerable intra-individual variation in both random and timed urine samples. On ROC analysis, the albumin/creatinine ratio in both random and timed urine samples predicted the 24-hour urine results and there was no difference between samples in prediction of albuminuria ≥ 2 g. A single optimal cut-off point was not available between samples. The positive and negative predictive values for optimal cut-offs ranged from 48%-88% and 94%-100%, respectively. *Conclusions:* The random urine albumin/creatinine ratio was a poor predictor for proteinuria ≥ 2 g in patients with preeclampsia.

Key words: Albumin-to-creatinine ratio; Albuminuria; Preeclampsia; Urine creatinine; ROC curve.

Introduction

Sampling random urine for the protein/creatinine ratio or albumin/creatinine ratio has been investigated as an alternative to 24-hour urine collection. There is sufficient data in the literature to support a strong correlation between the protein/creatinine ratio in a random urine sample and 24-hour protein excretion [1, 2]. However, there is no consensus regarding accuracy of the protein/creatinine ratio in prediction of significant proteinuria during pregnancy, possibly due to a high degree of variation in urinary protein concentrations during the course of the day [3, 4]. As a diagnostic test, it has a high number of false-positive and false-negative test results. Currently, the random protein/creatinine ratio has been advocated for ruling out significant proteinuria during pregnancy [1, 5].

Urinary albumin is considered to give a more accurate reflection of glomerular damage than total protein. Some investigators advocate the use of albumin as an alternative to total protein measurement [6-8]. Similar but few data exist for use of an albumin/creatinine ratio in pregnancy as a protein/creatinine ratio. In recent reports, however, it has been reported that both protein/creatinine ratio and albumin/creatinine ratio did not vary significantly over time in hospitalized patients. Data is limited as to whether it is a reliable method in detecting severe albuminuria or proteinuria (> 2 g/day or > 5 g). It is suggested that the protein/creatinine ratio underestimates the true level of proteinuria at higher levels of protein excretion [9, 10].

The objective of this study was to compare whether albumin/creatinine ratios calculated from random or 8-hour urine collected in different periods of the day differ in prediction of albumin excretion ≥ 2 g in 24-hour urine collection in preeclampsia. We also investigated whether these ratios vary across the day.

Material and Methods

The study was conducted prospectively between December 2006 and November 2007 at Aziziye Hospital. It was approved by the Ataturk University Intuitional Review Board.

All pregnant women at > 20 weeks of gestation who had new-onset elevations of systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm measured twice at least six hours apart and who had a repeated positive spot urine test for proteinuria of ≥ 0.3 g/dl were eligible for the study. Only women with significant proteinuria (≥ 300 mg) in the 24-hour urine sample were included in the final analysis. Patients were excluded if they had coexisting urinary tract infections based on culture, pre-existing intrinsic renal disease or diabetes. All eligible women were enrolled the study after giving informed consent.

All 24-hour urine collections were started between 07-08 hours in the morning immediately after the first voided morning urine and included final voiding at the completion of the 24-hour period. The patients were on modified bed rest in the hospital. The urine was collected in three separate drainage bags. The first drainage bag held the first eight hours of urine, the second container held the next eight hours of urine, and third one held the last eight-hour sample. When each time period ended, the urine volume in the drainage bag was measured and a 6-ml aliquot of urine sample was taken after the urine was stirred to ensure homogeneity. The first two 8-hour urine collections were store at 4°C and all 8-hour samples were pooled at the completion of the 24-hour period. A 6-ml aliquot of urine sample was taken from the total urine specimen. Three random

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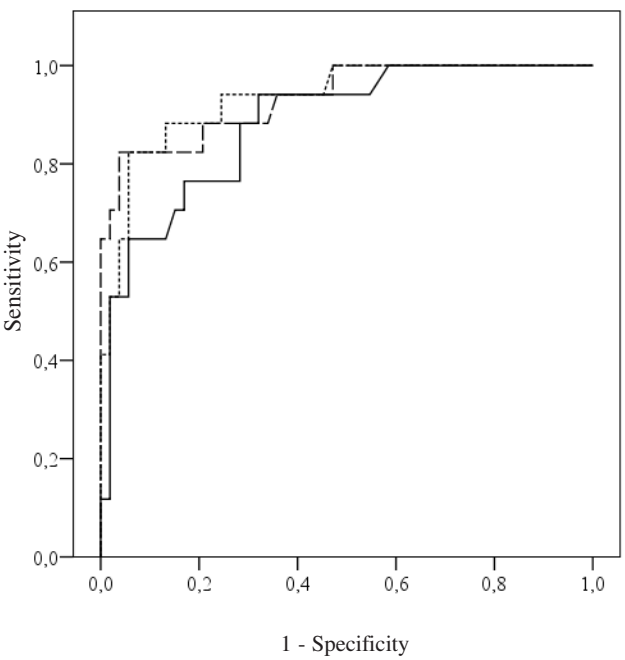

Figure 1. — Receiver operating characteristic curves for the random urinary albumin/creatinine ratio at different periods of the day as a predictor of albuminuria > 2 g (straight line represents 8 am, dotted line 4 pm, dashed line 0 pm).

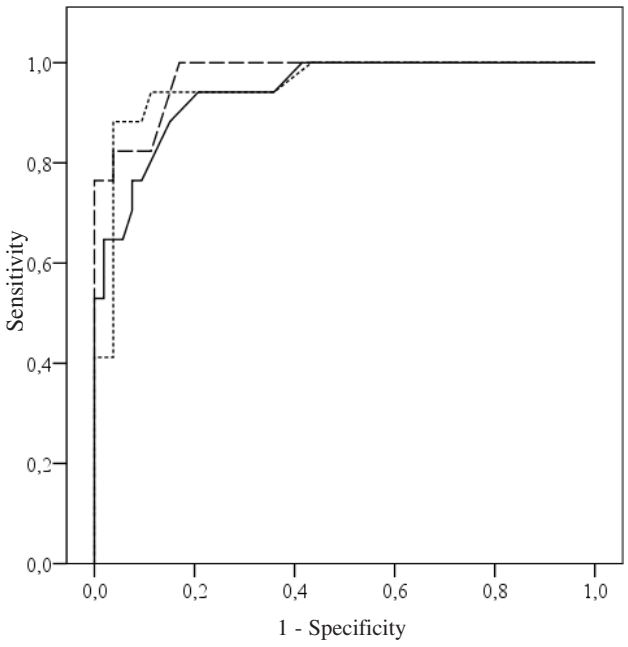

Figure 2. — Receiver operating characteristic curves for the timed urinary albumin/creatinine ratio at different periods of the day as a predictor of albuminuria > 2 g (straight line represents 08-16 period, dotted line 16-24 period, 00-08 period).

urine samples were collected before each time period. The first random urine sample was collected in the early morning (approx. 8 a.m.), the second random sample was collected in late afternoon (approx. 4 p.m.) and the third random urine sample was collected at midnight. An indwelling Foley catheter was used for collection of urine in all samples. Samples of creatinine were drawn from all of the patients at the initiation of the 24-hour urine collection.

All urine samples were analyzed for albumin and creatinine immediately after taken. Urine albumin concentration was measured using an OLYMPUS AU2700 Analyzer (Tokyo, Japan) by the pyrogallol red spectrophotometric method (CV of 1.82%). The creatinine test was analyzed using the Jaffe rate method with the same analyzer. The albumin/creatinine ratio was calculated by dividing protein (mg/dl) by creatinine (mg/dl).

Statistical analyses were performed with the SPSS 15.0 (SPSS Inc., Chicago, IL) and MedCalc 7.2.0.0 (Frank Shoonjans, Mariakerke, Belgium) statistical packages. Since normality tests failed, associations between maternal age, gestational age, albumin/creatinine ratios and 24-hour urine total albumin were assessed with Spearman's rho correlation coefficient. The results of the 24-hour urine collection were used as the gold standard, and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the random urine albumin/creatinine ratios at various cut-offs for prediction of > 2 g albuminuria were estimated. Receiver operator characteristic (ROC) curves were constructed to determine an optimal albumin/creatinine ratio value that maximized sensitivity and specificity in the prediction of significant albuminuria. Urine albumin/creatinine values across the day were analyzed by the Friedman test after pooling all samples. The amount of individual variation in the albumin/creatinine ratio over time was analyzed separately for random and 8-hour urine samples evaluating the inter-assay coefficient variation. The coefficient variation (σ/μ, where σ is the standard deviation, μ is the mean) for each patient was calculated and then the mean coefficient variation with standard deviation was calculated.

Results

A total of 77 consecutive patients with preeclampsia were identified during the study period. A complete 24-hour urine collection was not available for seven patients. Thus 70 consecutive patients constituted the study group. The mean maternal age was 29.5 ± 7.9 years, and mean gestational age was 36.7 ± 4.6 weeks. Ten patients (14.3%) were in the second trimester and 60 (85.7%) in the third trimester. Twenty-seven women (38.6%) were nulliparous. Median blood creatinine level was 0.8 mg/dl (0.4-2.0). Ten patients (14.3%) had a blood creatinine level of ≥ 1 mg/dl.

The median albumin level was 0.6 g (0.1-8) in 24-hour urine of the patients. Twenty-six patients (37.1%) had albuminuria below 0.3 g in 24-hour urine collection. Seventeen patients (24.3%) had a 24-hour albumin excretion of ≥ 2 g and four (5.7%) had ≥ 5 g.

Spearman's rho correlation coefficient between the 24-hour albumin excretion with spot and 8-hour urine albumin/creatinine ratios are given in Table 1. When patients with a creatinine level of ≥ 1 mg/dl were excluded, correlation coefficients were similar (data not shown). The associations of maternal age and gestational age at collection with 24-hour urine total albumin and albumin/creatinine ratios (data not shown) were not significant.

Table 1. — *Test performance of albumin-creatinine ratios for optimal cut offvalues and correlation with 24 hour albumin.*

Sample	C.C.[1]	AUC (95% CI)[2]	Cut-off	Sensitivity (95% CI)[2]	Specifity (95% CI)[2]	+PV	–PV
Random (hour)							
8 am	.79	.88 (.79-.97)	0.6	94 (71- 99)	68(54- 80)	48	97
4 pm	.85	.93 (.87-1.0)	1.4	82(57- 96)	94(84- 99)	82	94
0 pm	.86	.93 (.86-1.0)	1.6	82(57- 96)	96(87- 99)	87	94
8-hour (time period)							
08-16	.91	.94 (.88-1.0)	0.9	94(71- 99)	79(66- 89)	59	98
16-24	.90	.95 (.90-1.0)	1.3	88(63- 98)	96(87- 99)	88	96
00-08	.91	.97 (.94-1.0)	0.7	100(80-100)	83(70- 92)	65	100

[1, 2] $p < 0.001$ for all samples; C.C, correlation coefficient; AUC, area under curve, CI, confidence interval, PV, predictive value.

ROC curves for spot urine albumin-creatinine ratio values and 8-hour urine albumin-creatinine ratio values are shown in Figures 1 and 2, respectively. The area under the ROC curve was significant for each urine sample (Table 1). The areas under the ROC curves were not different in pairwise comparisons after pooling all samples (data not shown). The optimal albumin/creatinine ratio cut-off point that maximizes sensitivity and specificity are shown in the Table 1. The highest cut-off points that yielded 100% sensitivity for spot and 8-hour albumin/creatinine tests with PPV, false-positive rates (1-specifity), and percentage of screen positive patients are shown in Table 2.

Table 2. — *Test performance of albumin-creatinine ratio as a screening test to rule out albumin excretion ≥ 2 g.*

Sample	Cuf-off	False-positive rate (95% CI)	+PV (%)	Secreen positive (%)
Random (hour)				
08	0.37	58 (44-72)	35	67
16	0.39	47(33-61)	42	60
24	0.36	47(61-33)	41	59
8-hour (time period)				
08-16	0.46	41(28-54)	44	56
16-24	0.36	43(30-38)	43	57
00-08	0.75	27(8-28)	65	37

CI, confidence interval; PV, predictive value.

The albumin/creatinine ratio were not different between samples over time when both spot urine and 8-hour collection were analyzed as a whole. Inter-assay coefficient variation was 35.1% (± 26.2) in spot urine samples and 35.4% (± 33.8) in 8-hour urine samples.

Discussion

We found a strong correlation between the albumin/creatinine ratio and 24-hour albumin in women with preeclampsia. The albumin/creatinine ratio did not vary significantly across time when all samples were pooled. However, there was considerable intra-individual variation in both random and timed urine samples. On ROC analysis, the areas under the ROC curves showed that the albumin/creatinine ratio for both random samples and 8-hour urine collections were accurate in predicting the 24-hour urine results and there was no difference between samples. However, a single optimal albumin/creatinine ratio cut-off point for identifying albumin excretion ≥ 2 g was not available.

Interpretation of a test varies by prior probability of the disease. In the present study, we found the ratio of severe albuminuria to be 24.3% in a group of consecutive patients who had preeclampsia. The PPVs of the tests for optimal cut-offs were low and the test results above these cut-offs were not diagnostic for significant proteinuria. However, the NPVs of albumin/creatinine ratios were too high to be substituted for 24-hour collection. It seems, except for the 0-08 time period, that an albumin/creatinine cut-off point ranging from 0.36-0.46 can accurately exclude severe albuminuria with 100% sensitivity. The protein/creatinine ratio can be used as a screening test in preeclampsia for albuminuria to rule out 24-hour albumin excretion of ≥ 2 g.

Sampling random urine for a protein/creatinine ratio is based on the assumption that urinary protein and creatinine excretion in the presence of a stable glomerular filtration rate during the day remains constant [11]. Protein excretion rates, however, can vary hour to hour in preeclampsia due to renal vasoconstriction [3, 12]. Chesley reported up to a 5-fold variation of protein excretion in four hourly collections [3]. In most previous studies, a significant correlation between the protein/creatinine ratio or albumin/creatinine ratio with 24-hour urine were reported in women with hypertensive disease of pregnancy [1, 2, 13-15]. However, a high correlation does not necessarily support the fact that the ratio varies within a narrow range across the day. The albumin/creatinine ratio might be a better estimate of renal function at that moment than 24-hour collection. However, if it is necessary to know the total amount of the albumin excreted, a 24-hour urine sample must be collected.

Conclusions

The albumin/creatinine ratio is a poor predictor of albuminuria ≥ 2 g in patients with preeclampsia and should not replace the 24-hour urine collection as a diagnostic test. It has high intra-individual variation across the day. The ratio can be used to rule out albuminuria proteinuria ≥ 2 g due to high NPV. However, a single albumin-protein cut-off point is not available.

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Mid-trimester maternal serum hCG levels in predicting adverse pregnancy outcome

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Summary

Objective: In this prospective study, we investigated the association between mid-trimester maternal serum human chorionic gonadotropin (ms-hCG) levels and adverse pregnancy outcome in a South-Western Greek population. *Materials and Methods:* 130 healthy Greek women with spontaneous pregnancies were investigated for ms-hCG levels between the 13th and 24th weeks of gestation and followed for adverse pregnancy outcome. hCG levels > 2.0 multiples of the median value for gestation were considered abnormal. Statistical analysis was performed by Pearson's chi-square test. *Results:* Gestational complications developed in a total of 12 of the 130 women studied (9.23%). Elevated ms-hCG levels were detected in a total of 14 of the 130 women studied (10.77%). *Conclusion:* Multiparameter testing of placental function in the mid-trimester (uterine artery Doppler, placental morphology and ms-hCG screening) may allow us to identify women with increased risk of developing severe placental insufficiency and pregnancy complications.

Key words: Maternal serum hCG levels; Adverse pregnancy outcome.

Introduction

Maternal serum human chorionic gonadotropin (ms-hCG) was originally introduced into the screening assay to derive risks for trisomy 21. However, the introduction of high-resolution first trimester ultrasound (US) screening for aneuploidy at 11-13 weeks of gestation has greatly reduced the need for ms-hCG screening in mid-trimester [1].

Pregnancies with unexplained mid-trimester elevation in ms-hCG are at increased risk of pregnancy complications [intrauterine growth restriction (IUGR), intrauterine foetal death (IUFD), preeclampsia (PE)] resulting from placental insufficiency [2-5].

In our prospective study, we investigated the association between mid-trimester ms-hCG levels and adverse pregnancy outcome in a South-Western Greek population.

Material and Methods

Between February 2005 and February 2008, about 130 women with spontaneous pregnancies were referred to the Outpatient Clinic of the Obstetrics and Gynaecology Department of the University of Patras Medical School. All women were investigated for ms-hCG between the 13th and 24th weeks of gestation and followed for adverse pregnancy outcome.

Gestational age was estimated from the last menstrual period for women with regular (21-35 days) menstrual cycles or confirmed from US scan in the first trimester for women with irregular menstrual cycles. Women with multiple pregnancies, diabetes mellitus, pregnancy with chromosomal or structural abnormality, hypertension diagnosed before the 20th week of gestation and history of PE in previous pregnancy were excluded from the study.

All women had a dating US examination at their first visit, followed by a detailed examination at the 18th-22nd week of gestation. The study was approved by the Ethical Committee of the Hospital. Informed consent was obtained from each woman.

Serum samples were collected from all women between the 13th-24th weeks of gestation. All serum samples had been stored at -20°C. hCG levels were measured with immunoradiometric assay using two highly specific monoclonal antibodies for coating of the solid phase and the tracer. The tracer antibody and the coated antibody react simultaneously with the b-hCG present in patient samples or standards. Excess tracer is removed by a washing step and the radioactivity bound to the tube wall is measured in a gamma counter (b-hCG IRMA CT, Radim S.p.A.). Levels of ms-hCG > 2.0 multiples of the median value for gestation (MoM) were considered as abnormal.

As adverse pregnancy outcomes all gestational complications with fetomaternal circulatory disturbances [placental abruption (PA), IUGR, IUFD, PE] were considered.

PA was defined as the separation of the placenta from its site of implantation before delivery of the foetus [6].

IUGR was defined as a birth weight below the 5th percentile for gestational age [7].

IUFD was defined as foetal loss after 24 weeks' gestation.

PE was defined by a blood pressure above 140/90 mmHg after 20 weeks' gestation, proteinuria > 300 mg/24 hours or persistent 30 mg/dl (1+ dipstick) in random urine samples. The term severe preeclampsia is used when blood pressure above 160/110 mmHg is recorded at least six hours apart, and proteinuria of more than 5 g during 24 h occurs [8].

Statistical analyses were performed using the SPSS-12 for Windows. The chi-square test was used to assess the association between categoric variables.

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Results

Serum samples were collected at a median gestation of 19 weeks (range 13-24). The median weight of the women at the time of serum sampling was 71 kg (range 50-105). The median age at estimated delivery date was 30 years (range 17-50).

From the 130 women included in the study, 12 (9.23%) developed gestational complications during the follow-up of their current pregnancy. The demographics of women with gestational complications compared to those without are shown in Table 1.

Table 1. — *Women's demographics (n = 130).*

		Women with complications (n = 12)	Women without complications (n = 118)
Number of pregnancies	1 pregnancy	12 (100%)	100 (84.75%)
	≥ 2 pregnancies	0 (0%)	18 (15.25%)
Age of women	< 25	1 (8.33%)	23 (19.49%)
	25-35	7 (58.33%)	70 (59.32%)
	> 35	4 (33.33%)	25 (21.18%)
Complications in previous pregnancies	No	8 (66.67%)	106 (89.83%)
	Yes	4 (33.33%)	12 (10.17%)
Smoking	No	10 (83.33%)	106 (89.83%)
	Yes	2 (16.67%)	12 (10.17%)

Abnormal ms-hCG levels were detected in a total of 14 of the 130 women studied (10.77%). None of them developed gestational complications in the current pregnancy (Tables 2 and 3).

Table 2. — *Women's demographics (n = 130).*

ms-hCG levels	Women with complications (n = 12)	Women without complications (n = 118)	*p* value
ms-hCG > 2 MoM (n: 14)	0	14	ns
ms-hCG ≤ 2 MoM (n: 116)	12	104	

p value was calculated by the chi-square test.

Table 3. — *ms-hCG levels in women with specific gestational complications in current pregnancy (n = 12).*

ms-hCG levels	PA	IUGR	PE	IUFD
ms-hCG > 2 MoM (n = 14)	0	0	0	0
ms-hCG ≤ 2 MoM (n = 116)	4	6	0	2
Total	4	6	0	2

PA = placental abruption; IUGR = intrauterine growth restriction; PE = preeclampsia; IUFD = intrauterine foetal death.

Discussion

Serum hCG appears early during pregnancy [9]. Its concentration increases gradually by reaching a peak at the end of the first trimester, after which it progressively decreases until delivery [10].

During pregnancy hCG is produced almost exclusively in the placenta, but also is synthesised in the fetal kidney and foetal liver [11]. Most of the hCG in circulation is metabolized by the liver, whereas about 20% is excreted by the kidneys [12].

The aetiology of the increased hCG production by the placenta is not clear. Experimental evidence from trophoblastic cells cultured in vitro showed that hypoxia increases hCG production [13]. Many mechanisms leading to elevations of ms-hCG have been proposed.

Increased ms-hCG concentrations have been related to the presence of placental pathology, such as infarction, ischemic changes, villitis and intervillus thrombosis [3, 14]. Velamentous cord insertion has been described to be associated with elevated mid-trimester ms-hCG concentration [15]. The presence of chromosomally abnormal areas in the placenta known as confined placental mosaicism, has been found to be associated with high mid-trimester ms-hCG levels [16]. All these placental pathologies may be associated with overproduction of hCG [3, 14, 16-18].

Another possible explanation may be inadequate trophoblastic remodelling of the maternal uterine vasculature, with an absence of normal physiologic changes in the spiral arteries leading to placental hypoxia and hCG overproduction [3, 17, 18].

Pregnancies complicated by an unexplained mid-trimester elevation in ms-hCG are at increased risk of perinatal complications resulting from placental insufficiency, including combinations of IUGR, IUFD and PE [2-5, 19, 20]. In our study mid-trimester elevated ms-hCG levels were detected in a total of 14 from the 130 women studied (10.77%). None of them developed pregnancy complications.

In our study the main limitation was the small number of cases with gestational complications. It is possible that ms-hCG would perform better in a high-risk population.

According to the results shown in Table 2, elevated mid-trimester ms-hCG levels alone can not detect pregnant women with increased risk of developing pregnancy complications. However, uterine artery Doppler screening alone is superior to ms-hCG screening for the identification of significant placental pathology leading to PE and IUGR [21-23]. Multiparameter testing of placental function in the mid-trimester (uterine artery Doppler, placental morphology and ms-hCG screening) may allow us to identify women with increased risk of developing severe placental insufficiency and pregnancy complications [23].

Conclusion

Multiparameter testing of placental function in the mid-trimester (uterine artery Doppler, placental morphology and ms-hCG screening) may be useful in identifying women with increased risk of developing severe placental insufficiency and pregnancy complications.

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An objectıve method to determıne corneal changes durıng menopause

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Summary

Objective: We hypothesized that menopause has a measurable effect on corneal thickness. The aim of this study was to evaluate central corneal thickness (CCT) differences between women in the premenopausal and postmenopausal period. *Methods*: A prospective, case-control, single-blind study was designed. Two groups were included: Group I (premenopausal period) and Group II (postmenopausal period). Forty women were recruited in each group. The correlation between CCT with age, estradiol (E2) and follicle stimulating hormone (FSH) levels were evaluated. *Results*: CCT was significantly decreased in postmenopausal women compared to premenopausal women (521.18 ± 37.97 μm 561 ± 42.84 μm, respectively, $p < 0.005$). Similarly, there was a linear correlation between CCT and serum E2 levels of patients overall ($p < 0.01$). *Conclusion:* The data presented in this study suggest that menopause causes corneal changes, which may be documented by central corneal thickness measurement.

Key words: Cornea; Eye; Menopause; Estradiol.

Introduction

The ovary is unique in that age associated with a decline in function (to frank failure) appears to have remained constant, despite the increase in longevity experienced by women over the last century. Because the loss of ovarian function has a profound impact on the hormonal milieu in women, and also on the subsequent risk for the development of disease via the loss of estrogen production, improving our understanding of reproductive aging is critical to care for all women. It is now accepted that the cessation of menses for one year and/or increase in serum FSH levels above 40 IU/ml and decrease in serum estradiol levels below 100 pg/ml are essential for a diagnosis of menopause. Menopause occurs at a median age of 51.4 years, with the normal age range in women being 42-58 years. The age of menopause appears to be determined largely by genetics, and it is due to exhaustion of the oocyte pool. Menopause and the years preceding are characterized by hormonal changes, decline in reproductive potential, and increased risk for physical and psychological changes [1].

Several visual system abnormalities have been reported with menopause and hormonal status. Corneal changes are the most common. In the United States, it has been reported that 3.2 million women who are over 50 years old are inflicted with dry eye and corneal problems [2-5]. Epidemiologic studies reported that corneal variables including corneal thickness, curvature, and sensitivity could be regulated by sex hormones; however, the mechanism of this phenomenon is not apparent. These variables of the cornea are considered to be important parameters for contact lens wear, or a patient who is a candidate for corneal surgery. A change in thickness during the menstrual cycle of women and each trimester of pregnancy has also been reported [6, 7]. These cyclic changes are attributed to hormonal influences. Variations in corneal thickness may be enough to cause changes in visual performance. No report has been published about the changes of corneal thickness between premenopausal and postmenopausal women.

In this study our aim was to evaluate the central corneal thickness differences between women in the premenopausal and postmenopausal period.

Materials and Method

Study design

A prospective randomized, single-blind, case-control study was undertaken in 2006. Two groups were formed: Group I (premenopausal period) and Group II (postmenopausal period). Forty women aged between 40 and 50 years were recruited in each group to check for differences in corneal changes during menopause. Women over 50 years old were excluded. Thus, both Group I and II were in the same age group ($p > 0.05$). Women undergoing hormone replacement therapy, suffering from hypertension, diabetes mellitus, wearers of contact lenses, who had previously had corneal pathology, and who had had prior ocular surgery or dry eyes were also excluded from the study. We assessed FSH and E2 levels in the blood samples of postmenopausal women and undertook routine examinations of the premenopausal women on the third day of menstruation. This was done to standardize the time during which E2 levels were evaluated. Women who had had cessation of menses for one year and serum FSH levels above 40 IU/ml were defined as being in the postmenopausal period. The study was performed in accordance with the ethical standards that were reviewed in the Helsinki Declaration. Approval of the ethical committee of the institution was obtained. All subjects were informed of the study, and they participated of their own will and gave written consent.

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Measurment of the corneal thickness

All women were recruited from the outpatient clinic of the Department of Obstetrics and Gynecology, University of Istanbul. These women were sent to the Department of Opthalmology of the university, in accordance with the single-blind study design. Central corneal thickness values were taken and ultrasound (US) was used for evaluation (ultrasound pachometry is the most reliable method for the measurement of central corneal thickness [8]). The mean inter-observer difference for US pachometry was 0.001 mm (SD 0.009; SE 0.0015) and the mean intra-observer difference was 0.002 mm (SD 0.011; SE 0.0019)(5). Central corneal thickness (CCT) was measured by a Alcon Handheld Ultrasonic Pacimeter (Alcon, INC, Irvine, CA, USA). Measurements were taken in the sitting position, a local anesthethic (one drop of benoxinate) was applied, and the patients were asked to look straight ahead. The corneal center was detected by determining corneal light reflex where the US probe was set at 1.5 mm temporal to light reflex. The CCT was measured five times for each eye and the average of these readings was taken. Measurements were recorded from 10 a.m. to 12 p.m. to prevent diurnal variation.

Statistical analysis

Age is expressed as the median (min-max) values. Central corneal thickness and E2 levels are expressed as the mean ± SD values. The differences in Groups I and II according to the variables were evaluated by the t-test. Correlations between central corneal thickness and E2 levels were evaluated by Pearson's correlation test.

Results

Mean age of Groups I and II was 43.65 ± 2.85 (range 40-49) and 46.05 ± 2.56 (range 41-49). There was no significant statistical difference between the two groups according to age (Table 1).

Mean ± SD E2 levels in Groups I and II were 250.14 ± 190.62 pg/ml; and 33.11 ± 24.80 pg/ml, respectively. As expected E2 levels were significantly lower in the postmenopausal group compared to the premenopausal women ($p < 0.005$, u = 0.00) (Table 1).

Mean ± SD CCT values in Groups I and II were 561 ± 42.84 and 521.18 ± 37.97 μm, respectively. In Group II, central corneal thickness was significantly lower ($p < 0.005$, t = 3.12) (Table 1).

Correlation tests between CCT and E2 levels were performed. Central corneal thickness significantly correlated with menopause and E2 levels ($p < 0.01$, r = –0.051).

Table 1. — *Comparison of central corneal thickness, E2 and age in the groups*.

	CCT Mean ± SD (micrommeters)	E2 Mean ± SD (pg/ml)	Age Mean ± (year)
Group I (premenopausal period n = 40)	561 ± 42.84	250.14 ± 190.62	43.65 ± 2.85 (range 40-49)
Group II (postmenapausal period n = 40)	521.18 ± 37.97	33.11 ± 24.80	46.05 ± 2.56 (range 41-49
p values for pairwise group*	$p < 0.005$ t = 3.12	$p < 0.005$ u = 0.00	ns

*$p < 0.05$ is statistically significant (t-test values); CCT = central corneal thickness; E2 = estradiol; ns = not significant.

Discussion

Sex steroid hormones are present in all tissues of the body as they are circulated through the blood; however, their effects are seen only in cells that are armed with the corresponding receptors. Studies have shown the presence of sex steroid hormone receptors in various ocular tissues such as the lens, retina, choroid, cornea, iris, ciliary body, lacrimal gland, meibomian gland, lid, and palpebral and bulbar conjunctiva. They are also found in the nuclei of human corneal epithelial, stromal and endothelial cells [9-11].

Some of the earlier epidemiologic and laboratory studies revealed that the effect of sex steroids cause changes in the eye with increased age such as age-related macular degeneration (AMD), an idiopathic full-thickness macular hole, age-related cataract, tear function and dry eye [12-17]. Although specific sex hormone receptors have been shown in some tissues of the eye, the pathophysiologic process of sex steroids is not clear.

Menstrual cycle variations of corneal thickness, curvature, and sensitivity have been reported [18]. Millodot and Lamot suggest that the change in corneal sensitivity during the premenstrual phase may be due to a generalized increase in water retention or an increase in intraocular pressure [19]. Kiely *et al*. found steepening central curvatures in both horizontal and vertical meridians at the beginning of the cycle with flattening occurring after ovulation; in addition, cyclic changes in corneal thickness during the menstrual cycle and thickening of the cornea at ovulation were also found [20]. Giuffre *et al*. investigated that the thinnest cornea at the beginning of the cycle with significantly thicker at ovulation and at the end of the cycle, without substantial differences between the last two time points. Therefore, the thicker central cornea is found immediately after the peak of plasma E2 that occurs during the cycle [21].

Moreover, Sanchis-Gimeno *et al*. studied and compared corneal thickness values of postmenopausal women with and without dry eye [2]. They showed that postmenopausal women with dry eye had reduced corneal thickness values at each corneal location when compared with postmenopausal women without dry eye. They advocated that the decrease in corneal thickness was because of eye dryness, and this was not specific to menopause. They believed that a longer duration of dry eye symptoms might be the cause of reduced corneal thickness values found in postmenopausal women. However, they did not study and compare the corneal thickness values of premenopausal women with that of postmenopausal women. We have not found any literature studies of such comparison.

This study measured the corneal thickness values of postmenopausal women and compared the results with those of premenopausal women. We found that corneal thickness had significantly lower mean values in postmenopausal than in premenopausal women. Some evidence seems to confirm that hormones may play a role in corneal thickness, especially estrogen. Weinreb *et al*. showed that pregnant women had a central corneal thick-

ness that was greater than the control group, and they suggest that hormonal changes during pregnancy leads to retention of water in the cornea, with a concomitant increase in corneal thickness [22]. Affinito *et al*. studied the effects of hormone replacement therapy (HRT) on corneal thickness in postmenopausal women and discovered a thicker cornea in subjects receiving HRT with 17β-estradiol compared with untreated, control women, although the difference between the two groups was not significant [23]. However, there was a significant linear correlation between corneal thickness and serum E2 levels in our study. We found elevated E2 levels on the third day of menstruation. In our opinion, there were two reasons for this result: first, even though we accepted cyclic women with a 28-day period, E2 levels of women aged 40-50 years were unstable. Second, in five patients, E2 levels were higher than expected, thus the median was calculated as above the standard level, so the standard deviation was high.

A potential indirect mechanism of estrogen that could also have an impact on corneal thickness needs to be taken into account. Stefano *et al*. reported that physiological doses of estrogen immediately stimulate nitric oxide release from human endothelial cells through activation of a cell-surface estrogen receptor that is coupled with increase in intracellular calcium [24]. Yanagiya *et al*.*'s* investigations on the rabbit cornea suggested that nitric oxide is produced in the corneal endothelium, and that the nitric oxide/cyclic GMP pathway is involved in the maintainance of corneal thickness [25]. Thus estrogen may have an indirect impact on the cornea.

These reports seem to show a strong association between corneal thickness and female hormone levels, particularly estrogen levels. Estrogens reach the cornea through the tears and aqueous humor, and it is not apparent whether a hormonal influence is exerted through direct interaction in the cornea or via the secondary effects such as systemic water retention by estrogen-induced up-regulation of the renin-aldosterone system, dry eye, and nitric oxide mechanism. Further and more detailed studies are needed to reevaluate the reasons why postmenopausal women have thinner corneas.

Conclusion

The results of this study suggest that corneal thickness is significantly correlated with menopause and E2 levels. These data merit further study to evaluate the role of central corneal thickness measurements to document corneal changes during menopause in women, with the intention of objective clinical visual system evaluation.

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Effectiveness of transvaginal colporrhaphy with porcine acellular collagen matrix in the treatment of moderate to severe cystoceles

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Summary

Purpose: The aim of this study was to determine the effectiveness of transvaginal anterior colporrhaphy with the use of porcine acellular collagen matrix in the treatment of moderate to severe cystocele. *Materials and Methods:* This retrospective study included 95 patients who underwent anterior colporrhaphy with the use of porcine dermus from September 2003 through March 2008 at the Gynaecological Department of University General Hospital of Alexandroupolis in Greece. The inclusion criterion was a grade 2-4 cystocele by the Baden-Walker halfway system. Postoperatively patients were evaluated at one, six and 12 months. Objective cure was defined as no or grade 1 cystocele with an asymptomatic patient at 12 months postoperatively. Improved outcome was considered as an asymptomatic patient with a grade 2 cystocele and failure symptomatic patients or with grade 3 or 4 cystocele. *Results:* All of the patients had a 12-month postoperative follow-up or were noted as a failure prior to the 12-month assessment. The majority of the women were menopausal (88.4%) and overweight (mean BMI 26.1). The overall cure rate was 81.1%, the improvement of the cystocele was 10.5% while the failure rate was 8.4%. The complications we noted were vaginal erosion in 2.01% and graft extrusion in 1.05% of the patients. *Conclusion:* Transvaginal anterior colporrhaphy using porcine dermal in the treatment of moderate to severe cystocele is simple, safe, easily learned and performed with a high success rate and low morbidity.

Key words: Pelvic organ prolapse; Cystocele; Anterior colporrhaphy; Porcine collagen.

Introduction

Cystocele is defined as the extrusion of the bladder base beyond its original place towards the vaginal introitus with the patient in maximum straining. According to the level of the protruding anterior vaginal wall cystoceles are divided in grades 1-4 by using the Baden-Walker Halfway System [1]. Anterior vaginal wall prolapse results from increased weakness and laxity of periurethral, urethrovesical, and vesicovaginal ligaments or fascias. The collagen tissue is considered to be damaged along with the innervation of the perineal muscles resulting in malfunction [2]. The more severe cystoceles are less prone to cure and more prone to recurrence and represent a modern challenge to gynaecologists. These are accompanied with other prolapsed sites as rectocele, enterocele, lateral defects and vaginal vault prolapse [3, 4].

Many techniques have been used with unsatisfactory results such as the Marshall-Marchetti-Krantz urethropexy, the Burch colposuspension, paravaginal repairs and the typical anterior colporrhaphy with a Kelly suture. These stand especially for grade 3-4 prolapses. The recurrence rate is high and 18% of patients need a repeat operation. Cystoceles account for 70% of repair procedures in these women. Due to these facts surgeons used graft materials for the correction of pelvic organ prolapse transvaginally, as in abdominal hernias, to solve the problem [5]. A variety of grafts (Table 1) are used, but the most common are the synthetic polypropylene mesh and the xenograft porcine acellular collagen matrix [6, 7].

Permacol is one of the newest available materials in the past 20 years. Permacol is a natural, strong, biocompatible and permanent material. It is resistant to mineralisation, retains its shape despite stretching and is easily fixed to the underlying tissues by sutures. Once in place it is invaded by the host's fibroblasts within two weeks thus fixing it in place and subsequently it is vascularised within 60 days making it a permanent strong layer of fascia.

Pelvic floor reconstruction surgery is aimed to correct the various defective sites, restore the anatomy and mainly to maintain pelvic structural physiology and function. The aim of our study was to determine the effectiveness of anterior colporrhaphy with the use of porcine acellular collagen matrix (Permacol).

Materials and Methods

This study is a retrospective analysis of data that was collected on 95 women who underwent transvaginal anterior colporrhaphy with the use of porcine acellular collagen matrix between September 2003 and March 2008 in the Gynaecological Department of the University General Hospital of Alexandroupolis, Greece. The classification of cystocele was based on the Baden-Walker Halfway system. The inclusion criterion was a grade 2-4 cystocele without regard to the presence or absence of the uterus or whether there was recurrence of a cystocele. Table 2 shows patient demographics.

The operation was performed with spinal or general anaesthe-

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Table 1. — *Types of grafts*.

A. Synthetic non absorbable (Prolene, Mersilene, Gore-Tex)
B. Synthetic absorbable (Dexon, Vicryl)
C. Autologous (rectus fascia/fascia lata)
D. Xenografts - Porcine (acellular dermis, subintestinal mucosa)
E. Allografts - Donor (fascia lata, dura mater)

Table 2. — *Patient demographics*.

Age	Mean 66 (range 42-78)
Parity	Mean 3 (range 1-4)
BMI (kg/m^2)	Mean 26.1 (range 21.2-30.5)
Vaginal Deliveries	92/95 (96.8%)
Previous pelvic floor reconstruction	11/95 (11.6%)
Postmenopausal	84/95 (88.4%)

sia with the patient in the dorsal lithotomy position. Patients were given antibiotics intra- and postoperatively. The typical steps for anterior colporrhaphy were followed with the use of mixed vasopressin and normal saline at the preparation site under the vaginal mucosa for a better and bloodless dissection thereafter. A vertical suburethral incision was made after infiltration and the underlying vesicovaginal fascia was left on the vaginal site in order to leave the bladder free of any tissue to accept and fuse with the porcine matrix via infiltration and neovascularisation. Meticulous haemostasis, clean surgical gloves, a tension-free graft and wet porcine matrix are essentials for the overall success rate. In cases of a huge cystocele we use interrupted 2/0 vicryl sutures placed transversely 1 cm apart for bladder area shrinkage and a better end result. The vaginal mucosa trimming was limited offering the patient a normal length of vagina. Then a 5 x 8 cm piece of Permacol was anchored at the 12 o'clock position suburethrally and then laterally along the perivesical area at 2, 4, 8 and 10 o'clock with 2/0 vicryl sutures. This limits the chance of the graft slipping and furthermore extruding through the vaginal mucosa. A vaginal pack was placed for 24-48 hrs and a Folley catheter for 48-72 hrs according to the necessity of a tension free vaginal tape transobturator (TVT-O) placement.

Residual urine was measured on the third postoperative day and a volume of ≤ 50 ml was considered satisfactory for the woman to be discharged, whereas a volume of ≤ 80 ml warranted a second voiding measurement after adequate hydration. If the residual urine was ≥ 50 ml the catheter was reinserted for another 24 hrs along with antibiotics per os.

In cases of coexisting pathology, we performed posterior colporrhaphy (rectocele), vaginal hysterectomy (uterine prolapse), and placement of a TVT-O (SUI) or posterior IVS or Apogee tape (vault prolapse).

Regular follow-up was carried out at one, six and 12 months postoperatively. The pre- and postoperative examinations were carried out with the women in the Sim's position straining maximally. Surgical outcome was classified according to the repair of cystoceles as cured, improved and failed. The objective cure was defined as no or grade 1 cystocele with an asymptomatic patient at 12 months postoperatively. Improved outcome was considered an asymptomatic patient with a grade 2 cystocele. Failures could be reported at any time on follow-up and were considered symptomatic patients or with grade 3/4 cystocele.

Results

Ninety-five patients were included in this study. All of them had a 12-month postoperative follow-up or had failed prior to the 12-month assessment, thus qualifying them to be included in the analysis.

The majority of the women were menopausal (88.4%) due to the lack of estrogens as a supporting factor for pelvic floor endurance. Patient mean body mass index (BMI) was 26.1 kg/m^2 and placed the women within the overweight category (25-29.9).

Five women had a history of previous failed cystocele repairs. There were 11 patients with grade 2 cystoceles (11.6%), 61 with grade 3 (64.2%) and 23 patients with grade 4 cystoceles (24.2%). All of these women underwent anterior colporrhaphy with the use of Permacol.

Table 3 shows the coexisting surgical pathology and the procedures performed on our patients.

Table 3. — *Coexisting surgical pathology and operations performed respectively.*

Rectocele	17/95 (17.9%)	Posterior repair
Uterine Prolapse	54/95 (56.8%)	Vaginal hysterectomy
Vault Prolapse	6/95 (6.3%)	Infracoccygeal Sacrocolpopexy (posterior IVS)
SUI *	27/95 (28.4%)	Transobturator Vaginal Tape (TVT-O)

* Stress urinary incontinence.

Mean blood loss was 275 ml (200-350 ml) while mean operation time was 65 min (45-85 min) according to the presence or not of vaginal hysterectomy. As seen in Table 4, postoperative complications were low (9.47%). Most commonly erosions were observed (2.1%) after a local reaction to the vaginal epithelium. These were successfully treated with local antibiotics and estrogen cream. The extrusion was slight and after cutting a part of the graft and aseptic closure of the vagina the patient was cured without any further complications. A small haematoma was noted in one case of IVS insertion at the perineum which was successfully treated with antibiotics. The urinary catheter was reinserted in four cases (4.21%) because of increased residual urine ≥ 50 ml. After 24-48 hrs the catheter was removed and the patients were discharged after a normal voiding activity and residual volume. Delayed discharge beyond the third postoperative day was mainly for women who underwent total vaginal hysterectomy.

Table 4. — *Postoperative complications*.

Wound infection	0/95 (0%)
Urinary tract infection	1/95 (1.05%)
Pyrexia	0/95 (0%)
Hematoma	1/95 (1.05%)
Vaginal erosion	2/95 (2.10%)
Graft extrusion	1/95 (1.05%)
Catheter reinsertion	4/95 (4.21%)

Table 5. — *Postoperative outcomes*.

Cured, asymptomatic with no or grade 1 cystocele	77 (81.1%)
Improved, asymptomatic with a grade 2 cystocele	10 (10.5%)
Failure, symptomatic or with a grade 3 or 4 cystocele	8 (8.4%)
Total	95 (100%)

Using our definition for determining success, the overall failure rate was 8.4% (8 women) as shown in Table 5. Two were noticed at six months and six at 12 months of follow-up. Five patients had grade 3 cystoceles and three symptomatic grade 2 cystoceles. Seventy-seven women had no or asymptomatic grade 1 cystocele at 12 months after the anterior repair (overall cure rate 81.1%). Improvement of the cystocele was noticed in ten patients (10.5%). Of the 18 improved or failed outcomes, seven had coexisting apical prolapse and three of these patients requested and have undergone further surgical repair.

Discussion

The occurrence of severe cystoceles is associated with a few risk factors such as high parity, postmenopausal period, prolonged vaginal delivery and unsuccessful previous attempts for pelvic floor reconstruction. The main reason for cystocele and vaginal prolapse in all three compartments (anterior-middle-posterior) is believed to be due to the defective fascial support (urethrovesical-vesicovaginal-rectovaginal) along with ligament dysfunction owing to loose connective tissue [2, 8].

The paravaginal repairs and the typical anterior colporrhaphy had a high failure rate and low success rate. Fixing, reinforcing and placating the abnormal pelvic fascia have not been as successful as once thought accounting mainly for central defects or herniations of the bladder (cystocele) [9-11]. Interest in the use of synthetic and biologic materials in the anterior compartment is increasing. The use of mesh or porcine dermis decreases the failure rate (6-22%). However, permanent synthetic mesh causes erosion with rates ranging from 3% to 25% and xenograft use has the potential of an unpredictable immune reaction to the graft during tissue healing, manifested as early postoperative superficial dehiscence [12-17].

It is difficult to reach a consensus with regard to which graft to use in pelvic surgery. Even after a thorough review of the literature, most studies report outcomes that are based on small case series without control groups and short-term to medium-term follow-up. The variety of definitions of surgical success in these studies makes it difficult to interpret and compare results. The ideal graft has not yet been developed. Two general categories of graft materials have promising results with respect to restoring anatomic and functional outcomes – the synthetic grafts and the biomaterials (xenografts).

Conclusion

Transvaginal anterior colporrhaphy reinforced with a porcine acellular collagen matrix (Permacol) in the treatment of moderate to severe cystocele appears to be the best solution for the time being. It is a simple technique, easy to learn and applied with a high success rate and low morbidity.

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Uterine myoma in pregnancy: report of 19 patients

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Summary

Purpose of investigation: To evaluate the effect of pregnancy on uterine myoma and the effect of uterine myoma on the pregnancy prospectively. *Methods:* Prospective evaluation of 19 pregnant women with uterine myomas was done between January 2005 and February 2008 at the Gynecology and Obstetrics Department Gaziantep University. The number and changes in size of the uterine myomas during pregnancy, and perinatal complications were documented. *Results:* Totally 37 fibroids in 19 pregnant women were observed. Neither enlargement of myomas nor serious perinatal complications were observed. *Conclusion:* We suggest that in contrast with the general opinion there is not much effect of pregnancy on uterine myoma size, and most cases are not affected by the presence of uterine fibroids resulting in severe perinatal complications. Expectant management may be an option for uterine myomas determined before gestation.

Key words: Uterine myoma; Pregnancy.

Introduction

Uterine leiomyomas are the most common gynecologic neoplasm, occurring in 30%-70% of reproductive age women. The general sentiment about enlargement of myomas with estrogens in pregnancy has not been supported recently [2-6]. In this study we evaluated the effect of pregnancy on uterine myoma and the effect of uterine myoma on pregnancy prospectively.

Materials and Methods

A prospective evaluation of 19 pregnant women with uterine myomas was done between January 2005 and February 2008 at the Gynecology and Obstetrics Department of Gaziantep University. Nine uterine myoma cases were diagnosed before gestation while the other ten were diagnosed in the first trimester of the pregnancy. Measurements are done at least twice during pregnancy with HDI (high definition imaging; A 3.5 MHz convex transducer, Aplio 50, Toshiba®, Otamara, Japan) by the same two observers. In this study, 37 uterine myomas were observed and documented ultrasonographically in four to eight week periods. Each pregnant woman was examined two to five times (3.6 average) during pregnancy and a final examination was performed at the third month postpartum. Observed alterations in size and number of leiomyomas throughout gestation and the third month postpartum were documented. In the cases with multiple myomas the largest myomas were considered and then recorded. Perinatal complications such as pain, antepartum hemorrhage, preterm labor, and postpartum hemorrhage were evaluated and recorded.

Results

Patient characteristics (Table 1): Mean age of the population was 29.38 ± 3.49 years and mean body mass indices of these cases was 28.1 ± 2.2 kg/m^2.

Table 1. — *Patient characteristics*.

Average age	29.38 ± 3.49
Average birth weight (g)	2,900 ± 310.56
Average gestation time (weeks)	36.72 ± 1.14
Body mass index kg/m^2	28.1 ± 2.2

Uterine myoma number and size: Totally 37 fibroids in 19 pregnant women were examined with the largest size 10 cm in diameter and at most a number of four multiplets in one case. In pre-gestational diagnosed cases the size of the myomas were distributed between 4 cm and 10 cm., while it was between 3 cm and 9 cm in post-gestationally diagnosed cases. The number of myomas determined per case were between one and four in pregestationally diagnosed cases and one and three in postgestationally diagnosed cases.

Changes in size of uterine myomas during pregnancy: No enlargement was observed either in pre-gestational diagnosed myomas or post-gestational diagnosed myomas. Uterine myoma sizes were unchanged in most of the cases, however in five the fibroid sizes decreased. Postpartum rescanning also revealed that two-thirds of fibroids had decreased in size.

Complications: All patients suffered from pain with irregular contractions other than Braxton Hicks contraction without cervical effacement and dilation. Hydration and single dose 500 mg hydroxyprogesterone caproate IM (Proluton depot®) injection was applied to patients with preterm contractions diagnosed between the 28th and 37th week. Abortus imminence was observed in six cases with an average of 14.5 week's gestation and 800 mg progesterone was applied intravaginally. In three cases extended postpartum hemorrhage was observed. No transfusion was needed. All of the pregnancies were terminated by cesarean section. Average delivery time was 37.46 ± 1.14 weeks; mean birth weight was 3,226.92 ± 310.56 g.

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Discussion

The effect of pregnancy on size of the myoma is not clear and reported results of the effects of myomas on the gestational period also differed in similar studies. Although, some studies have indicated the probability of serious implications in pregnant women with uterine myomas [7, 8], others put forward that most pregnant women with myomas were not affected by uterine fibroids resulting in perinatal complications [9, 10]. Conversely the general opinion about enlargement of myomas in gestation due to increased estrogen levels is not supported by recent studies [2-6]. Our results are consistent with the previous aforementioned studies. There was no enlargement in uterine myoma size in any case. Only in five pregnant women (26%) were decreases in myoma sizes observed while the other 14 (74%) showed no significant changes in size of uterine myomas. Rosati *et al*. examined 36 pregnant women with a single uterine myoma by US in two- to four-week intervals in pregnancy and 34 of them were also examined four weeks after delivery. An increase in volume during pregnancy, particularly the first trimester was observed in 31.6% of cases. In the puerperium a reduction in myoma size was noted, which may indicate a return to its initial volume [11]. We also found a decrease in the size of uterine myomas in 12 cases (63%) at the third month postpartum. This result is also supported with epidemiological data. Epidemiological observations show that pregnancies reduce the risk of fibroids [12]. Baird and Dunson attempted to explain the protective effects of parity on uterine fibroids through uterus involution. The protective effects of pregnancy were also shown with studies on female Eker rats [13]. In this study, it was shown that tumor development was 71% in female rats with singleton delivery and 10% with multiple parity. In our study we observed premature delivery risk in all pregnant cases. This situation may be due to having less durability of the uterus with a myoma stretching the myometrium [14] or lower oxytocinase activity of the uterus due to a myoma in a pregnant woman [15].

Conclusion

We suggest that in contrast with the general opinion that there is not too much effect of pregnancy on uterine myoma size, and most cases are not affected by the presence of uterine fibroids with an extended result as severe perinatal complications. However, further multicenter randomized controlled prospective studies are needed in this field for a more evidence-based approach.

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Perceived pain and anxiety before and after amniocentesis among pregnant Turkish women

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Summary

Purpose of investigation: To examine maternal perception of pain and anxiety before and soon after midtrimester genetic amniocentesis. *Methods:* Two hundred and ninety-two women consecutive were prospectively included in the study between March and December 2002. Study variables included age, gestational age, gravidity, parity, educational history, history of previous invasive prenatal procedures, indication for amniocentesis and source of information regarding amniocentesis. Maternal pain and anxiety associated with performing amniocentesis were subjectively quantified with the use of the visual analog scale (VAS). *Results:* Actual pain after amniocentesis was significantly lower compared with perceived pain before the procedure (3 [0-10] vs 5 [0-10], $p < 0.001$). Perceived anxiety before amniocentesis was significantly higher than perceived anxiety immediately after amniocentesis (7 [0-10] vs 5 [0-10], $p < 0.001$). Women who were informed about the procedure beforehand perceived the procedure to be less painful and expressed less anxiety before and after amniocentesis. *Conclusions:* Pre-amniocentesis counseling should emphasize that the actual pain and anxiety experienced during the procedure are low in intensity and significantly lower than expected.

Key words: Amniocentesis; Pain; Anxiety; Perception; Prenatal diagnosis.

Introduction

Midtrimester amniocentesis is often associated with a high degree of anxiety. Previous studies have shown that most women exhibit great anxiety before the procedure and the anxiety level reduces only when the karyotype results turn out to be normal. There is strong evidence that the anxiety with amniocentesis is related to both the procedure and perceived likelihood of an abnormal result. The women mostly worry about miscarriage, fetal injury due to the procedure and waiting for the test results [1-5].

As every invasive procedure, midtrimester amniocentesis causes pain. In the literature, although various factors that modulate anxiety have been investigated, the association between perceived pain and maternal anxiety during amniocentesis has been examined in few studies [6, 7]. In these studies, a strong association between perceived pain and anxiety was reported. This issue needs further study.

The aim of this study was to investigate maternal perception of both pain and anxiety before amniocentesis and the actual pain and anxiety reported immediately after the procedure.

Methods

The study was conducted prospectively at the Perinatology Unit of Ankara Maternity and Women's Health Teaching Hospital of the Social Security Institute between March and December 2002. All women who had singleton pregnancies and underwent midtrimester genetic amniocentesis were eligible for the study. Patients were excluded from the study if a major structural abnormality was detected on ultrasound (US), if either parent was carrying a balanced translocation, or if the patient was illiterate.

The patient and her partner were given verbal information by the physician performing the amniocentesis procedure. The information concerned philosophy of the screening, fetal karyotyping in general, and included the risks and benefits of the procedure. The women were informed that there was an increased risk of miscarriage of 1% for amniocentesis and that the probability of an abnormal result was around 1:40. She was also informed that the probability of an incorrect result after amniocentesis was around 0.01%. Afterwards the subject was asked to complete a data collection form before and after amniocentesis. The form did not include any personal information that could identify participants and consisted of two parts: a questionnaire and visual analog scale (VAS). The questionnaire included socio-demographic information and amniocentesis-related questions: age, gestational age, gravidity, parity, educational history, history of previous invasive prenatal procedures, indication for amniocentesis and source of information regarding amniocentesis. Patients were asked about their perception of the anxiety and pain related to amniocentesis using VAS to evaluate changes before and soon after amniocentesis. The VAS score was measured by a 10-point Likert-type scale from ''not at all'' to 'extremely high''. Higher scores imply higher levels of perception of pain and anxiety. Amniocentesis was performed under US and a 20 G 15 inch needle was inserted through the abdomenal wall. Two well trained perinatologists performed all procedures. Informed consent was obtained before amniocentesis. Finally the level of difficulty of amniocentesis was evaluated by the physician conducting the procedure on a 5-point Likert-type scale from "not at all'' to "extremely difficult''. Neither the patients nor physician were aware of each other's perception regarding the procedure. A nurse stored the data forms and when the study was completed all forms were evaluated together.

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Data were analyzed by the SPSS 9.0 statistical package program (SPSS Inc. IL). The Wilcoxon signed rank test and Mann-Whitney test were used for non-parametric comparisons. Associations of variables were analyzed by Spearman's Rho test.

Results

During the study period, 328 eligible women underwent amniocentesis, and 292 women participated in the study. Median maternal age was 35 (range 18-44) and median gestational week was 18 (range 16-22). Maternal age was under 35 years in 133 women (45.5%). Sixty-three women (21.4%) were nulliparous. Thirty-three women (11.3%) were college graduates, 103 (35.3%) high school graduates, and 156 (53.4%) attended only elementary school. Indications for amniocentesis was advanced maternal age in 159 cases (54.5%), abnormal triple test results in 92 cases (31.5%), soft markers in 27 cases (9.2%) and a previous child with chromosomal abnormalities in 14 cases (4.8%). One hundred and twenty-seven women (43.5%) were unaware of amniocentesis. Of the remaining 165 women, the main source of information regarding amniocentesis was a physician or nurse in 104 cases (35.6%), family or friends in 13 cases (4.5%), media (written or electronic) in 28 cases (9.6%) and 20 cases (6.8%) had undergone amniocentesis in a previous pregnancy.

All amniocentesis procedures were performed with a single needle insertion. Most of the procedures (90.8%) were described by the performing physician as "not at all difficult" whereas 27 (9.2%) were reported to be "somewhat difficult".

The actual pain after amniocentesis was significantly lower compared with the perceived pain before the procedure (3 [0-10] vs 5 [0-10], $p < 0.001$, respectively). When comparing women's expectations, 64% expressed less actual pain whereas 13% a higher level of pain. Twenty-three percent of women expressed no change in their perception. Perceived anxiety before amniocentesis was significantly higher than perceived anxiety immediately after amniocentesis (7 [0-10] vs 5 [0-10], $p < 0.001$, respectively). When comparing women's expectations, 55% expressed less actual pain whereas 24% a higher level of pain. Twenty-one percent of women expressed no change in their perception. VAS scores of perceived anxiety and pain before amniocentesis were not significantly different ($p < 0.001$) whereas after amniocentesis, perceived anxiety was higher than actual pain ($p < 0.001$).

Perception of pain and anxiety was found to be significantly and positively correlated before (Spearman's rho = 0.60, $p < 0.001$) and after (Spearman's rho = 0.60, $p < 0.001$) amniocentesis. Perceived pain before amniocentesis was not associated with actual pain (Spearman's rho = 0.10, $p = 0.09$). There was a weak correlation with perceived pain and actual pain (Spearman's rho = 0.18, $p = 0.18$, $p = 0.002$). Amount of change in pain or anxiety after amniocentesis was not related to any variable.

There was no correlation between age, education, parity and indication for amniocentesis with pain or anxiety scores. Information status about amniocentesis prior to the procedure was positively correlated with anxiety and pain before (Spearman's rho = 0.19, $p = 0.001$, Spearman's rho = 0.33, $p < 0.001$, respectively) and after the procedure (Spearman's rho = 0.17, $p = 0.003$, Spearman's rho = 0.16, $p = 0.006$, respectively). Patients who were informed about the procedure for the first time had lower VAS scores of anxiety and pain than those had some information about the procedure before (8 [0-10] vs 6 [0-10], $p = 0.001$; 7 [0-10] vs 5 [0-10], $p < 0.001$, respectively) and after (5 [0-10] vs 4 [0-10], $p = 0.003$; 4 [0-10] vs 3 [0-10], $p = 0.007$, respectively) the procedure. When only women who had some information about the procedure were analyzed, the information source was not associated with pain or anxiety. History of previous amniocentesis was correlated with perceived anxiety (Spearman's rho = 0.20, $p = 0.001$) and pain (Spearman's rho = 0.22, $p < 0.001$) before the procedure. Patients who underwent amniocentesis previously had lower anxiety (8 [0-10] vs 4 [0-10], $p < 0.001$) and pain (6 [0-10] vs 4 [0-10], $p < 0.001$). Difficulty in amniocentesis was correlated with actual pain. However, neither anxiety nor pain scores were different between women who had a difficult amniocentesis or who had not.

Discussion

The major outcome of the study was that amniocentesis was a painless procedure as reported previously [6-9]. Some reported both actual pain and anxiety at very low levels after the procedure in contrast to the current study. That controversy might depend on differences in populations studied. When a procedure gains public acceptance, behavior and response may change.

We found that pain levels were well correlated with anxiety before and after the procedure and both decreased after amniocentesis. It is out of the scope of this study to evaluate the causes of anxiety-related amniocentesis. However, it seems that fear of pain makes a considerable contribution to perceived anxiety. In the current study, anxiety was still at a medium level after amniocentesis and higher than perceived pain. It is well known that most women are concerned about risk of abnormality and abortion as well as awaiting results.

Previously two studies investigated the association between maternal anxiety and perceived pain during amniocentesis. Both Ferber *et al*. and Harris *et al*. reported that perception of pain and anxiety before and after amniocentesis were positively correlated [6, 7]. In contrast to the current report, Harris *et al*. also reported that maternal anxiety and actual pain during amniocentesis was correlated [6].

It seems that perceived risk of an abnormal outcome exceeds real risk. Serious complications of amniocentesis are infrequent and the probability of an abnormal test result or abortion after amniocentesis is very low. The procedure causes pain at a very low intensity. Perceived

anxiety and pain levels could be decreased by counseling before amniocentesis [4]. The way women are informed might be an important issue. In the current study, women who were informed about the procedure for the first time before undergoing it perceived the procedure to be less painful and expressed less anxiety before and after amniocentesis. Women who had had amniocentesis in a previous pregnancy also expressed lower pain and anxiety before the procedure. During counseling, patients may be reassured to know that most women find the procedure to be only mildly painful.

Conclusion

Pain during amniocentesis is low in intensity. When a woman is counseled for amniocentesis, it should be emphasized that the actual pain experienced during the procedure is significantly lower than that expected.

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Case Reports

Ectopic pelvic spleen. Presentation of two cases

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Summary

We present two cases of nulliparous women with ectopic pelvic spleens who were hospitalized in our department during the last decade. The clinical and laboratory characteristics and the management of such a rare entity are discussed.

Key words: Spleen; Ectopic; Pelvis.

Introduction

The normal location of the speen is the left hypochondrium. It is attached by the gastrosplenic and splenorenal ligaments. According to autoptic studies, accessory spleens may be found in 10% to 15% of the population [1]. The ectopic spleen is a migration of the spleen from its normal anatomic location because its ligaments have not developed properly. The spleen can migrate anywhere in the abdomen or pelvis [2]. After splenorenal fusion, they can be found pararenally and retroperitoneally, and after splenogonadal fusion they can descend into the pelvis or scrotum [1].

The case of ectopic pelvic spleen is a rare condition in which the spleen can be found in the pelvis. The symptoms depend on spleen size and/or torsion of its peduncle. More specifically, the enlarged spleen might press the gastrointestinal tract and/or the bladder, whereas torsion could present with symptoms of acute abdomen, especially with hypogastric pain. The preoperative diagnosis is difficult to make and is based on radiological (ultrasound and computed tomography) features.

We carried out a retrospective search in the archives of our department and found two cases of ectopic pelvic spleen in a ten-year period (1997-2007).

Case Reports

Case 1

A single, nulliparous woman aged 21 was hospitalized in our department due to pervasive hypogastric pain mainly localized in the left iliac fossa. Her history was free of disease. She declared that her menarche was at 14 years old. She had a normal cycle of 28-30 days and her last period was 11 days before the beginning of symptoms. The uterus was found to be of normal size but a soft tissue mass was palpated in front of it. The adnexa were also of normal size. Laboratory controls revealed hematocrit: 40%, hemoglobin: 13.3%, WBC: 7500/ml (neutrophils: 55% and lymphocytes: 41%), urea: 28% and glucose: 84%. Urine test was normal and pregnancy test was negative. Intravenous pyelogram revealed double renal calyxes bilaterally with a recess in the bladder. Transvaginal ultrasound (TVS) showed an oval mass, 10 cm in diameter, in the bladder base. Differential diagnosis included an ovarian dermoid cyst or endometrioma. Computed tomography (CT) confirmed the diagnosis of a pelvic mass and showed the absence of the spleen in its normal position. Laparotomy was performed and the uterus and adnexa were normal. However, an ectopic spleen two times larger than normal size was found in the space between the uterus and the bladder. Splenectomy was performed. Histology showed a spleen which weighed 380 g and was 17 x 9 x 6 cm in size. The structure was normal but it was characterized by increased hyperemia (Figure 1).

Case 2

A single, nulliparous 17-year-old woman was hospitalized in our department due to acute hypogastric pain and hyperemesis. Her history was free of disease. She declared that her menarche was at 15 years old. She had a normal cycle of 28-35 days and her last period was 18 days before the beginning of the symptoms. She was examined through the rectum because she was a virgin and examination of the cervix was painful. The uterus was found to be of normal size but a soft tissue mass was palpated behind it. The adnexa were also of normal size. Laboratory controls revealed hematocrit: 36%, hemoglobulin: 11.8%, WBC: 9100/ml (neutrophils: 70% and lymphocytes: 25%), urea: 31 mg% and glucose: 140 mg%. Urine test was normal and pregnancy test was negative. TVS revealed a solid mass, 9 cm in diameter, between the posterior wall of the uterus and the umbilicus. CT scan confirmed the diagnosis of a pelvic mass and showed the absence of the spleen in its normal position. The patient received an intravenous antibiotic scheme which included cephalosporine, metronidazole and an aminoglycoside. However, laboratory controls revealed hematocrit: 36%, hemoglobin: 11.9%, WBC: 14700/ml (neutrophils: 92% and lymphocytes: 7%). Laparotomy was performed and free hemorrhagic peritoneal fluid was found. The uterus and the adnexa were normal. However, an ectopic spleen two times larger than normal size was found in the space between the uterus and the rectum. Splenectomy was performed. Histology showed a spleen which weighed 395 g and was 15.5 x 9 x 6 cm in size. The structure was normal but it was characterized by increased hyperemia. Moreover, the fibroadipose tissue was characterized by inflamed lymph nodes.

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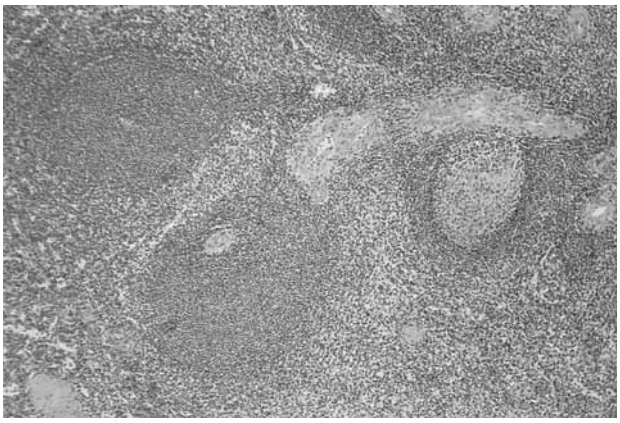

Figure 1. — Histological section of the pelvic mass showing the typical features of splenic tissue (hematoxylin-eosin x 25).

Discussion

Ectopic pelvic spleen is a very rare entity. Women between the ages of 20-40 years are more likely affected [3]. The common clinical presentation is an abdominal mass with pain [3]. However, in our two cases we were impressed by the different symptomatology. Hypogastric pain was the main symptom in the first case, whereas the second woman had more acute symptoms (acute abdomen) due to peritoneal inflammation.

The preoperative diagnosis is very difficult and is based first on a high index of suspicion and second on the TVS, CT or magnetic resonance imaging (MRI) scan findings [4]. Color Doppler imaging and power Doppler imaging could also be used to confirm the occurrence of torsion or infarction of the spleen. A scintigram with technetium-99-marked, heat-damaged red blood cells could also be helpful [1]. MRI angiography might also be useful [4]. The differential diagnosis of an irregular pelvic mass should include colonic diverticulosis, wandering kidney, coprolites, colon and mesentery tumors and ectopic spleen [5]. The diagnosis is made after abdominal laparotomy.

An ectopic located spleen may be complicated by an acute abdomen due to torsion of the splenic vascular pedicle, resulting in splenic infarction [4]. Although, splenopexy was used some years ago in the management of such pelvic masses [3, 6], the proposed treatment is splenectomy to avoid future torsion or rupture due to pressure, especially during pregnancy. If the diagnosis is made before severe complications occur, elective laparoscopic splenopexy could also be proposed [7]. However, Cobellis *et al*. proposed observation of a patient with a pelvic spleen diagnosed during pregnancy which came to term uneventfully [8]. Doppler monitoring was used till delivery to achieve possible early torsion diagnosis [8].

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Sympathomimetic amine therapy may markedly improve treatment resistant headaches related to a vascular permeability defect common in women - presentation of two cases

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Summary

Purpose: To determine if sympathomimetic amine therapy, which has been effective in alleviating pain from various areas of the body in women previously refractory to conventional therapy, could help refractory migraine headaches. *Methods:* Two cases with severe migraines resistant to conventional therapy were evaluated to see the response to dextroamphetamine sulfate. *Results:* Both women dramatically responded. Case 1 showed that the treatment benefit is long lasting and not merely transient as long as the woman remained on the sympathomimetic amine therapy. Case 2 showed that even premenstrual migraines can respond to this therapy. *Conclusions:* It is not clear if therapy would only benefit women with an abnormal water load test or not. To determine if this therapy could be effective in refractory headache cases, even in women who pass the water load test, one would have to try the dextroamphetamine under similar circumstances and see the response. Similarly it is not known if it could help males with refractory headaches.

Key words: Sympathomimetic amines; Migraine headaches; Fluid retention; Cerebral edema.

Introduction

There is evidence that increased capillary permeability in the standing position is related to a deficit in the sympathetic nervous system [1]. The leakage of this fluid leads to various clinical conditions which frequently puzzle the consulting physician, because despite the frequency of this condition, intelligent physicians and patients are generally unaware of the condition known as idiopathic orthostatic cyclic edema [1].

One of the most common manifestations is the inability to lose weight despite proper dieting [2]. A randomized study comparing the efficacy of a diuretic, a converting enzyme inhibitor, spironolactone and a sympathomimetic amine on weight loss in diet refractory women found that only the latter in the form of dextroamphetamine sulfate demonstrated significant weight reduction over a six-month time span [2]. In fact, dextroamphetamine sulfate proved effective when given in the next six months to the three groups failing to respond for the first six months [2].

The diagnosis of a deficit in sympathomimetic amines is established by demonstrating an abnormal clearance of water load in the erect position and exclusion of other conditions that are associated with an abnormal free-water clearance, e.g., hypothyroidism, renal, or liver disease, or congestive heart failure [3, 4]. The original definition of an abnormal water load test was excretion of < 55% of a 1500 ml water load in six hours but we found that < 75% defines a greater population who suffer from this problem [2, 3]. There are several conditions that have proven refractory to conventional therapy that respond quickly and effectively to sympathomimetic amines.

There have been many anecdotal reports of relieving intractable pain syndromes quickly and efficiently with sympathomimetic amine therapy, despite failure with a multitude of other therapies. These include interstitial cystitis [5], pelvic pain that was attributed to endometriosis [6], gastrointestinal pain including esophagitis [7], gastroparesis [8], joint pain [9], fibromyalgia, and carpal tunnel syndrome [1]. It is not clear if the improvement in pain is related to a decrease in fluid retention or a direct effect of the sympathomimetic amines on the sympathetic nervous system. Sympathomimetic amine therapy has helped other conditions besides pain, e.g., chronic fatigue, vasomotor symptoms in young women not associated with decreased ovarian egg reserve [10], and chronic urticaria resistant to all other therapies [11, 12].

The present study demonstrates the efficacy of sympathomimetic amine therapy for treatment refractory headaches in two cases.

Case Reports

Case 1

The woman presented at age 33 for secondary infertility of two years duration. Her only previous pregnancy ended in a first trimester miscarriage. In taking her history she also mentioned severe intractable migraine headaches that had intensified to the point that they had been unbearable for the last two years and were on a daily basis. She had consulted several neurologists and pain management specialists but nothing abated the symp-

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toms including pharmacologic therapy of beta-blockers, ergotamines, gabapentin, and topiramate. She also failed to respond to biofeedback and acupuncture and had various other symptoms suggestive of idiopathic orthostatic cyclic edema.

She was advised that many of her symptoms, e.g., nocturia, swelling of the face and fingers in the morning and swelling of the feet in the evening, decrease in urination when standing or walking, and abdominal distention by the end of the day, were consistent with this condition [1, 13]. She was told that the possibility could exist that her migraines were related to this capillary permeability defect. She was further advised since this condition is associated with various other treatment resistant pain syndromes that respond to sympathomimetic amine therapy that her migraines could possibly also respond to therapy. However, she was told that since dextroamphetamine sulfate may possibly cause fetal harm that we should probably defer the investigation until after she delivered.

The patient decided to perform the water load test out of curiosity to see if she may have orthostatic water retention. She excreted supine in four hours 1650 ml of the 1500 ml water load that she ingested vs only 650 ml in four hours the second day in the standing position.

The headache pain was so intense she asked if she could begin therapy immediately since it could take several months before she achieved a pregnancy. She stated that she had not had one day of relief of pain from the headaches in six months and she could not bear the pain any longer.

She was started on dextroamphetamine sulfate 10 mg daily of sustained release capsules at 8:00 a.m. and noon. She called the next day to say that her headaches were completely gone. She continued to show marked improvement in the headaches but had occasional episodes of less duration and intensity. The dosage was increased to 15 mg morning and noon and the headaches completely disappeared.

Several months later she conceived so it was decided to stop the dextroamphetamine sulfate. Rather than abruptly stop she was decreased to 10 mg sustained release capsules once daily. The intense headaches returned and she could not bear the pain. She returned to 15 mg twice daily and the pain immediately disappeared and she was headache-free during the pregnancy.

Since she preferred not to stop the medication she was advised not to nurse. She remained headache-free for three and a half years. The laws changed in her state in that a physician could no longer use this drug off-label so prescriptions for dextroamphetamine sulfate could not be filled in her state unless for narcolepsy or attention deficit hyperactive disorder. She thought this might be a good time to test whether she could actually stop the drug. Unfortunately the headaches returned within three days and were not relieved despite the maximum dose of nonsteroidal anti-inflammatory drugs and narcotics. She then came to our office in another state, restarted the medication, and within two days the headaches completely disappeared. They have remained gone now for six months.

Case 2

Case 2 was a 45-year-old female referred by a pain specialist for migraine headaches. Since these headaches were associated with her menstrual cycle he referred her to a reproductive endocrinologist to see if a hormonal cause could be found with treatment directed to correct a potential hormonal imbalance.

The headaches lasted one day to one week and were so incapacitating that she was admitted to the hospital with an overdose of pain killers.

She did not have the classic symptoms of idiopathic orthostatic cyclic edema, i.e., no obvious swelling and no nocturia. However she did have an abnormal water load test (1700 lying 1070 ml standing with 1500 ml ingested).

The first treatment tried was progesterone supplementation during the luteal phase. She was then put on norithindrone acetate 5 mg twice daily. Neither treatment worked.

She next tried dextroamphetamine sulfate 10 mg morning and noon. For the first time in five years she did not get a premenstrual migraine headache. She has had six more menstrual cycles without any headaches.

It should be noted that previously over the course of five years this patient was treated with similar pharmacologic therapy (but no sympathomimetic amines) as Case 1 without any improvement.

Discussion

These two cases show that migraine headaches refractory to standard therapy may respond to sympathomimetic amine therapy. Both women had headaches that would fit with the diagnosis of migraines. For example in case 2, she stated that she would start with an indescribable feeling at the base of her skull. It would move up to her temple when she would develop intense pain, nausea and vomiting and flashing lights.

Though case 2 did not have the classic symptoms of idiopathic edema both women had abnormal water load tests. Interestingly case 2 lost 11 pounds after five weeks of treatment without lowering caloric intake. Whether this therapy could also be effective for refractory migraines in women passing the water load test remains to be tested.

Why headaches related to idiopathic edema may be premenstrual is not known for sure but it can be speculated that this may be the time that premenstrual edema peaks, thus adding additional premenstrual cerebral edema superimposed on a pre-existing generalized edema that previously did not attain a sufficient level to cause sufficient cerebral edema to cause the headache.

Thus migraine headaches can be added to the list of various pain syndromes previously resistant to standard therapy that dramatically responds to sympathomimetic amine therapy [5-9, 13].

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Extrauterine pregnancy resulting from late spontaneous rupture of an unscarred gravid uterus: case report

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Summary

Purpose: Rupture of the unscarred grand uterus is a rare obstetric event associated with major perinatal mortality and a high incidence of maternal mortality and morbidity, particularly peripartum hysterectomy. *Methods & Results:* We present the case of a primigravida woman who was admitted at 38 weeks of gestation complaining of intermittent abdominal pain and vaginal bleeding. Although initial evaluation suggested that both mother and fetus were doing well, continuous assessment resulted in cesarean section due to variable decelerations and increasing abdominal pain. An unexpected abdominal pregnancy was discovered resulting from a complete uterine rupture. A healthy infant was delivered and hysterectomy was performed. *Conclusion:* Although extrauterine advanced abdominal pregnancy resulting from late uterine rupture is associated with high maternal and perinatal mortality, a high index of suspicion, close surveillance and ultrasonography can achieve good outcome for both mother and infant. We strongly believe, that this case report contributes to the insight and further knowledge of this rare pregnancy complication.

Key words: Spontaneous uterine rupture; Hysterectomy; Pregnancy.

Case Report

A 39-year-old primigravida was admitted to our hospital with vaginal spotting and intermittent lower abdominal pain especially when the fetus was moving. Obstetrical and gynecological history were negative for previous spontaneous miscarriages, dilatation and curettage or any operation in the uterus or ovaries. The last scan at 23 weeks of gestation had shown an intrauterine pregnancy with normal fetal development, normal amniotic fluid and a placenta previa. The patient mentioned that this was the first episode of vaginal bleeding, which started a few hours prior to her admission.

Clinical assessment showed stable vital signs, and uterine size was equivalent to 38 weeks of gestation. The abdomen was soft and nontender, and there were no contractions. Abdominal ultrasound (US) findings were consistent with a single living fetus in transverse lie, satisfactory growth and parameters well-corresponding to 38 weeks of gestation. The estimated fetal weight was 3.0 kg with normal volume of amniotic fluid. The placenta was adjacent to the cervical os and the fetal head was close to the maternal left abdominal wall. The ultrasonographer did not find the uterus to surround the fetus and this, together with the previous US findings, was very suspicious. The cardiotocograph showed a reactive fetal heart rate pattern, however within eight hours of admission and due to severe variable fetal heart rate decelerations in the presence of persistent increasing abdominal pain, an emergency cesarean section was decided.

The peritoneal cavity was covered with a thick layer of dense tissue. Beneath that mass, a viable fetus was found in a transverse position within a "pseudosac" on a bed of small bowel loops. The male infant weighed 2.9 kg, with Apgar scores of 8 at 1 min and 9 at 5 min. The amniotic fluid was stained with discolored meconium and old blood. At the left uterine lateral fundal region, a large area of rupture measuring about 10 cm in diameter was found, through which the umbilical cord was protruding with no extrauterine placental parts. Uterine decidual membranes were diffused all over the abdominal cavity including the omentum, the lateral abdominal walls and the bowel loop surface (Figures 1a, 1b/2). Active heavy bleeding was noticed from the site of the rupture while the placenta was totally covering the cervical os. Hysterectomy and partial infracolic omentectomy were performed, with an estimated blood loss of about 2,000 ml. The postoperative period was uneventful and the patient was discharged five days later.

Histopathology described the growth of placental tissue into the myometrium (placenta accreta) with complete anterior uterine rupture. The microscopic appearance of the placenta was characterized by the presence of multiple infarcts and calcifications. The omentum had decidual reaction and inflammatory infiltration, while inflammation of the fetal membranes clearly showed a chronic subacute intrauterine infection.

Discussion

Uterine rupture in pregnancy is an uncommon but potentially frightening complication that frequently results in life-threatening maternal and fetal compromise. It is defined as a full-thickness separation of the uterine wall and the overlying serosa. Uterine rupture is associated with clinically significant uterine bleeding, fetal distress, expulsion or protrusion of the fetus, placenta, or both into the abdominal cavity, and the need for prompt cesarean delivery, uterine repair, or hysterectomy.

In the present case, the patient's obstetric history did not include a previous cesarean section or any other uterine pathology considered as risk factors including uterine trauma, uterine overdistention, congenital uterine anomalies, placenta percreta or choriocarcinoma that could result in a scarred uterus.

Perhaps the only risk factor was the age of the patient. It has been described that increasing maternal age has a detrimental effect on the rate of uterine rupture [1]. Also, placenta accreta defined as the abnormal trophoblastic attachment and/or invasion into the underlying musculature, could be complicated with spontaneous rupture of the uterus. In our case, placenta accreta was a pathologic

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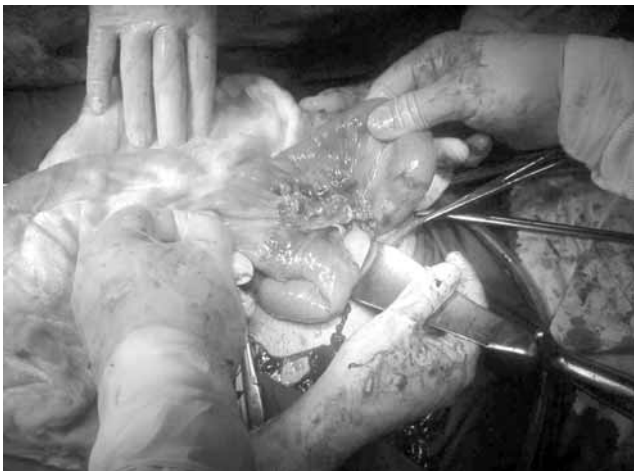
Fig. 1a



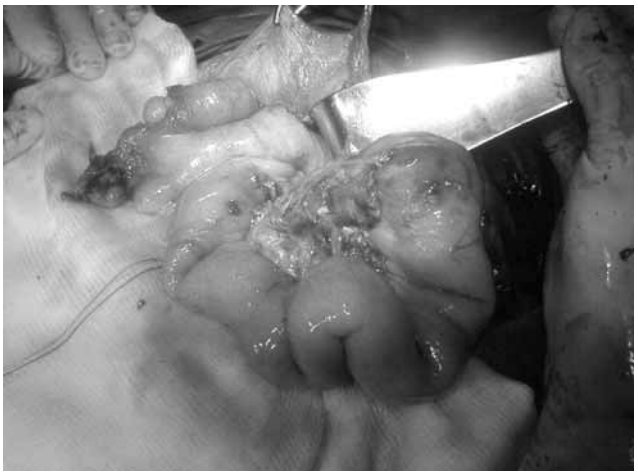


Fig. 1b

Fig. 2

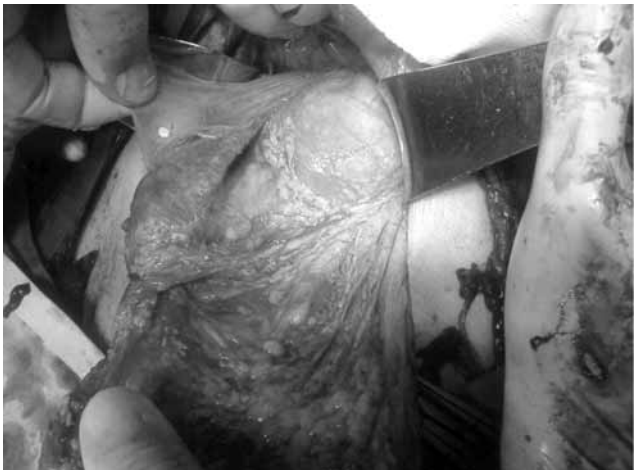


Figure 1a, b. — Overview of the abdomen during laparotomy showing the decidual membranes covering the small bowel mesentery.

Figure 2. — Overview of the abdomen during laparotomy showing the decidual membranes covering the omentum.

finding and we doubt whether a detailed US examination of the uterine wall could have revealed abnormal placentation. Finally, malpresentation (transverse lie of the fetus in our case) could be a risk factor for uterine rupture in an unscarred uterus.

Despite the uterine rupture and the resulting abdominal pregnancy, the fetus was still deriving its blood supply from the placenta, while the "pseudosac" was representing a normal amniotic sac. An emergency laparotomy was decided due to fetal distress and increasing maternal abdominal pain. Indeed, abnormal patterns in fetal heart rate were the first manifestation of uterine rupture in 87% of patients while sudden or atypical maternal abdominal pain occurred more rarely [2]. It has been demonstrated that definitive therapy for the fetus is delivery and should be accomplished immediately in order to avoid fetal morbidity and mortality [3], while the most critical aspect in the treatment of the mother in the presence of uterine rupture was hysterectomy. Since the uterus was not deemed repairable and in the presence of intractable (profuse) uterine bleeding, hysterectomy was considered to be the treatment of choice.

Spontaneous uterine rupture and secondary abdominal pregnancy is associated with high perinatal and maternal mortality and morbidity, particularly peripartum hysterectomy. The most important early sign of uterine rupture is prolonged and persistent fetal bradycardia. Although abdominal pain and vaginal bleeding remain consistent symptoms, they are less valuable in establishing the appropriate diagnosis.

Since diagnostic error is usual, it is important when a pregnant woman presents with persistent abdominal pain and transverse lie of the fetus, to look for an intact uterus by experienced ultrasonographers, thus minimizing maternal and fetal compromise.

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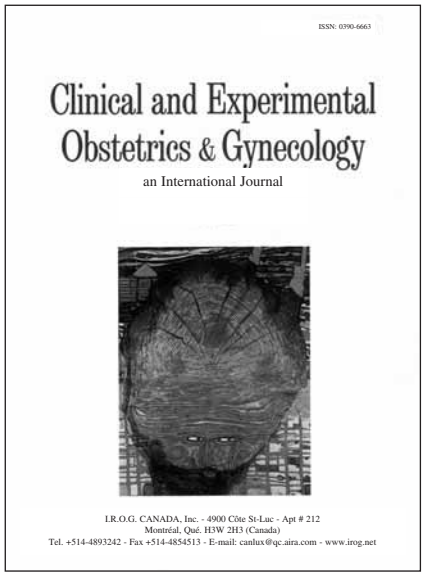

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