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Acknowledgments

Acknowledgments should only be made to funding institutions and organizations and, if to persons, only to those who have made substantial contributions to the study.

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List all authors when six or less. When seven or more, list only first six and addetal. Toppozada MK, Gaafar AA, Shaala SA. In - vivo inhibition of the human non pregnant uterus by prostaglan din E2. Prostaglandins, 1974; 8: 401 - 406.

2- Books:

(a) Personal author: Speroff L, Glass RH, Kase NO. clinical gynecologic endocrinology and infertility. 4th edition, Baltimore, Williams & Wilkins; 1988: 105

(b) Chapter in book; Wilhelmsson L, Norstrom A, Tjugum 1, Hamberger L. Interaction between prostaglan dins and catecholamines on cervical collagen. In: Toppozada M., Bygdeman ‘. M., Hafez ESE, Eds. Prostaglandins and fertility regulation. Advances in reproductive health care. Lancaster, England, MTP Press Ltd., 1985 : 75 - 80.

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Letter from the Editor:

Dear colleagues,

The new issue of the journal is out , we have tried to increase the number of reviews to two per issue at your request , and we are increasing the number of review articles to give our readers a broader spectrum about the current trends in our field .

We are urging all of you to participate in the next meeting of the society we are calling for abstracts and the there is a prize for the best research. We definitely need your help and support to keep the journal going , as well as your feedback , so please feel free to send us any remarks or ideas to help us through the coming issues. Lastly but not least we wish our beloved Egypt peace, unity and prosperity.

Editor in Chief,
Prof. Mohamed Yehia

Oocyte quantity and quality: Bases for confusing ART outcome and women's fecundity

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Abstract

Through a quarter-century of clinical experience, the outcome of assisted reproductive technologies (ART) became intimately intertwined with the response of controlled ovarian stimulation (COS). This led to purport that the functional testing that predicts COS responses – dubbed 'ovarian reserve' – foretells ovarian aging and the degree of remaining fecundity. The highly publicized 'ovarian reserve' concept in turn led to spark an emerging business of advanced or 'provisional' ART for the purpose of saving cryopreserved oocytes for later use in women whose ovarian reserve is diminished.

Our ART experience in case of poor COS responses due to an age-dependent process – endometriosis – enabled us to conclude that issues of oocyte quantity and quality are not inherently linked however. On the contrary, the lingering belief that a decreased oocyte quantity – and, diminished ovarian reserve – is associated with diminished oocyte quality results from confounding effects of aging. It is therefore important to realize and make known the fact that poor ovarian reserve scores that predict poor COS responses merely assess the efficacy of ART as a clinical tool, not a woman's fecundity.

Key words: Assisted reproductive technologies (ART); Controlled ovarian stimulation (COS); ovarian reserve, AMH, antral follicle count (AFC); ovarian aging.

Introduction

In vitro fertilization (IVF), originally developed for bypassing the diseased tubes that caused infertility, has indications that evolved and became widely extended. In a semantic adjustment tailored to reflect this broadening of scope, IVF and its variant intra-cytoplasmic sperm injection (ICSI) conceived for male-factor infertility, are now collectively called 'assisted reproductive technologies' (ART). In modern-day medicine, ART is not only indicated for tubal and severe male factor infertility, but is also the ultimate treatment of practically all forms of infertility.

Right from inception, it stood as evidence that the results of IVF – then distressingly low – could be boosted by inducing multiple-ovulations and in turn multiple oocyte and embryo harvests. Looking back over 30 years of ART history, multiple-ovulation stands out as the single most effective measure ever taken for improving ART outcome. Practically, multiple-ovulation is accomplished by fouling the natural system that normally assures single follicular maturation and ovulation in the menstrual cycle1. In cycling women, single-ovulation is secured by the feedback mechanisms that rapidly turn off the slight inter-cycle FSH elevation at the origin of follicular recruitment2. Indeed, the inter-cycle FSH elevation acts on the cohort of antral follicles present, leading to the production of E2 and inhibin-B, which in turn feeds back on FSH release by the pituitary. The ensuing decrease in circulating FSH is responsible for the fact that only the largest – at times two – of the responding follicles continues to develop,

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2014

whereas the smaller ones undergo irreversible atresia3. Hence, the regulation of the inter-cycle slight FSH elevation by negative feedback is the primary mode of control of single follicular dominance and ovulation that characterizes reproduction in women3.

As FSH levels decrease in the mid follicular phase, only the largest – at times two – follicles endowed with more FSH receptors continue to grow 4. Ultimately, the selected follicle(s) acquire(s) LH receptors in its granulosa cells, a process that is key for the later stages of follicular maturation and ovulation that occur in a LH-dominant environment 2. Meanwhile, as said above, the smaller follicles undergo atresia brought by the decreasing FSH levels. Logically therefore, multiple-ovulation has been induced by artificially maintaining FSH levels elevated throughout the entire follicular phase5. The ensuing effect is that more follicles – possibly, the whole cohort – continue to grow and ovulate, as an increasing number of smaller follicles are rescued from their destined atresia6. The means used for maintaining FSH elevated throughout the follicular phase have evolved over the years. The options have spanned from stimulating endogenous FSH – by different means – to administrating exogenous FSH preparations – purified from human sources or genetically-engineered.

Throughout 30 years of ART practice, the induction of multiple-ovulation has evolved to become a true science in its own right, now known as controlled ovarian stimulation (COS). Today COS has its rules, recognized pitfalls and risks, and follows sets of preferred protocols 7. The elevation of endogenous FSH to therapeutically effective levels is brought by a timely administration of anti estrogen compounds such as clomiphene citrate and/or aromatase inhibitors. Exogenous FSH preparations include: (i) human menopausal gonadtropins (hMG), (ii) ultra-purified FSH (u-FSH) or, (iii) recombinant FSH (r-FSH). In spite of the great efforts taken for individualizing the doses of FSH used in ART, it is notorious that individual responses to COS greatly vary and to some degree, remain poorly predictable 8. At one end of the spectrum, certain women have strong possibly excessive responses, which may expose them to the risk of frank ovarian hyperstimulation syndrome (OHS), a potentially serious complication of ART. At the other end of the spectrum, other women have insufficient or 'poor' responses to COS in spite of using larger doses of FSH. An international consensus conference – the Bologna Conference 9 – has defined 'poor response' as one that is either cancelled for lack of response or yields <3 oocytes. Underscored in the term 'poor response' is the concept that COS responses of diminished magnitude bear an ominous prediction for ART outcome. While this is true for most of the poor responses encountered in older women, it is not necessarily the case, as shown below, for the poor the responses to COS that are due to causes other than aging 10.

An emerging challenge in modern-day infertility management is therefore to sort out the issues of oocyte quantity – impacting on COS responses – from those of poor oocyte quality causing poor ART outcome. Distinguishing the problems of diminished oocyte quantity and quality is the core topic of the present review. The lines above sketched the backdrop of our discussion, one in which COS responses – oocyte quantity – have been intimately intertwined with ART outcome, a surrogate marker of oocyte quality.

Decreased oocyte quality in aging women

Throngs of evidence indicate that COS yields dwindle down, as women are getting older 11. Data from national registries – for example, SART data reported by the CDC in the US

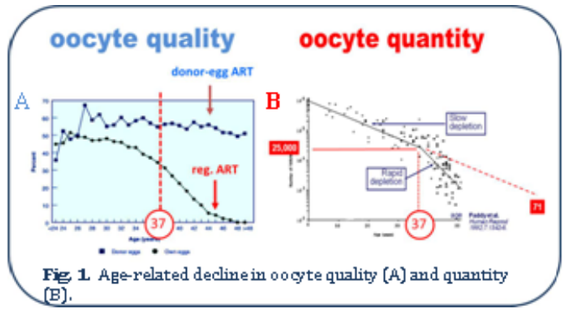

Fig. 1. Age-related decline in oocyte quality (A) and quantity (B).

(Fig. 1, A) – depict a typical age-related decrease in ART outcome 12. Characteristically, this phenomenon parallels the fact that oocyte harvests become meager in older women. The latter itself reflects the progressive age-dependent shrinkage of the pool of primordial follicles seen as women get older (Fig. 1, B) 13. In striking contrast, the results of donor-egg ART show a totally different pattern (Fig. 1, A) with results that remain constant over time 12. Taken together, these two findings indicate that the age-related decrease in ART outcome stems from a decrease in oocyte quality. On the contrary, the reproductive potential of a properly primed uterus remains practically unchanged in aging women, as evidenced by donor-egg ART data.

Looking at the number of primordial follicles observed in the ovary as a function of age, Gougeon's team reported that the age-related decrease is bi-modal 13,14. Strikingly, the dwindling of primordial follicles parallels the decline in ART outcome, which led to postu-

late the existence of an inherent link between oocyte quantity and quality. As described below however, any link between oocyte quantity and quality results in fact from the confounding effects of age.

Age-independent alteration of oocyte quantity: the endometriosis model

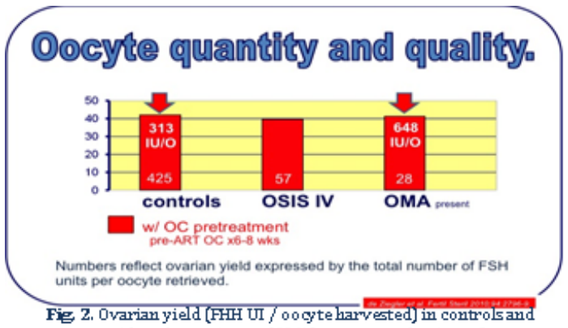

Fig. 2. Ovarian yield (FHH UI / oocyte harvested) in controls and women with endometriomas (OMA) present at the time of oocyte retrieval.

Endometriosis – a disease of unknown origin – often affects ovarian function as well 15. This is notably the case when endometriotic cysts – known as endometriomas – develop and particularly, when they extend bilaterally 16. In a recent analysis of AMH levels, we reported that the reduction in ovarian follicles susceptible of responding to COS primarily stems from surgery for endometriosis, not from the disease itself 17. In case of severe endometriosis and history of past surgery, the reduction of ovarian function can be profound 10.

In spite of severely altered of ovarian function often encountered in endometriosis, we 10 and others 18,19 reported that ART at par with the results obtained in age-matched controls. The fact that poor responses to COS due to endometriosis do not necessarily carry the ominous prediction known when poor responses are due to aging sheds new lights on issues of oocyte quantity and quality. Indeed, there is overwhelming evidence that decreased oocyte quantity due to an age-independent process such as notably endometriosis is not necessarily accompanied by a decrease in oocyte quality.

Oocyte quantity and fecundity

The links between COS responses and ART outcome have led to extrapolate on women's fecundity based on COS responses and ovarian reserve testing, a highly erroneous process as it turns out. On the contrary, there is now accumulating evidence that COS responses and by extension ovarian reserve parameters that predict COS responses 20 do not reflect a woman's fecundity. In France, oocyte donors are mandated to be fertile and bared from receiving monetary stipends. Hence, women in need of oocyte donation motivate friends or acquaintances to become oocyte donor, but without assessing their ovarian parameters and disposition to respond to COS. Under the circumstances, a third of our oocyte donors – normal parous women whose mean age is of 31.8 years – turn out to be poor responders. In these women, basal AMH predict the poor response to COS, but yet they are all fertile. Hence, ovarian reserve parameters predict ovarian responses to COS – and in turn the efficacy of ART for these women – but not their fecundity.

The misleading concept of 'ovarian reserve'

The magnitude of COS responses can be predicted by sets of tests that directly or indirectly assess the number of antral follicles susceptible of responding to exogenous FSH administration. These tests include: (i) the actual counting of antral follicles identified on ultrasounds (2-9mm) or antral follicle count (AFC) score: (ii) antimullerian hormone (AMH) levels and; (iii) day-3 or 'baseline' FSH levels. Collectively, these parameters are identified as 'ovarian reserve' testing. Implicit in the 'ovarian reserve' term is the concept that such tests predict the 'quantity of ovarian function' that remains at a given time, or an individual's own advancement on her personal ovarian aging course. Hence for doctors and patients alike, the term of 'ovarian reserve' invites to believe that such testing – AMH levels notably – predicts the amount of remaining fecundity. Reeling from the oocyte quantity and quality issues addressed in the prior sections of this review, we realize that this is far from being true. Hence, calling the clinical tests that are mere predictors of COS responses by a term that opens and suggests wild generalizations on further fecundity as 'ovarian reserve' does is a true misnomer.

The widely publicized term of 'ovarian reserve' has led for example to recommend to measure AMH in women in their thirties. Most pernicious in this practice is the recommendation of advanced or 'provisional' ART procedures for the purpose cryopreserving oocytes for later use often made when AMH values are low. In reality, low ovarian reserve testing – low AMH levels – only predicts that the efficacy of ART will be reduced in that patient, but does not foretell her fecundity. Hence, it is rather the individuals who score high on 'ovarian reserve' testing who could be prone to benefit from advanced or 'provisional' ART, as they can harvest large numbers of oocytes, not the poor responders. Indeed, women who score low on 'ovarian reserve' testing are going to be poor ART performer, but yet do not necessarily suffer from decreased fecundity. This lingering confusion has sparked a lucrative business that markets advanced or 'provisional' ART procedures. We must realize that this has emerged from erroneous interpretations of clinical data that merely predict COS responses, not fecundity. The targeted population – women in their thirties – and the medical community at large should be made aware of a confusion that is at times disseminated by the medical profession itself.

Conclusion

Through thirty years of ART experience, COS responses and ART outcome became intimately interwoven. While COS responses bear practical and direct consequences on ART chances, we have learned that the quantitative markers of ovarian response do not reflect a woman's inherent fecundity. Moreover, if poor COS responses due to aging bear an ominous prediction for live birth rates, the situation is drastically different when the cause of poor ovarian response is not aging, but say endometriosis. When facing poor COS responses, patients should be therefore counseled on the value of pursuing ART and going through the oocyte retrieval based on not just on the number of follicles growing, but also the cause of poor response. When poor ovarian response is due to endometriosis, we believe that the oocyte retrieval is worth undertaking even if there are as few as 2 mature follicles (>17mm) developing, whereas 5 are probably needed when poor response is due to aging.

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Pathogenesis of endometriosis

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Introduction

Endometriosis is a benign gynecological disease associated to an extensive impact on women's health, whose diagnosis, classification and management are still debated.

Millions of women worldwide are affected by endometriosis, predominantly in reproductive age 1. Endometriosis is often disabling, leading to a chronic condition that deeply undermines the quality of life of the patient with a negative impact on work and personal life, and therefore has high costs2. It is time to pay attention not only to the morbidity associated with endometriosis, but also to the economic burden that endometriosis imposes on society. The high rates of hospital admissions, surgical procedures, medical treatments and incidence of comorbid conditions make endometriosis a high costly public health 3.

Cellular mechanisms

Retrograde menstruation is the most classic hypothesis for endometriosis 4. The most recent proposals suggest that extrauterine stem-progenitor cells originating from bone marrow may differentiate into endometriotic tissue 5 or that ectopic endometrial implants are the result of lymphatic or hematogenous dissemination of endometrial cells 6.

Role of hormones and cytokines

The pathogenesis of the disease is multifactorial including: a) an altered hormonal milieu with estrogen dependence and progesterone resistance; b) an inflammatory response with evasion of the immune clearance; c) a modified endometrial cell proliferation, attachment and invasion ability 7.
In particular, the role of ovarian sex steroid hormones remains critical: the most recent researches focused on the effect of endocrine disruptors (plastic, food and water) that may represent alternative sources of sex steroid hormones derivates, enhancing the pathological estrogen activity 8.
In addition to estrogen dependence, there is increasing evidence to support a profile of progesterone resistance in the pathophysiology of endometriosis. Endometriotic lesions exhibit a reduction in progesterone receptor expression relative to eutopic endometrium and an absence of progesterone receptor-beta. Additionally, endometrial expression profiling has documented dysregulation of progesterone-responsive genes in the luteal phase 9. An incomplete transition of endometrium from the proliferative to secretory phase has significant implications toward enhancing the survival and implantation of refluxed endometrium. The relative progesterone resistance within the endometrium and in endometriotic lesions could lead to further escalation of estradiol actions on these lesions, because progesterone generally downregulate estrogen receptors 10.

When considering the inflammatory response, it is clear that endometriosis is associated with increased pelvic inflammation, including increased macrophage concentration and activity 11, increased oxidative stress 12 and increased concentration of inflammatory cytokines (IL-1, IL-6, IL-8, TNF-alpha) 13, indicating an impaired immune activity in women with endometriosis 14.

Endometrial changes

The endometrial dysregulation in women with endometriosis, likewise a differential ovarian steroid-dependent expression of CRH and urocortin mRNAs in eutopic endometrium from women with endometriosis has been shown15,16. An impaired sensitivity of endometrial tissue to spontaneous apoptosis also contributes to the abnormal implantation and growth of endometrium at ectopic sites.

Moreover, recently an increased density of nerve fibers was also demonstrated in the myometrium in the lower half of the uterus in women with endometriosis; in this context, new molecules have been studied and nerve fibers shown to stain PGP9.5 in endometrium and myometrium in presence of endometriosis. This finding with the increased nerve fiber density in endometrium of sensory C fibers and adrenergic nerve fibers in women with endometriosis may play an important role in the mechanisms of pain generation 17,18. At last, new genomic and proteomic approach is undergoing to understand the complex and multifactorial etiology of endometriosis 19.

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Basal serum follicle stimulating hormone / luteinizing hormone ratio as a predictor of the outcomes of intracytoplasmic sperm injection: a cohort study

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Abstract

Background: The objective of this study was to assess the value of basal serum follicle stimulating hormone (FSH)/ luteinizing hormone (LH) ratio as a predictor of the quantitative and qualitative outcomes in women undergoing intracytoplasmic sperm injection (ICSI).

Methods: This prospective study was carried on the couples recruited for management of infertility for different causes by ICSI. For each woman included in the study, basal (day 3) serum FSH and LH were assayed within 3 cycles of the scheduled ICSI cycle. The total participants were divided according to basal serum FSH/LH ratio into two groups: (i) group I that included women with FSH/LH ratio < 2; and (ii) group II that included women with FSH/LH ratio ≥ 2. The long luteal gonadotropin releasing hormone agonist (GnRHa) protocol was used for controlled ovarian hyperstimulation (COH). After fertilization through ICSI, 2-4 good quality embryos were transferred transcervically 3-5 days after oocyte retrieval. The primary outcomes were the number of oocytes retrieved and the percentage of good quality embryos. The secondary outcomes were the clinical pregnancy rate and implantation rate.

Results: The number of follicles ≥ 12 mm in diameter by transvaginal sonography (TVS) on day of human chorionic gonadotropin (HCG) administration, peak serum estradiol (E2) level, number of oocytes retrieved, percentage of good quality embryos, clinical pregnancy rate and implantation rate were significantly higher in group I (FSH/LH ratio < 2) than in group II (FSH/LH ratio ≥ 2) while the total FSH dose and cycle cancelation rate were significantly higher in group II (FSH/LH ratio ≥ 2) than in group I (FSH/LH ratio < 2).

Conclusion: Basal serum FSH/LH ratio can be used as a predictor of the quantitative outcomes of COH (number of follicles on day of HCG administration and number of oocytes retrieved) and it may be able to predict the qualitative outcomes of IVF/ICSI (clinical pregnancy and implantation rates); however, further studies are needed to clarify the efficacy of FSH/LH ratio as a reliable predictor for the qualitative IVF/ICSI outcomes.

Key Words: FSH/LH ratio, intracytoplasmic sperm injection, ICSI, ICSI outcome.

Background

The in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have spread throughout the world, with around 5 million babies born worldwide by 2012. The need for assisted reproductive technology (ART) is greater than ever, since up to 10% of couples may suffer from some form of infertility. Since 1978, the field of ART has grown immensely and its success has improved steadily and strikingly as measured by the increase in live birth rate per cycle initiated from < 1% to a notable rate of 33% in just over 35 years. Moreover, the pregnancy rates using embryos generated from one stimulated cycle are now up to 50-60% for women aged < 35 years 1. Women undergoing ART are unsurprisingly concerned about the procedure success rates 2.

Since the outcomes of IVF/ICSI are highly dependent on ovarian reserve, much effort has been put into identifying good clinical markers of ovarian reserve regarding individual prognosis for success and to design appropriate stimulation protocols 3. Several markers have been used for prediction of ovarian response and one of them was the basal (day 3) FSH level alone 4; however, in spite of normal basal FSH level in some women undergoing IVF/ICSI, unexpected poor ovarian response (POR) may occur 5, therefore there was a need for other markers to detect POR. It has been demonstrated that an increase in FSH occurs several years before elevation in LH 6. Basal FSH/LH ratio has been reported as a useful marker of ovarian reserve and IVF/ICSI outcomes 7, and elevated basal FSH/LH ratio (≥ 2) even with normal basal FSH level has been reported to be a sign of diminished ovarian reserve and poor IVF/ICSI outcomes 5-8.

In this prospective observational study, we are evaluating the value of basal serum follicle stimulating hormone (FSH)/ luteinizing hormone (LH) ratio for prediction of the quantitative and qualitative outcomes in women undergoing intracytoplasmic sperm injection (ICSI).

Methods

The study comprised of 239 couples among those attending the Fertility Care Unit (FCU) at Mansoura University Hospitals for treatment of their infertility problem by ICSI. A written informed consent was taken from each couple selected to participate in the study and the study was approved by the Departmental ethical committee. For each woman included in the study, basal (day 3) serum FSH, LH, thyroid stimulating hormone (TSH), and prolactin were assayed within 3 cycles of the scheduled ICSI cycle. The antral follicle count (AFC) in both ovaries (follicles 25 mm) was also assessed on day 3 of the cycle within 3 cycles of the scheduled ICSI cycle using transvaginal sonography (TVS) scan (Sonoace 3200, Medison, South Korea, 5-7 MHz). Women who were excluded from the study included those > 40 years old and those with high basal serum FSH level (> 10 mIU/ml), polycystic ovarian syndrome (PCOS), previous history of ovarian surgery or surgical removal of one ovary, previous exposure to cytotoxic drugs or pelvic irradiation, hormonal therapy in the preceding 6 months and those with BMI < 19 kg/m2 or > 35 kg/m2. All participants were divided according to basal FSH/LH ratio into two groups: (i) group I that included women with FSH/LH ratio < 2; and (ii) group II that included women with FSH/LH ratio ≥ 2.

The long luteal GnRHa protocol was used for COH. The GnRHa for pituitary down regulation (Triptorelin, Decapeptyl®, Ferring, Germany) was administered subcutaneously in a dose of 0.1 mg/day starting in the mid-luteal phase (day 21) of the preceding cycle then the dose was reduced to half the dose (0.05 mg/day) from the day of ovarian stimulation. Ovarian stimulation using human menopausal gonadotropins (HMG, Menogon®, Ferring, Germany) was commenced on day 3 of the next cycle (stimulation cycle) after ensuring adequate pituitary and ovarian suppression (serum E2 level < 50 pg/ml), and performing TVS scan to confirm absence of ovarian cysts. The HMG was given daily by deep intramuscular injection and the starting dose depended on the age, BMI, basal serum FSH level, AFC and previous IVF/ICSI trials between 300-375 IU/day. The TVS scan was performed regularly for monitoring of the follicular growth (folliculometry); starting from day 8 of the stimulation cycle and repeated every 2-3 days. The dose of HMG was then modulated according to ovarian response. The cycle was cancelled when poor ovarian response (POR) (< 4 follicles not reaching 18 mm correlated with serum E2 level < 400 pg/ml) was detected during the follow up visits after counseling the couple regarding the success rates. The cycle was also cancelled when there is a high risk for ovarian hyperstimulation syndrome (OHSS).

Final oocyte maturation was induced by intramuscular administration of 10000 IU of human chorionic gonadotropins (HCG, Choriomon®, IBSA, Switzerland), when there were at least 3 leading follicles > 18 mm in diameter. The total number of follicles ≥ 12 mm in diameter and serum E2 level were evaluated on day of HCG administration. After HCG injection by 34-36 hours, oocyte retrieval was performed through transvaginal aspiration of follicles under TVS guidance. Endometrial preparation for embryo transfer (ET) was started on the day of oocyte retrieval by giving 100 mg intramuscular natural progesterone supplement (Prontogest®, IBSA, AMSA, Italy) once daily. After fertilization through ICSI, 2-4 good quality embryos were transferred transcervically 3-5 days after oocyte retrieval. Luteal phase support was continued by the same regimen started on the day of oocytes retrieval until 2 weeks after ET. Biochemical pregnancy was documented by performing quantitative serum β-HCG assay 2 weeks after the ET ≥ 20 mIU/ml. Cases with positive pregnancy test were examined by TVS 24 weeks later (46 weeks after ET) to document clinical

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intrauterine pregnancy which is defined as presence of at least one intrauterine gestational sac with fetal pole and cardiac activity on TVS scan at 46 weeks after ET.

The primary study outcomes were the number of oocytes retrieved and the percentage of good quality embryos (calculated for each couple by dividing the number of good quality cleavage-stage embryos by the total number of cleavage-stage embryos). The secondary study outcomes were the clinical pregnancy rate (calculated by dividing the number of clinical pregnancies by the number of ET procedures) and the implantation rate (calculated for each couple by dividing the number of gestational sacs on TVS scan at 4-6 weeks after ET by the number of transferred embryos).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, Version 16.0 (SPSS, Inc., Chicago, Ill., USA) for Windows. Continuous variables were analyzed as mean ± standard deviation (SD). Differences among continuous variables with normal distribution were analyzed by t test and Chi-Square test ($\chi 2$ test). For continuous variables without normal distribution, non-parametric tests were used and differences were analyzed by the Mann-Whitney U-test. Correlations between different parameters were determined by using Pearson's correlation coefficient (Pearson's r) and Spearman's correlation coefficient (Spearmann's rho). P value ≤ 0.05 was considered statistically significant and P value ≤ 0.01 was considered highly significant.

Results

The total participants included in the study were 239 couples. There were no dropped out cases in any step in the study. Out of the total 239 patients included in the study, 26 patients had cycle cancellation (22 patients due to POR and 4 patients due to risk of OHSS), while the remained 213 patients continued the cycle and underwent oocyte retrieval. Out of the 213 patient who underwent oocyte retrieval, 199 patients had ET, while the other 14 patients did not have ET (4 patients due to absence of oocytes in follicular fluid, 4 patients due to non occurrence of fertilization after ICSI, 2 patients due to non occurrence of cleavage after ICSI, and 4 patients due to moderate OHSS before ET). Out of the 199 patients who had ET, 86 patients achieved clinical pregnancy (43.22%) (105 patients had negative pregnancy test and 8 patients had biochemical pregnancy only).

Group I (FSH/LH ratio < 2, 118 women) included 112 women underwent oocyte retrieval and only 106 women had ET while group II (FSH/LH ratio ≥ 2, 121 women) included 101 women underwent oocyte retrieval and only 93 women had ET. The demographic, clinical, ultrasonographic and biochemical characteristics of the 2 study groups showed statistical significant difference between the 2 groups as regards the age and duration of infertility. Bilateral AFC is significantly higher in group I (Table 1). Table 2 for the COH and ICSI outcome of the 2 study groups shows statistical significant increase in the total dose of FSH and cycle cancellation in the group II while group I had higher Number of follicles ≥ 12 mm, oocyte retrieved, good quality embryos, clinical pregnancy rate and implantation rate.

Discussion

One of the most challenging aspects in the IVF/ICSI treatment is to predetermine the success rate or to indentify couples with low chance of achieving pregnancy. In the past, initial assessment of fecundity depended on the chronological age of the woman as it was documented that the reproductive capability decline with advanced age 9; however, the rate of this decline was found to be variable in women of the same age 10.

As the most determining factors of success of IVF/ICSI treatment is good ovarian response and subsequently, ovarian yield of sufficient number of mature oocytes, many predictors have been studied to foresee the ovarian response and the competence of production of satisfactory numbers of oocytes. These predictors included basal (day 3) serum FSH level, serum antimullerian hormone (AMH) level and AFC. Both FSH and LH are needed for normal follicular growth based on the two-cell theory (11). Sustained basal secretion of LH and LH receptors expression early in follicular development is necessary for follicular growth as it has been shown that ovulation could not be induced by FSH in absence of LH receptor expression 12, 13. Also, the production of intraovarian regulators, acting by autocrine, paracrine or hormonal routes is essential for follicular growth and development. The secretion of these proteins occurs under gonadotropin stimulation 11. This prospective study evaluated the basal serum FSH/LH ratio for prediction of the outcomes of ICSI among 239 couples undergoing ICSI.

Several previous studies had evaluated the predictive role of day 3 FSH/LH ratio on IVF outcomes 8, 14-16. In these studies, decreased ovarian response and lower pregnancy rates with an elevated FSH/LH ratio in the presence of a normal basal FSH were reported. Liu et al. 7 and Mukherjee et al. 8 showed that women with high FSH/LH ratio (>3) had significantly higher cycle cancellation rate. Kofinas and Elias 17 reported that an elevated FSH/LH ratio >3 was more likely to result in the individual's cycle cancelled (15 vs 5.24%). The total gonadotropin dosage was greater in the higher ratio versus lower ratio group (2636 vs 2242 IU) and the peak E2 was significantly lower in the FSH/LH >3 group (1635 vs 1942 pg/ml). Our findings are consistent with the finding of these previous studies as we found decreased ovarian response in the patients with elevated FSH/LH ratio (≥ 2) which was evident by the significant increase in the gonadotropins dose needed for ovarian stimulation and the significant lower number of oocyte produced by the ovaries in this group. Also, we found that the frequency of cancelled cycles due to POR was significantly higher in the group II where FSH/LH ratio was elevated.

As regard the pregnancy outcome in both groups, we found that the clinical pregnancy rate and implantation rate were significantly higher in patients where FSH/LH ratio is lower. This mostly can be explained by the significant higher number of good quality embryos among this group. Mukherjee et al. 8 demonstrated in a previous study that pregnancy rate was lower in patients with elevated FSH/LH ratio; however, he used FSH/LH ratio > 3 as a cut off value. Parasad et al. 18 reported Elevated day 3 FSH/LH ratio (≥2) is associated with inferior outcome in IVF treatment cycles and it could be used as an additional predictor of decreased ovarian reserve. Additional studies are needed to elucidate the value of FSH/LH ratio as a reliable predictor for the qualitative IVF/ICSI outcomes. Also, we recommend a comparative study to other marker like AMH which is widely used in assisted reproduction centers as a predictor for IVF/ICSI cycles outcomes.

Conclusions

Basal serum FSH/LH ratio (≥2) can be used as a prognosticator of the quantifiable outcomes of COH (number of follicles on day of HCG administration and number of oocytes retrieved) and it may be able to forecast the qualitative outcomes of IVF/ICSI (clinical pregnancy and implantation rates).

Competing interests

The authors declare that they have no competing interests

Authors' contributions

WE and MSA conceived and coordinated the study design, wrote the first draft of the manuscript and participated in patients' recruitment. MS helped draft the manuscript and participated in patients' recruitment. MSA performed the statistical analysis. AB participated in conceiving the study design and its coordination & reviewed the manuscript. All authors read and approved the final manuscript.

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Table (1)
Demographic, clinical, ultrasonographic and biochemical characteristics of the study groups:

		Group I (n = 118)	Group II (n = 121)	P value
Age (years)		28.80 ± 4.94	32.25 ± 5.05	< 0.001
BMI (kg/m2)		29.76 ± 3.28	29.76 ± 3.99	1
Duration of infertility (Y)		6.34 ± 3.79	8.05 ± 3.64	< 0.001
Type of infertility	Primary	87/118 (73.73%)	80/121 (66.12%)	0.200
	Secondary	18/118 (15.25%)	24/121 (19.83%)	0.352
	Relative	13/118 (11.02%)	17/121 (14.05%)	0.479
Cause of infertility	Male factor	63/118 (53.39%)	65/121 (53.72%)	0.959
	Tubal factor	21/118 (17.80%)	19/121 (15.70%)	0.665
	Endometriosis	17/118 (14.41%)	13/121 (10.74%)	0.393
	Uterine factor	10/118 (8.48%)	13/121 (10.74%)	0.552
	Unexplained	15/118 (12.71%)	19/121 (15.70%)	0.508
Previous IVF/ICSI trials	No trials	64/118 (54.24%)	26/121 (21.49%)	< 0.001
	One trial	30/118 (25.42%)	42/121 (34.71%)	0.118
	≥ 2 trials	24/118 (20.34%)	53/121 (43.80%)	< 0.001
Bilateral AFC		13.67 ± 3.67	10.98 ± 3.93	< 0.001
Serum TSH (uIU/ml)		1.84 ± 1.01	1.91 ± 1.03	0.584
Serum prolactin (ng/ml)		12.35 ± 6.65	12.96 ± 6.52	0.474
Basal serum FSH (mIU/ml)		6.18 ± 1.76	7.95 ± 1.42	< 0.001
Basal serum LH (mIU/ml)		4.40 ± 1.25	3.42 ± 0.78	< 0.001

Table (2)
COH and ICSI outcomes of the study groups:

	Group I (FSH/LH ratio < 2)	Group II (FSH/LH ratio ≥ 2)	P value
Total FSH dose (IU)	2698 ± 589	3128 ± 727	< 0.001
Number of follicles ≥ 12 mm in diameter by TVS on day of HCG administration	11.36 ± 1.47	11.89 ± 1.55	0.007
Stimulation days (days)	17.15 ± 7.41	9.91 ± 6.63	< 0.001
Peak serum E2 (pg/ml)	3644 ± 1962	2269 ± 1797	< 0.001
Cycle cancelation due to POR	2/118 (1.7%)	20/121 (16.53%)	< 0.001
Number of oocytes retrieved	11.91 ± 4.92	8.28 ± 4.53	< 0.001
Oocyte maturation rate (%)	84.75 ± 15.90	82.94 ± 16.25	0.419
Fertilization rate (%)	76.32 ± 17.58	78.90 ± 18.02	0.301
Good quality embryos (%)	81.60 ± 22.91	65.09 ± 34.31	< 0.001
Clinical pregnancy rate (%)	60/106 (56.60%)	26/93 (27.96%)	< 0.001
Implantation rate (%)	32.39 ± 34.62	12.37 ± 22.61	< 0.001

Thyroid peroxidase antibodies in euthyroid women with unexplained infertility: Effect of levothyroxine treatment

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Abstract

Objective: to estimate the prevalence of thyroid peroxidase antibody among a cohort of unexplained infertile euthyroid women and to evaluate the effect of levothyroxine therapy on spontaneous pregnancy and miscarriage rate in antibody +ve patients. Methods: The study comprised of 500 infertile women aged 25 to 35 years with unexplained infertility. All patients were tested for TPO Ab together with ultrasensitive serum TSH and FT4 levels. A Control group of 100 age matched fertile women were tested for TPO Ab. Infertile cases with TPO Ab +ve were then randomly allocated using a computer generated random table and sealed envelopes to receive LT4 in a dose of 50 mcg/day or placebo tablets. The outcome measures of the study were the occurrence of pregnancy and miscarriage. Results: The prevalence of TPO Ab+ve was significantly higher (60%) among infertile women than among the control group (10%) (P <0.001). Associated autoimmune clinical disorders was more common in TPO Ab+ve women mostly in the form of small non visible diffuse goiter (34%) plus 4 cases with bronchial asthma and 2 cases with vitiligo. TPO Ab+ve receiving LT4 had significantly higher pregnancy rate (50%) than those under placebo treatment (9.02%). The miscarriage rate was significantly lower in LT4 treated group (10.2% vs 38.46%).
Conclusion: Screening thyroid function including FT4, TSH together with assessment of ATA (TPO Ab) in women with reproductive failure is recommended. In women with TPO Ab+ve, LT4 50 mcg/ day will improve their reproductive potentials.

Key Words: thyroid peroxidase antibody, levothyroxine, unexplained infertility.

Introduction

Thyroid diseases are common in women in the reproductive age. Autoimmune thyroid diseases (ATD) are characterized by the existence of antithyroid peroxidase (TPO) and antithyroglobulin antibodies which are termed collectively as anti-thyroid antibodies (ATA) 1, 2. Although normal thyroid function is essential for normal function of the gonadal axis and thus important in upholding normal reproductive capacity 3, the exact role of ATA in reproductive performance is not clearly established. While various studies revealed a noteworthy higher ATA in subfertile women with endometriosis, premature ovarian failure 4-7, polycystic ovary syndrome (PCOS) 8, hyperprolactinemia 9 and low pregnancy rate in IVF (10, 11), other studies failed to detect any difference in IVF success rate between ATA +ve and -ve women 12, 13, 14.

It is now clear that reproductive abnormalities are not primarily related to the functional status of the thyroid gland but to the presence or absence of ATA. Poppe et al., 2008, found that thyroid antibodies were linked to infertility or increased abortion in the absence of hypo or hyperthyroidism 15. During pregnancy, the demand for thyroid hormone increases by

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30 to 50% and iodine supplementation may be needed together with early supplementation with levothyroxine (LT4) to avoid clinical or subclinical hypothyroidism especially in women with ATA positivity (Gartner 2009). Hence, euthyroid ATA +ve women, undergoing IVF might have better outcome after LT4 therapy 18. Poppe and Velkeniers, 2002, reported that subclinical hypothyroidism can be reversed by thyroxine therapy with improvement in infertility and thus avoiding the exploitation of assisted reproductive maneuvers 19.

Egypt (especially, Upper Egypt and Oasis) is known to be one of the areas with subclinical iodine deficiency 16, 17. The aim of this prospective randomized controlled study was to screen a cohort of unexplained infertile euthyroid women for thyroid peroxidase antibody and then to evaluate the effect of levothyroxine therapy on management their infertility problem.

Subjects and Methods

The study comprised of 500 infertile women aged 25 to 35 years among those attending the outpatient clinic of Mansoura University Hospital, Egypt and a private practice setting during the period from January 2009 to January 2013. All patients had at least 2 years of continuous marital relationship without conception. All patients were diagnosed to have unexplained infertility after confirming normal ovulation with day 21-23 serum progesterone, patency of tubes by hysterosalpingography, normal anatomy of the uterus and normal semen analysis of male partners. All patients included in the study had normal thyroid function. The study was approved by the Institutional Ethical Committee MUH and all patients gave informed consents before inclusion in the study.

All patients were tested for TPO Ab together with ultrasensitive serum TSH and FT4 levels were estimated in the morning to avoid the normal nocturnal surge of TSH. Thyroid peroxidase antibodies were determined using a radioimmunoassay kit (B.R.A.H.M.S. Diagnostica, Germany). The reference range was 0–100 kIU/l. TPOAb titres >100 kIU/l were considered positive. Serum TSH and FT4 were measured using a third-generation electrochemiluminescence immunoassay (Roche, Germany). The reference values were 0.27–4.2 mIU/l for TSH and 9.3–18.0 ng/l for FT4. A Control group of 100 age matched fertile women were tested for TPO Ab in the first phase of the study.

Infertile cases with TPO Ab +ve were then randomly allocated using a computer generated random table and sealed envelopes to receive LT4 (study group) in a dose of 50 mcg/day (Eltroxin@, MSD, Berlin, Germany) or placebo tablets (control group). The study group were followed up with periodic checking of their clinical and laboratory data every two month for one year and were instructed not to receive other forms of treatment for conception. The outcome measures of the study were the occurrence of pregnancy and miscarriage. Cases who became pregnant were asked to continue with their LT4 therapy till the end of pregnancy. There was about 15% of the patients dropped-out during the follow up period because they used different medications to attain pregnancy or declined the follow up protocol.

Statistical analysis

Statistical analysis was performed by using the statistical package for social science program (SPSS) version "16". The qualitative data were presented as frequency and percentages. The quantitative data were examined by using Kalmogrov-Smirnov test for normal distribution of the data and when parametric, expressed as mean and standard deviation. Student t test was used, to test for difference in normally distributed quantitative data between the two groups. Mann-Whitney-µ test was used for comparison between two groups when data are not normally distributed. Significance was considered when P value less than 0.05.

Table (1)
Patients' characteristics

	TPO +ve (N=300)	TPO -ve (N=200)	Control gp (N=100)	P1-2	P1-3	P2-3
Age (years)	29.8±5.1	29.1±4.9	29.1±4.8	0.124	0.214	1
BMI	23.1±2.6	22.9±3.1	23.2±2.1	0.69	0.698	0.32
Consanguinity	210 (70%)	40 (20%)	20 (20%)	<0.001	<0.001	1
TSH (mIU/L)	3.3±1.1	2.1±0.9	1.8±1.7	<0.001	<0.001	0.09
FT4 (ng/ml)	11.1±1.1	12.4±1.5	12.1±1.3	<0.001	<0.001	0.07

Table (2)
The relation of infertility to the level of TSH in women with TPO Ab

	TSH (2.5-4 mIu/L)	TSH (1.5-2.5 mIu/L)	TSH (0.3-1.5mIu/L)	P1-2	P1-3	P2-3
TPOAb +ve	180 (60%)	90 (30%)	30 (10%)	<0.001	<0.001	<0.001
TPOAb -ve	100 (50%)	60 (30%)	40 (20%)	<0.001	<0.001	<0.02

There was significant positive correlation between the level of TSH and the number of patients with TPOAB +ve.

Table (3)
Characteristics of TPO Ab +ve patients

	TPO+ve on Placebo (n=127)	TPO+ve on LT4 (n=130)	P
Age	29.2±5.1	30.1±4.1	0.09
BMI	23.3±2.6	22.8±2.1	0.069
Diffuse small goiter and radiological thyroiditis	55 (43.3%)	57 (43.8 %)	0.767
TSH (mIU/ L)	2.8±0.9	2.9±0.8	0.311
FT4 (ng/ ml)	11.7±2.1	11.2±1.9	0.08

Table (4)
The effect of levothyroxine therapy on pregnancy rate and the miscarriage rate in TPOAb + ve patients

	TPO+ve on Placebo (n=127)	TPO+ve on LT4 (n=130)	P
Pregnancy rate	13 (10.2%)	78 (60%)	<0.001
Abortion rate	5 (38.5%)	8 (10.2%)	<0.007
TSH (mIU/L)	2. 9±0.2	0.8±0.2	<0.001
FT4 (ng/ml)	10.8±2.1	12.7±2.8	<0.001

Results

The prevalence of TPO Ab +ve was significantly higher (60%) among infertile women than among the control group (10%) (P <0.001). There was insignificant difference between TPO Ab +ve and TPO Ab –ve infertile cases and the control fertile group as regards age, BMI but there was significant increase in serum TSH with significant lower free T4 in TPO Ab +ve infertile group in comparison to the other two groups (table 1). Family history of consanguinity and associated autoimmune clinical disorders in the form of small non visible diffuse goiter with radiological evidences of thyroiditis was significantly more common in TPO Ab+ve infertile group when compared to the other two groups (34% vs 10% and 5%) (P<0.001). Four cases with bronchial asthma and 2 cases with vitiligo were encountered in TPO Ab +ve infertile group. There was tendency for infertile cases to have higher normal levels of TSH in both TPO Ab +ve and TPO Ab –ve cases. High normal TSH levels were associated with infertility rate of 50% in TPO Ab –ve and 60% TPO Ab +ve cases. While in the low normal TSH levels the infertility rate were significantly lower (20% in TPO Ab –ve and 10% TPO Ab +ve cases) (P< 0.001) (table 2).

Table 3 for TPO Ab+ve patients' characteristics showed no difference between therapy and placebo groups. TPO Ab +ve receiving LT4 achieved pregnancy at a rate of 60% while the pregnancy rate in placebo group was only 10.2% with significant difference between both groups. The miscarriage rate was significantly lower in LT4 treated group 10.2% vs 38.5% in placebo group. There was insignificant differences at the start of the study between TPO Ab +ve cases receiving LT4 or placebo treatment as regards their demographic characteristic and thyroid function tests (table 4).

Levothyroxine therapy for TPO Ab +ve infertile cases for one year significantly improved the spontaneous pregnancy rate (50%) compared to the placebo TPO Ab +ve infertile groups. Also LT4 therapy significantly reduced the miscarriage rate (10.2% versus 38.46%). Thyroid function tests were significantly improved in TPO Ab +ve cases treated with levothyroxine therapy when compared with the placebo TPO Ab +ve infertile group.

TSH in cases who became pregnant were significantly lower when compared to the non-pregnant cases (2.5±0.7 vs 0.9±0.7) with significant higher FT4 (11.1±0.1 vs 12.9±2.3) and the hormonal pattern in miscarriage cases showed significant higher TSH (2.3±0.7 vs 0.8±0.8) and lower FT4 when compared to non-miscarriage cases (10.1±1.1 vs 12.8±2.5).

Discussion

Despite of the fact that thyroid disorders and subclinical iodine deficiency are well known throughout Egypt and Nile Valley countries, the studies that addressed the relationship between thyroid autoantibodies and infertility are, yet, scarce at least in our locality (16). On the other hand, the published studies are controversial as regards the effect of the antithyroid antibodies on the female reproductive potential 14, 15.
The high prevalence of TPO Ab among cases in this study (60%) which is much higher than that reported by many investigators 8, 20, 21, may be due the high prevalence of consanguinity among the studied cases as the familial intermarriage is the rule in rural localities 16. Another explanation for this high prevalence of TPO Ab is the high prevalence of associated autoimmune disorders encountered in the studied cases (small diffuse goiter; non visible but palpable with radiological evidence of thyroiditis in 34%). Associated autoimmune disorders in the ovary and pituitary gland are possible explanations but awaits onrushing studies. The presence of ATA in ovarian follicle may play a critical role 24. Also the presence of thyroid autoimmunity is thought

to be associated with inappropriately low levels of thyroid hormones despite apparent biological euthyroidism 14, 15. The high prevalence of TPO Ab+ve among the infertile women in comparison to the fertile parous reference group can't be explained by the older age group of the infertile cases as in the study by Prunmel and Wiersingar 2004 22. But could also be explained by the relatively high normal levels of serum TSH among the infertile group 15, 23.
In the present study, the relation of infertility rate to different levels of TSH was undertaken both in TPO-Ab+ve and TPOAb-ve groups table. Infertility was significantly higher among the high normal TSH levels especially when associated with TPO Ab+ve. This comes in agreement with Gartner 2009 who concluded that thyroid disorders may be the cause of infertility and miscarriage and increased morbidity of pregnancies 23. This study didn't include cases with manifest hyper or hypothyroidism. TSH has a normal wide range (0.3 to 4.5 mIU/ L) 25. Our finding of high normal TSH in TPO Ab+ve is in accordance with Glinoer et al. 1994 26 who showed a trend towards a slightly higher TSH level and significantly reduced serum T4 levels in women with thyroid autoantibodies. We also found a higher normal TSH level among the infertile group although still below the normal upper limit of TSH. During pregnancy it is always advisable to have a TSH level of less than 2.5 mIU/ L 27. The ACOG Committee Opinion 2007 settled that treating subclinical hypothyroidism would decrease morbidity associated with pregnancy 28.
Administration of LT4 therapy to a randomized group of infertile women with TPO Ab+ve in a dose of 50 mcg/ day increased the pregnancy rate significantly to 50% in comparison to 9.02% in placebo group. ATA can lead to subclinical and clinical thyroid disorders especially in area like ours of subclinical iodine deficiency and in the present study TPO Ab+ve women who despite being euthyroid received low T4 doses for one year showed a significant higher spontaneous conception rate (50% versus the placebo group 9.02%). This came in agreement with the findings of Maruo et al. 1992 29 and Raber et al. 2003 30 who found that LT4 treatment of infertile women may improve the conception rate.

A significantly higher miscarriage rate (38.46%) in TPO Ab+ve in the placebo group versus 10.2% in LT4 treated group was observed. This high abortion rate was observed by many authors 31, 10, 13, 14, 15. Our finding of significant diminution in abortion rate in women with TPO Ab+ve treated with thyroxine is in agreement with many previous studies 10, 13, 14, 15, 31. The mechanism of diminishing the abortion rate with T4 therapy in TPO Ab+ve women awaits further studies, but could be due to the restoration of a true euthyroid state specific for such women. The ovarian follicle hypothesis could be an explanation of the lower fertility rate and the increased abortion rate in euthyroid women with slightly elevated TSH. Montelone et al 2011 suggested that the presence of antithyroid antibodies in ovarian follicles may play a critical role in infertility 24.

Conclusion

Screening thyroid function including FT4, TSH together with assessment of ATA (TPO Ab) in women with reproductive failure is recommended before resorting to sophisticated techniques of assisted reproduction. In women with TPO Ab+ve, LT4 50 mcg/ day to maintain a TSH level at the lowest possible normal range will improve their reproductive potentials.

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Cervical cerclage versus weekly progesterone injection in prevention of preterm labor

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Abstract

Objective: Prematurity is the leading cause of neonatal death and handicap. Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks. Improvements in neonatal care have led to higher rates of survival among very premature infants, but a major effect on the associated mortality and morbidity will be achieved by better Identification of women at high risk for preterm delivery and by development of an effective intervention to prevent this complication. The aim of this study is to compare the effect of weekly progesterone injection and cervical cerclage on the outcomes of pregnancy in patients with history of preterm labor.

Methods: 60 patients were involved in the study. Patients were randomly allocated to two groups by sealed envelopes. Group A: (30 patients) in this group we had given them 17 OH progesterone (cidulot depot 250 mg) IM weekly starting from 16-20 Weeks till 36 weeks gestation. Group B: (30 patients) in this group we had done cervical cerclage operation at 14 weeks. First we assessed the effect of cidulot depot on the gestational age in comparison to the gestational age at previous preterm deliveries in group A. Secondly we assessed the effect of cervical cerclage on the gestational age in comparison to the gestational age at previous preterm deliveries in group B.

Results: All obtained data we represented from table 1-6.

Conclusion: The prophylactic administration of progesterone beginning in mid-gestation to women who previously had a preterm birth has been shown to reduce the rate of recurrence. Also use of prophylactic cervical cerclage reduces preterm labor but the preference of which method remains an area of discussion.

Key Words: Preterm labor, 17 OH progesterone, cervical cerclage.

Introduction

Preterm birth, defined as childbirth occurring at less than 37 weeks. Preterm labor is a major determinant of neonatal mortality and morbidity and has long term adverse consequences on health (1). Preterm birth rates have been reported to range from 5% to 7% of live births in some developed countries, but are estimated to be substantially higher in developing countries (2).

These figures appear to be on the rise. Events leading to preterm birth are still not completely understood, although the etiology is thought to be multifactorial. It is, however, unclear whether preterm birth results from the interaction of several pathways or the independent effect of each pathway. Causal factors linked to preterm birth include medical conditions of the mother or fetus, genetic influences, environmental exposure, infertility treatments, behavioral and socioeconomic factors and iatrogenic prematurity (3).

Children who are born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term. The morbidity associated with preterm birth often extend to later life, resulting in enormous physical, psychological and economic cost (4).

Although progesterone is known to have many actions beneficial to the maintenance of pregnancy, the exact mode of action of 17 alpha hydroxyprogesteronecaproate therapy in preventing preterm labor is not known (5). Intervention with weekly progesterone injections (250 mg 17 alpha hydroxyprogesteronecaproate (17OHPC) from 16–20 weeks up to 36 weeks of gestation had been chosen as it has been proven that this prophylactic administration of 17OHPC injections is effective in reducing the preterm birth rate in singleton pregnancies at high risk for spontaneous preterm delivery but, there are no data on the effectiveness of progesterone in the prevention of preterm birth in multiple pregnancy.(6).

In four trials that compared elective cerclage versus no cerclage or bed rest, no overall reduction in total pregnancy loss and early pregnancy loss (less than 24 weeks' gestation) was observed in the women who underwent cerclage [relative risk (RR) 0.86; 95% confidence interval (CI) 0.59–1.25]. There were also no overall significant differences between preterm delivery rates (RR 0.88; 95% CI 0.76–1.03). The largest among the four trials was coordinated by MRC/RCOG and this trial yielded a small reduction in births under 33 weeks of gestation (RR 0.75; 95% CI 0.58–0.98). (7).

The aim of this study was to compare the effect of cervical cerclage and weekly progesterone injection on outcome of pregnancy in patients with past history of preterm labor.

Subjects & Methods

The patients were selected from the outpatient clinics in Fayoum, kaser Al- Alini and AL-Azhar university hospitals. 60 patients were involved in this study and the study started in Jun 2011 for a period of two years.

Inclusion criteria:

1. Age of patients between 20-40years.
2. Single living fetus at least
3. The patient has history of preterm labour (preterm labour between 28 weeks and 34 weeks) once or more.
4. Intact membrane.
5. Time of inclusion at 12 weeks gestational age.
6. Nonsmokers or Alcoholic women.
7. Average BMI 20-25.
8. Women are getting pregnant spontaneously or by induction of ovulation but not by ART.
9. women not known to have uterine anomalies documented by previously done HSG.
10. No history of Scarred uterus (previous CS or myomectomy).
11. Not known diabetic patient or hypertensive.
12. No history of ablative or excision procedures of the cervix.

Exclusion criteria:

1. cervical length less than 2.5cm during antenatal period.
2. Congenital anomalies in the fetus discovered during the follow up.
3. Myoma with pregnancy.
4. Polyhydramnios.
5. Rupture of membranes during follow up
6. Placenta previa diagnosed during the follow up.
7. Accidental hemorrhage happens during the follow up.
8. IUFD.
9. Medical disorders predisposing to preterm delivery.

All the patients will be submitted to:

- Informed consent was taken from each patient.
- Full history.
- General, abdominal examination, and obstetric ultrasound for checking the number of the fetuses, viability, gestational age and placental location.
- Routine antenatal investigations.
- Single course dexamethasone 12 mg IM every 12 hours for 48hs for improvement of fetal lung maturity given at gestational age 32 weeks.
- Documentation of receiving tocolytic drugs or not and time of delivery.

First, we selected 80 patients involved in the study then, 20 patients were excluded from the study due to different causes. Patients were randomly allocated to two groups by sealed envelopes. Group A: (30 patients) in this group we had given them 17 OH progesterone (cidulot depot 250 mg) IM weekly starting from 16-20 Weeks till 36 weeks gestation. Group B: (30 patients) in this group we had done cervical cerclage operation at 14 weeks. First we assessed the effect of cidulot depot on the gestational age in comparison to the gestational age at previous preterm deliveries in group A. Secondly we assessed the effect of cervical cerclage on the gestational age in comparison to the gestational age at previous preterm deliveries in group B and then, we compared between the 2 groups regarding:

The primary outcome:

The gestational age at time of delivery documented by the LMP and abdominal u/s

The secondary outcomes:

1. The need to the tocolytic therapy.
2. Estimated fetal weight at the time of delivery
3. The neonatal outcome regarding admission to the incubator or the need to ICU admission.
4. Neonatal mortality.

Statistical analysis

Results were expressed as means ±standard deviation of the means (SD) or number (%).Comparison between different parameters in the two studied groups was performed using unpaired T test. Comparison between categorical data was performed using Chi square test. The data were considered significant if P value was equal to or less than 0.05and highly significant if P value<0.01. Statistical analysis was performed with the aid of the SPSS computer program. Data are expressed as mean ± standard deviation or number (%)

Results

Table (1)
Mean age in the two studied groups.

	Cidulotdepot group(n=30)	Cerclage group (n=30)	P value
Age(yrs.)	27.43±4.00	27.77±3.48	0.732(NS)

Table (2)
Gravidity and parity in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	p value
G2P1	14 (46.67%)	11 (36.67%)	0.272 (NS)
G3P1	0 (0%)	2 (6.66%)	
G3P1A1	2 (6.67%)	5 (16.67%)	
G3P2	9 (30%)	7 (23.33%)	
G4P1A2	1 (3.33%)	0 (0%)	
G4P2A1	2 (6.67%)	2 (6.67%)	
G4P3	2 (6.67%)	0 (0%)	
G5P2A2	0 (0%)	1 (3.33%)	
G5P3A1	0 (0%)	2 (6.67%)	

Table (3)
GA in previous delivery in comparison to GA at current delivery (weeks) in group A (Cidulot depot group).

	Previous delivery	Current delivery	P value
	30 (100%)	6 (20%)	0.001**
	0 (0%)	24 (80%)	

Table (4)
GA in previous delivery in comparison to GA at current delivery (weeks) after cerclage in group B (Cerclage group).

	Cidulot depot group (n=30)	Cerclage group (n=30)	p value
< 34	30 (100%)	10 (33.3%)	0.001**
≥ 34	0 (0%)	20 (66.7%)	

Table (5)
Mean gestational age in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
Gestational age (wks.)	36.33 ± 2.51	34.60 ± 2.55	0.010**
< 37 wks.	11 (36.67%)	20 (66.67%)	P= 0.020* RR= 0.5500 95% CI= 0.3224 -0.9382
≥ 37wks	19 (63.33%)	10 (33.33%)	

RR= Relative risk CI= confidence interval*p< 0.05= significant. **p< 0.01= highly significant

Table (6)
Need for Tocolysis between the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
Positive	7 (23.33%)	25 (83.33%)	P= 0.001** RR= 0.2800 CI= 0.1436 - 0.5461
Negative	23 (76.67%)	5 (16.67%)	

Table (7)
Fetal birth weight in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	p value
FBW (kg.)	2.58 ± 0.66	2.26 ± 0.64	0.065 (NS)
< 2.5 kg	8 (26.67%)	14 (46.67%)	0.108 (NS) RR = 0.5714 95 % CI= 0.2821 - 1.1577
≥ 2.5 kg	22 (73.33%)	16 (53.33%)	

Table (8)
Need for NICU admission in the two studied groups

	Cidulot depot group (n=30)	Cerclage group (n=30)	p value
Positive	8 (26.67%)	13 (43.33%)	0.176 (NS) RR= 0.6154 95% CI= 0.2993 - 1.2653
Negative	22 (73.33%)	17 (56.67%)	

Table (9)
Neonatal deaths in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	p value
Positive	5 (16.7%)	11 (36.7%)	0.080 (NS) RR= 0.4545 95% CI= 0.1797 - 1.1499
Negative	25 (83.3%)	19 (63.3%)	

Discussion

Preterm labor defined as childbirth occurring at less than 37 weeks is estimated to annually affect approximately 12.9 million births or 9.7% of all births worldwide. Although the prognosis of preterm infants has significantly improved through recent developments in neonatal medicine, complications and aftereffects influencing preterm infants are still a major concern not only for medical management but also for the medical cost of neonatal care. 8 Prematurity is the leading cause of neonatal death and handicap. Although all births before 37 weeks of gestation are defined as preterm, most damage and deaths occurs in infants delivered before 34 weeks. Progesterone has an important role in maintaining quiescence acting to reduce calcium influx to smooth muscles through suppression of calcium_calmodulin_myosin light chain kinase system. 9 In four trials that compared elective cerclage versus no cerclage or bed rest, no overall reduction in total pregnancy loss was observed in women who underwent cerclage 7.

In study done by Groom et al 2004 comparison between elective cerclage in the first trimester and the control group but in this control group cerclage done only if short cervix proved by serial vaginal ultrasound done in the second trimester. this is done to be matched with the ethics of research .So the results showed no difference between both groups regarding the gestational age at time of delivery and cerclage is indicated to the ultrasound finding of short cervix .In present study cerclage is done based on history indication and not on ultrasound indication and done at 13- 14 weeks and is found to improve the gestational age at time of delivery 10.

Alfirevic et al 2004 selected the high-risk group for early preterm delivery depending on the transvaginal sonographic measurement of cervical length. They undertook a multicenter randomized controlled trial to investigate whether, in women with a short cervix identified by routine transvaginal scanning at 22-24 weeks' gestation, the insertion of a Shirodkar suture reduces early preterm delivery. Cervical length was measured in 547pregnant women. One hundred and twenty three women were excluded. The cervix was 15 mm or less in 470, and 253 (54%) of these women participated in the study and were randomized to cervical cerclage (127) or to expectant management (126) no cerclage. Primary outcome was the frequency of delivery before 33 completed weeks of pregnancy. The results were the proportion of preterm delivery before 33 weeks was similar in both groups, 22% (28 of 127) in the cerclage group versus 26% (33 of 126) in the control group (relative risk=0.84, 95% CI 0.54-1.31, p=0.44), with no significant differences in perinatal or maternal morbidity or mortality. They concluded that the insertion of a Shirodkar suture in women with a short cervix does not substantially reduce the risk of early preterm delivery. In this study we see that the cerclage has no significant benefit even in cases with short cervix.11 This is in contrast to present study, cerclage improved the gestational age depending on history of preterm labour.

Berghella et al 2005 carried out A meta-analysis of trials of women with singleton gestations and second-trimester transvaginal sonographic CL < 25 mm randomized to cerclage or no cerclage. The degree of CL shortening was correlated to the efficacy of cerclage in preventing preterm birth. There was a significant reduction in preterm birth < 35 weeks in the cerclage compared with no cerclage groups in 208 singleton gestations with both a previous preterm birth and CL < 25 mm (relative risk, 0.61; 95% CI, 0.40-0.92). In these women, preterm birth < 37 weeks was significantly reduced with cerclage for CL more than15 mm and < 25 mm. None of the analyses for 344 women without a previous preterm birth was significant. They concluded that cerclage, when performed in women with a singleton gestation, previous preterm birth and cervical length < 25 mm, seems to have a similar effect regardless of the degree of cervical shortening, including CL 16-24 mm. In this study the comparison between 2 groups, both having short cervix, one group undergo cerclage and the other group no cerclage and the study shows that the cerclage improves the pregnancy outcome regardless the degree of cervical shortening.This study goes in favor with our study, where cerclage improves the gestational outcome of patients with history of preterm labour.12

Meis et al 2003 conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle. Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. Meis et al 2003 concluded that weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants. So there is difference between our study and Meis et al 2003, as the second group in our study did not take placebo but undergo cervical cerclage. Our study Support the results of Meis t al 2003 regarding that 17 OH progesterone reduce the rate of preterm labor and decrease the infant morbidity and mortality and when 17OH progesterone compared to cerclage ,progesterone was better regarding the gestational age with (RR=0.5500 ,95% CI= 0.3224 -0.9382) and less need for tocolysis with RR= 0.2800, CI= 0.1436 - 0.5461) . Moustafa Ibrahim 2009 has compared between 2 groups. Both have history of spontaneous preterm labor .One group received cidulot depot 250 mg (17 hydroxy progesterone) once weekly and the other group received placebo 13

According to Moustafa Ibrahim 2009, the mean age in progesterone group was 25.32±4.15 vs. 25.60±3.85years in placebo group with no significant difference (P>0.05) between both groups. Gravidity in progesterone group was 3.96±1.06 vs. 4.08±0.997 in placebo group with no significant difference (P>0.05). The mean gestational age was 37.47±1.559 in progesterone group vs. 34.71±2.49 in placebo group (P<0.05). In the progesterone group 8 of 25 women delivered before completion of 37 weeks of gestation (32%) and 17 women delivered full term (68%). In placebo group 13 of 25 women delivered before completion of 37weeks of gestation (52%) and 12 women delivered full term (48%). Fetal birth weight (FBwt) in progesterone group was 2988.00±477.031 vs. 2702.00±501.140 in placebo group with significant difference (P>0.05) while an increase in the rate of fetal birth weight over 2500g that occurred in progesterone group was 20 (80%) vs. 15 (60%) in placebo group.

Three of neonates in progesterone group needed NICU for different causes and represented 12% vs. 9 and represented 36% in placebo group. Also 1 neonatal death occurred in progesterone group and represented 4% vs. 4 and represented 16% in placebo group with significant difference (P<0.05) between two groups. The results of Moustafa ibrahim study demonstrated the positive effect of injectable progesterone on the incidence of preterm labor. Delivery at <37 gestational weeks was reduced by 20% compared with the placebo group. Similar reductions were seen in delivery less than 34weeks. Additionally, he had demonstrated that patient compliance with the use of the inexpensive injectable progesterone is not of concern 13

The results of our study support Moustafa Ibrahim study 2009 as the progesterone improve the gestational age in group A with the mean gestational age in our study is 36.33 ± 2.51and higher in Mostafa Ibrahim study in the same group 37.47±1.559. Regarding the fetal weight the mean Fetal birth weight (FBwt) in progesterone group was 2988.00±477.031 and the mean FBW in our study in group A (injectable progesterone) 2.58 ± 0.66 and the rate of fetal birth weight over 2500g that occurred in progesterone group according to Mostafa Ibrahim study 2009 was 20 (80%) and according to our study 22 (73.33%)13

Condo et al 2013 had done a retrospective indirect comparison between progesterone and cervical cerclage in prevention of preterm labor as no randomized controlled trial has compared vaginal progesterone and cervical cerclage directly for the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous spontaneous preterm birth. Condo et al 2013 performed an indirect comparison of vaginal progesterone versus cerclage using placebo/no cerclage as the common comparator .They taken four studies that evaluated

vaginal progesterone versus placebo (158 patients) and 5 studies that evaluated cerclage versus no cerclage (504 patients) were included in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous spontaneous preterm birth. Both interventions were associated with a statistically significant reduction in the risk of preterm birth at <32 weeks of gestation and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect Meta analyses did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes. Based on state-of-the-art methods for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous preterm birth. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences14.This study goes in contrast to our study as our study is direct comparison between cerclage and progesterone and our study shows that progesterone is better than cerclage regarding the gestational age and less need for tocolysis.

Conclusion

17 OH progesterone 250 mg weekly IM injection starting at 16- 20 weeks gestational age and prophylactic cervical cerclage operation reduce the recurrence of preterm labor. 17 OH progesterone 250 mg weekly IM injection more superior as this method was associated with longer gestational age at time of delivery, less need to tocolysis and patient's compliance is good. Moreover more complications associated with cerclage regarding need to tocolysis.

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Prevalence of Gestational Trophoblastic Diseases after Histopathologic Examination of Specimens of Pregnancy Termination and Post-abortive Bleeding

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Abstract

Objective: To determine the prevalence of GTD in the referred specimens of uterine evacuation after miscarriage, in clinically diagnosed molar pregnancies, and post-abortive bleeding.
Methods: The referred clinical reports to Pathology department of Mansoura University& private practice settings and their corresponding histopathologic diagnoses during the period from 1/1/2009 to 31/3/2014 were reviewed.
Results: The study included 640 referred specimens of contents of uterine evacuation. The mean age of the cases was 26.5 years (range: 15.0-54.0 years). The mean GA was 10.3 weeks (range: 5.0-19.0 weeks).The commonest clinical diagnosis of the referred cases was missed abortion (329 cases, 51.4%). Molar pregnancy was diagnosed histologically in 103 of 499 referred cases as miscarriage (20.6%). Histopathological examination of specimens of uterine curettage due to post-abortive bleeding revealed GTN in 12 of 27 cases (44.4%).
Conclusion: Molar pregnancy was diagnosed histologically in 20.6% of the referred cases as various types of miscarriage. We recommend histopathologic examination of uterine contents after pregnancy termination and post-abortive bleeding. Further studies are needed to confirm this high prevalence of molar pregnancy in our locality.

Key Words: Miscarriage; Pathology; Molar.

Introduction

Gestational trophoblastic disease (GTD) includes several disease processes that originate in the placenta. Under the WHO classification, gestational trophoblastic disease includes hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumors, and epithelioid trophoblastic tumors 1. The majority of both complete and partial hydatidiform moles present as early pregnancy failure with or without vaginal bleeding 2. This mimics miscarriage, the most common complication of pregnancy, occurring in 15-20% of all pregnancies 3. Not all women with a miscarriage will consult a gynecologist, or undergo ultrasonography. Even when women visit a gynecologist because of symptom of bleeding in early pregnancy the diagnosis of a molar pregnancy can be missed by clinical and ultrasound examination. Fowler et al 4 concluded from their large retrospective study that routine pre-evacuation ultrasound examination identified less than 50% of hydatidiform moles. Detection rates in their study were higher for complete compared to partial moles.
Routine histopathologic assessment of products of first-trimester miscarriages may therefore diagnose important pathologies such as molar pregnancy and placental site trophoblastic disease 5. But in many cases, histopathological examination of the products of conception is not performed. Post molar GTD was reported to occur in 7.5-20% of patients after evacuation of complete hydatidiform moles and in 2.5-7.5% following evacuation of partial moles. The vast majority of cases occur during the first 6

months after molar evacuation 6.
There is worldwide geographic variation in incidence of GTD. The incidence of molar pregnancy in south-east Asia was reported to be 1-12 per 1000 pregnancies which is 7-10 times higher than that in Europe or North America where it is reported to be 0.5-1 per 1000 pregnancies (7,8,9).In Africa, the incidence of molar pregnancy and choriocarcinoma was 1.2 and 0.5 per 1000 deliveries, respectively 10. The aim of this retrospective study is to determine the prevalence of GTD in the referred specimens of uterine evacuation after miscarriage, in clinically diagnosed molar pregnancies, and post-abortive bleeding.

Patients and Methods

This retrospective study was performed in the department of Pathology and department of Obstetrics &Gynecology, Mansoura University as well as private practice settings. The referred clinical reports and their corresponding histopathologic diagnoses in the period from 1/1/2009 to 31/3/2014 were reviewed. The clinical data were collected from the referral letters (age, gestational age, and ultrasound diagnosis). Histopathological diagnoses were obtained by an expert gynecologic pathology team after hematoxylen and eosin staining. In doubtful cases, the diagnoses were confirmed by immunohistochemical staining.

Inclusion criteria
Referred specimens of products of uterine evacuation with a gestational age of 19 weeks or less (spontaneous, missed, and incomplete miscarriage), referred specimens as products of uterine evacuation of clinical (and ultrasound) diagnosed molar pregnancy, and post-abortive bleeding in which initial specimens of miscarriage were not examined.

Exclusion criteria
Cases with miscarriage who were managed by expectant treatment with no available specimens and referred cases that were clinically diagnosed as ectopic pregnancy.
The histopathologic diagnosis was compared to the clinical (including ultrasound) diagnosis as stated by the gynaecologist who referred the patient. Hospital files were retrieved for cases with histopathologic diagnosis GTD, to obtain all clinical and follow up data.

Statistical analysis
Data was analyzed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data was presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data was presented as mean ± SD. $P < 0.05$ was considered to be statistically significant.

Results

The study included 640 referred specimens of contents of uterine evacuation after early pregnancy loss, clinically diagnosed molar pregnancies, and post-abortive bleeding. The mean age of the cases was 26.5 years (range: 15.0-54.0 years). Gestational age (GA) was available in 613 cases. The mean GA was 10.3 weeks (range: 5.0-19.0 weeks). The commonest clinical diagnosis of the referred cases was missed abortion (329 cases, 51.4%). Molar pregnancies, spontaneous abortion, incomplete abortion and post abortive bleeding represented 114 cases (17.8%), 96 cases (15%), 74 cases (11.6%), and 27 cases (4.2%) respectively.
Table 1 summarizes the correlation of the clinical diagnosis to the histopathological diagnoses of the referred cases. There were 499 cases referred to the pathologist as various types of miscarriage (missed, incomplete, and spontaneous miscarriage), the pathologic diagnoses of these cases revealed that 103 of them (20.6%) were complete or partial mole. As can be seen from table 1; the clinical and ultrasound diagnosis "molar pregnancy" was confirmed pathologically in 101 of 114 cases (88.6%). In the other 13 cases (11.4%) the clinical diagnosis molar pregnancy was not confirmed by histopathology. Post-abortive bleeding represented 27 (4.2%) of the referred cases, 12 of them (44.4%) were found to be GTD, including five cases of choriocarcinoma, two cases of PSTT, one case of invasive mole, and four cases of vesicular mole (table 1). For none of the 27 cases, histopathological examination of products of conception was performed at the time of miscarriage. Uterine curettage was performed 7- 42 days thereafter.
The progression to GTN was significantly correlated to the extremes of the reproductive age of the patient ($P < 0.0001$). The correlation of age of the patient to development of post-molar GTN is represented in table 2.

Table (1)
Histopathological diagnoses of uterine contents in different clinical types of abortions.

	Products of conception	Decidual reaction&IER*	Partial mole	Complete mole	Other GTD	Total
Missed abortion**	221 (67.2%)	39(11.9%)	65 (19.8%)	4(1.2%)	0	329
Incomplete abortion	45(60.8%)	13(17.6%)	5 (6.8%)	10(13.5%)	1 (1.4%), CC#	74
Spontaneous abortion	63(65.6%)	14 (14.6%)	13(13.6%)	6(6.3%)	0	96
Molar pregnancy	12(10.5%)	1(0.9%)	37(32.5%)	64(56.1%)	0	114
Post abortive bleeding	9(33.3%)	6(22.2%)	0	4(14.8%)	8(29.6%), 5 cases of CC# 2 cases of PSTT## 1 case of invasive mole	27
Total	**350**	**73**	**120**	**88**	**9**	**640**

IER*: Irregular endometrial response.
Missed abortion**: including recurrent missed abortion.
CC#: choriocacinoma.
PSTT##: placental site trophoblastic tumor

Table (2)
Correlation of the age of the patient to development of GTN.

Age group	Non GTN	GTN	Total
<20y	101	16 (13.7%)	**117**
20-30y	371	13 (3.4%)	**384**
30-40y	107	7 (6.1%)	**114**
>40y	18	7 (28%)	**25**
Total	**597**	**43**	**640**

Chi-Square Tests

	Value	Asymp. Sig. (2-sided)
Pearson Chi-Square	33.968	0.000

Discussion

It is often difficult to differentiate between retained products of conception and GTD solely on the basis of clinical criteria. Furthermore, the sonographic appearance of products of conception can share similar imaging findings with early GTD (11). Histopathological examination of products of conception remains the current gold standard for the detection of gestational trophoblastic diseases 4,12,13.
The study included 640 referred specimens of contents of uterine evacuation after early pregnancy termination and post-abortive bleeding. The histopathological diagnoses were correlated to the pre-evacuation clinical and ultrasound data as supplied to the pathologists through the referred clinical reports.
Partial and complete molar pregnancies were diagnosed histologically in 103 of 499 referred cases as products of uterine evacuation of miscarriage (20.6%). This figure is much higher than reported by Tasci et al 2 who reported that by histopathologic examination of products of conception partial hydatidiform mole was diagnosed in 2.1%, complete hydatidiform mole in 0.43% and placental site trophoblastic tumor was detected in 0.12%. This discrepancy may be due to larger sample size of their study (1606 cases versus 499 cases in our series).Other explanation of overestimation of molar pregnancy in our study that we only included only cases who referred for histopathological assessment and not all cases of miscarriage. A third reason is the different incidence of GTD with different geographic distribution.
The histopathological examination confirmed the pre-evacuation clinical and ultrasound diagnosis of molar pregnancy in101 of 114 cases (88.6%). Again, this figure is higher than reported by Fowler et al 4, who reported that routine pre-evacuation ultrasound examination identified less than 50% of hydatidiform moles. The difference in our figures may be due to the selection bias; our center is a tertiary referral center

and including the high number of patients with clinical molar pregnancy influenced this percentage.
Molar pregnancy was more common in extremes of reproductive age in our cases (P < 0.0001), this finding was also reported by Bracken 14.
Histopathological examination of specimens of uterine curettage in cases of post-abortive bleeding diagnosed 12 of them (44.4%) as GTD. The high incidence of GTD among studied cases with post-abortive bleeding arouses the importance of mandatory histological examination of uterine contents of this group of patients. To the best of our knowledge; this finding was not reported by other authors.
There is no doubt that many cases of pregnancy termination in our locality were not subjected to histopathological examination. The authors tried to investigate for the cause. The most important cause was that the clinician was satisfied with his /or her clinical and ultrasound diagnosis. Other causes were presentation of some patients with emergency vaginal bleeding and non-availability of pathology laboratories in the rural areas. Furthermore, expectant management of miscarriage decreased the chance of specimen examination because in most cases the products of conception were expelled at home. Expectant management of miscarriage was recommended by many authors 15,16,17.
Although ideally all specimens removed should be assessed by histopathology, routine assessment of miscarriage will be costly and time consuming. We should at least try to identify those cases that are at risk of gestational trophoblastic disease; as women in the extremes of reproductive age, women with remarkable findings on ultrasound, and women with recurrent miscarriage.
The limitations of this study are scanty clinical data in the referred clinical reports and its inclusion only cases that referred for histopathological assessment and not all cases of miscarriage and post-abortive bleeding which overestimated the prevalence of GTD in the studied cases.

Conclusion

Unsuspected molar pregnancy was diagnosed histologically in 103 of 499 referred cases as miscarriage (20.6%). Histopathological examination of specimens of uterine curettage due to post-abortive bleeding revealed GTD in 12 of 27 cases (44.4%). We recommend histopathologic examination of uterine contents after pregnancy termination and post-abortive bleeding. Further studies are needed to confirm this high prevalence of molar pregnancy in Egypt.

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Antenatal Dexamethasone in Elective Caesarean Section at 37-39 Weeks Gestation. Is it effective in Reducing Respiratory Dysfunction in Neonates?

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Abstract

Objective: To evaluate the effectiveness of antenatal dexamethasone before elective caesarean section at 37-39 weeks of gestation in reducing respiratory dysfunction in the neonates.
Patients and Methods: A randomized controlled study was done in the Department of Obstetrics and Gynecology, Mansoura University Hospital. The intervention group received 3 doses of dexamethasone (8 mg), 2-7 days before elective caesarean section. Control group received the usual management. Neonatal resuscitation and assessment was done by the neonatology team.
Results: The study included 314 eligible cases. Hundred and fifty-five cases (49.36 %), received single course of antenatal dexamethasone and 159 control cases (50.64%). No significant difference were found between the intervention and the control group as regards Apgar 1, Apgar 5, presence of transient tachypnea of newborn (TTN), and respiratory distress requiring admission to neonatal care unit (P =0.47,0.99,0.58,0.65 respectively).
Conclusion: Administration of antenatal dexamethasone prior to elective CS at 37-39 weeks of gestation did not improve 5-minutes Apgar score, incidence of TTN, or admission to special care units due respiratory distress. Gestational age was independent prognostic factor for neonatal outcome.
Key Words: Elective CS; Antenatal corticosteroids; Neonates.

Introduction

The benefits of antenatal glucocorticoids for the preterm neonate include reduction in the risk of respiratory distress syndrome, intra-ventricular hemorrhage, and neonatal mortality. However, the greatest benefit is seen in infants born within seven days of treatment (1). Most glucocorticoid hormones, natural and artificial, are capable of crossing the placenta and trigger the maturational process that leads to the production and release of surfactant into the alveoli of the fetal lungs (2). Furthermore, Hjalmarson and colleagues (3) reported that antenatal treatment with corticosteroids does not permanently affect lung structure or function. There were no signs of disturbed gas mixing or changed lung volume or mechanics in the treated patients.
Neonates born late preterm or at term by elective cesarean before the onset of labor are more likely to develop respiratory distress than those born vaginally. Based on the mechanism of action of antenatal corticosteroids, these drugs may be beneficial in the clearance of fetal lung fluid in this population (4). The incidence of respiratory dysfunction in neonates born by elective caesarean section (ECS) is inversely related to gestational age, even in the term infant. It is important to delay ECS until 39 weeks gestation whenever possible, in order to minimize the risk of respiratory dysfunction in the newborn infant (5,6).
Sotiriadis et al (7), performed a Cochrane review of a single randomized study to assess the effect of prophylactic corticosteroid administration before elective caesarean section at term, as compared to usual manage-

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ment without corticosteroids. They concluded that prophylactic betamethasone appeared to significantly decrease the risk of admission to the neonatal intensive care unit for respiratory morbidity. However, no statistically significant reduction was found in the incidence of neonatal respiratory distress syndrome, transient tachypnoea of the newborn, need for mechanical ventilation and length of stay in neonatal intensive care unit. To the best of our knowledge, there is only one published randomized study to assess the effect of prophylactic corticosteroid administration before elective caesarean section at term.

Patients and Methods

This randomized controlled trial was done in Department of Obstetrics and Gynecology, Mansoura University Hospital during the period from 1/4/2012 to 30/9/2013 (18 months). It included the admitted cases for elective caesarean section at 37 to 39 completed weeks of gestation.

The patients were exposed to initial evaluation by history taking, general, and obstetric examination. Ultrasound was performed to assess fetal morphology and well-being. Routine laboratory investigations were done. A written consent was obtained from all cases. The study was approved by the local ethical committee of Mansoura University Hospital. Inclusion criteria were, pregnant ladies at 37-39 weeks of gestation who were planned for elective C.S and accepted to be enrolled in the study.

Exclusion criteria were: Pregnant ladies at gestational age less than 37 weeks or more than 39 weeks., Multiple pregnancies, Premature rupture of membranes, Presence of fetal congenital malformations or intrauterine growth restriction, Diabetic mothers and Ladies who refused randomization. Eligible patients were randomized by asking her to choose one of 2 closed envelopes, one of them for the study and the other for the control group.

The study group received 3 doses of intramuscular dexamethasone 8 mg ampoules (Elamrya co., Egypt) at 8-hourly interval to be ended at least 48 hours (2-7 days) before time of delivery. Neonatal resuscitation and management was performed by a specialized neonatology team.

Statistical Analysis

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data was presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data was presented as mean ± SD. Student t-test was used to compare between two groups. F-test (One Way ANOVA test) was used to compare between more than two groups. $P < 0.05$ was considered to be statistically significant.

Results

The study included 314 eligible cases. Hundred and fifty-five cases (49.36 %), received single course of antenatal dexamethasone and 159 control cases (50.64%) received the usual management.

The mean age, parity, gestational age (GA), and body mass index (BMI) of the studied cases were showed in table 1. Anemia (hemoglobin <10.5 gm/dl) was diagnosed in 129 cases (41.1%). Regarding the criteria of the neonates; mean birth weight was 3104.55 ± 322.72 grams .These criteria were summarized in table1. Also it shows that there were no significant difference between the two groups regarding age, parity, BMI, presence of anemia, GA, birth weight and fetal gender (p = 0.07,0.36,0.14,0.94, 0.34,0.056,0.73 respectively).

Table (1)
Demographic criteria of the intervention and control group.

	Dexamethasone group (n = 155)	Control group (n = 159)	P value
Age (mean)	26.45 ± 4.00	25.65 ± 3.86	0.071
Parity (mean)	1.21 ± 0.89	1.30 ± 0.96	0.361
BMI (mean)	26.97 ± 2.78	26.55 ± 2.21	0.140
Anemia (%)	64 (41.3%)	65 (40.9%)	0.941
Gestational age (mean)	38.00 ± 0.53	38.06 ± 0.52	0.338
Neonatal weigh(mean)	3139.87 ± 345.21	3070.13 ± 296.24	0.056
Neonatal gender Male (%) Female (%)	74 (47.7%) 81 (52.3%)	79 (49.7%) 80 (50.3%)	0.730

Table 2 summarizes the indications of CS in our study. As can be noted; repeated CS and CPD were the main indications (76.11%&13.38% respectively).

Table (2)
Indications of elective CS.

	Number	Percentage
Previous 1 CS	137	43.6
Previous 2 CS	83	26.4
Previous 3 CS	14	4.5
Previous 4 CS	5	1.6
CPD	41	13.38
non reactive NST	23	7.21
Other indications	11	3.43
Total	314	100

Table 3 summarizes the impact of antenatal dexamethasone on the Apgar 1, Apgar 5, presence of transient tachypnea of newborn (TTN), and respiratory distress requiring admission to neonatal care unit. As can be noted, no significant difference were found between the intervention and the control group (P =0.47,0.94,0.58,0.65 respectively). Administration of antenatal dexamethasone before elective CS at 37-39 gestational weeks was not associated with improved neonatal outcome in our study.

Table (3)
Neonatal outcome of both groups.

	Dexamethasone group	Control group	P value
Apgar 1 score (mean)	4.07 ± 0.55	4.03 ± 0.41	0.472
Apgar 5 score (mean)	8.75 ± 0.79	8.76 ± 0.69	0.941
TTN	27 (17.4%)	24 (15.1%)	0.577
Respiratory distress & NC admission	16 (10.3%)	14 (8.8%)	0.647
Total	155	159	314

Gestational age significantly affected the 5 minutes Apgar score, TTN, and admission to NCU (P=0.002, <0.001, 0.001 respectively). So, increased gestational age was associated with better neonatal outcome. Fetal sex significantly affected the 5 minutes Apgar score, TTN (P = 0.022&0.029 respectively). However, it did not affect the need for NCU admission (P=0.36). Neonatal outcome was better with increased neonatal weight (P <0.001, <0.001, 0.10), however, increased BW may be a reflection to increased gestational age. These results were clarified in table 4.

Table (4)
Impact of GA, fetal sex, and birth weigh on the neonatal outcome.

	No	Apgar 1 (mean)	Apgar 5 (mean)	TTN (no-%)	Resp. distress & NC admission (n-%)
GA					
37 weeks	42	4.0 ± 0.66	8.43 ± 1.02	15 (35.7%)	10 (23.8%)
38 weeks	225	4.04 ± 0.46	8.78 ± 0.69	34 (15.1%)	19 (8.4%)
39 weeks	47	4.17 ± 0.38	8.96 ± 0.59	2 (4.3%)	1 (2.1%)
P value		0.169	0.002	< 0.001	0.001
Fetal sex					
Male	153	4.03 ± 0.43	8.66 ± 0.75	32 (20.9%)	17 (11.1%)
Female	161	4.07 ± 0.53	8.85 ± 0.72	19 (11.8%)	13 (8.1%)
P value		0.374	0.022	0.029	0.360
Birth weigh (gm)					
Less or =2500	8	3.63 ± 1.06	7.88 ± 1.13	6 (75%)	3 (37.5%)
2501-3000	227	4.02 ± 0.35	8.73 ± 0.63	36 (15.9%)	22 (9.7%)
3001-3500	51	4.29 ± 0.61	9.06 ± 0.83	4 (7.8%)	1 (2%)
More than 3500	28	4.0 ± 0.72	8.68 ± 1.02	5 (17.9%)	4 (14.3%)
P value		< 0.001	< 0.001	< 0.001	0.010

There were no reported events of neonatal sepsis, intraventricular hemorrhage, or perinatal deaths in the studied cases.

Discussion

Elective CS at term is associated with significant neonatal morbidity; respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and the need for mechanical ventilation (8,9,10). The Antenatal Steroids for Term Elective Caesarean Section (ASTECS) study (11) demonstrated decreased risk of TTN (0.040 vs 0.021; relative risk (RR) 0.54, 95% CI 0.26 to 1.12) and RDS (0.011 vs 0.002; RR 0.21, 95% CI 0.03 to 1.32). Moreover, antenatal dexamethasone has no long term adverse effects on child physical and cognitive development (12).

We conducted a prospective randomized study included 314 pregnant ladies undergoing elective CS. The neonatal outcome of the study group who received antenatal dexamethasone to the control group who received the usual management was compared. Dexamethasone was used in the study due to its availability in our locality.

No significant differences were found between the intervention and the control group (P = 0.47,0.99,0.58,0.65 respectively). Administration of antenatal dexamethasone before elective CS at 37-39 gestational weeks was not associated with improved neonatal outcome in our study. These results were not matching with ASTECS study (11), This discrepancy may be due to smaller number of cases and using dexamethasone instead of betamethasone in our study.

Gestational age was independent prognostic factor for neonatal outcome. It significantly affected the 5 minutes Apgar score, TTN, and admission to NCU (P = 0.002 < 0.001, 0.001 respectively). This finding was also reported by other authors (5,6). It is important to delay ECS until 39 weeks gestation whenever possible, in order to minimize the risk of respiratory dysfunction in the neonates (13).

Repeated CS was the commonest indication of elective CS in our study (76.11%), Labib and colleagues from Egypt (14) and Tampakoudis from Greece (15) reported the same finding.

The incidence of anemia (hemoglobin <10.5 gm/dl) in the mothers of our study was 41.1%. Anemia is a common health problem among the pregnant ladies in our developing country because of low income and absence of health education programs. Other authors (16,17), reported that 56% of pregnant women in developing countries are anemic. South Asia and Africa are the most vulnerable regions.

Conclusion

Administration of antenatal dexamethasone prior to elective CS at 37-39 weeks of gestation did not improve 5-minutes Apgar score, incidence of TTN, or admission to special care units due respiratory distress. Gestational age was independent prognostic factor for neonatal outcome. A future randomized trial using betamethasone is required.

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Roadmap of Lymph nodes sampling in endometrial cancer

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Abstract

Objective: The aim of this study was to evaluate para-aortic lymph node metastasis in cases with endometrial cancer and to correlate it with pelvic node metastasis.

Method: Retrospective analysis of data from patients' records who had total abdominal hysterectomy and bilateral salpingo-oophrectomy for endometrial cancer between 2007 till 2013, and the procedure involved pelvic lymphadenctomy and para-aortic lymphadenctomy or sampling of enlarged lymph nodes. A total of 202 patients who had their surgery at Mansoura University were enrolled in this study.

Results: Twenty two patients were found to have metastasis for PANs. Twenty out of 26 patients with common and/or external iliac positive lymph nodes had shown PAN metastasis. Two out of 176 patients with negative pelvic lymph nodes had shown positive PAN metastasis. Based on these data, common and/or external iliac lymph nodes had 90.9% sensitivity (20/22) and 96.7% specificity (174/180) for detecting PAN metastasis.

Conclusion: Para-aortic lymphadenectomy might be avoided by the negativity of pelvic lymph nodes, thereby minimizing post-operative complications.

Key words: endometrial cancer, lymphadenectomy

Introduction

Endometrial cancer is the most common gynaecological malignancy in western Europe and North America. About 6400 women are affected every year in the UK(1), 81 500 in the European Union (2), and 40000 women in North America.(3) here is no national register for cancer in Egypt to give a definitive incidence.

In 1988, according to the FIGO guidelines, the stage of endometrial cancer is mainly categorized by pathological status. Therefore, occasionally there is an elevation of stage following surgery, as the status of the lymph node cannot be precisely predicted prior to surgery. FIGO recommended the treatment of endometrial carcinoma as the primary surgical procedure total hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node (PAN) dissection (4).

At diagnosis, about three-quarters of women have disease confined to the uterine corpus. Most tumours are of endometrioid type; other histological types include serous, mucinous, clear cell, and mixed epithelial. Endometrial tumours are graded as well (grade 1), moderately (grade 2), or poorly (grade 3) differentiated, apart from clear cell and serous, which are generally regarded as grade 3. Endometrial cancer spreads beyond the uterus by infiltrating directly through the myometrium, extending into the cervix, and metastasising most often to the pelvic nodes and less frequently directly to the para-aortic nodes. Pelvic lymph node metastases occur in about 10% of women with clinical stage I (ie, confined to the corpus) endometrial cancer (5.6). Within stage I disease, 3–5% of women with well differentiated tumours and superficial myometrial invasion will have lymph node involvement. This proportion rises to roughly 20% of women with poorly differentiated tumours and deep myometrial invasion

Previous studies have estimated different patterns of lymphatic spread to the pelvic lymph nodes and PANs in endometrial cancer (7,8). Mariani et al. reported that external iliac lymph nodes are the most commonly involved lymph nodes in endometrial cancer, and PAN metastases spread via a route shared by the common iliac lymph nodes when tumor involves the cervix (9). Thus the common iliac and external iliac lymph nodes could be the key lymph nodes in metastasis and that their involvement could indicate either involvement of other lymph nodes or the need for complete systematic lymphadenectomy.

Some propose that adjuvant radiotherapy can be avoided and treatment morbidity reduced when lymphadenectomy shows no indication of the disease in the nodes. However, evidence is scarce of a therapeutic benefit for lymphadenectomy in terms of survival. Lymphadenectomy and increased survival, lend support to the procedure (6,10,11). Other observational studies, however, have not shown any such benefit (12).

The aim of this study was to evaluate metastasis to pelvic lymph nodes and PAN which will help to plan for comprehensive guidelines for future management of endometrial cancer.

Patients & Methods

A retrospective analysis of a total of 202 patients having endometrial cancer who had undergone total hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy or sampling at Mansoura University Hospital between 2007 and 2013. Staging system (2): stage I, 138 patients; stage II, 8 patients; stage III, 54 patients; stage IV, 2 patient.

Case records were identified with endometrial cancer, hysterectomy and lymphadenctomy by laparotomy. Then it were reviewed to verify the procedure. Histopathological reports were reviewed to establish the characteristics of the disease for those cases.

Results

Data were collected and then analyzed .The characteristics of the 202 patients are summarized in Table 1, (age range, 30–76 years mean age, 57.0 ± 8.6 year). The cases were categorized according to the FIGO surgical staging system: stage I, 138 patients; stage II, 8 patients; stage III, 54 patients; stage IV, 2 patients.

Table (1)
Patients characteristics (n=202)

Variables	
Age Median (Range)	57 (30-76)
BMI	29—39
Histology	
• Endometroid adenocarcinoma G1-2	146
• Endometroid adenocarcinoma G3	38
• Clear cell adenocarcinoma	12
• Other	6
Stage	
• I	138
• II	8
• III	54
• IV	2

The numbers of patients with lymph node metastasis at each location were shown in Table 2. The total numbers of patients with lymph node metastasis were 32 cases .Obturator nodes, 20 patients; internal iliac nodes, 14 patients; and PANs, 22 patients. The obturator lymph nodes were the most commonly involved as single pelvic lymph node site. However, the combination of external iliac nodes and/or common iliac nodes was a more frequent site for metastasis than the obturator lymph nodes.

Table (2)
Numbers of patients with lymph node metastasis at each location (n =32; total positive lymph nodes)

L. N.	N	%
External iliac	16/32	(50%)
Common iliac	14/32	(43%)
External and/or Common iliac	26/32	(81%)
Oburator	20/32	(62.5%)
Internal iliac	14/32	(43%)
PAN	22/32	(68.8%)

There was no skipping of lymph nodes (i.e. PAN positive but external iliac nodes and/or common iliac nodes negative). Of note, only 2 patient had PAN direct metastasis without pelvic lymph node metastasis and the reported histology was clear cell carcinoma in one case and the other was very poorly differentiated adenocarcinoma. 22 patients were found to have metastasis for PANs. Among 26 patients with common and/or exter-

nal iliac positive lymph nodes, 20 had PAN metastasis (Table 3). Of the 176 patients with negative lymph nodes, 174 showed no PAN metastasis. Based on these data, common and/or external iliac lymph nodes had 91% sensitivity (20/22) and 97% specificity (174/180) for detecting PAN metastasis. However, among the 20 patients with positive obturator lymph nodes, 14 had PAN metastasis (Table 3). Obturator lymph nodes had 64% sensitivity (14/22) and 97% specificity (174/180) for detecting PAN metastasis. The sensitivity was much lower than that for the common and/or external iliac lymph nodes.

Table (3)
Association of PAN* metastasis with common iliac and/or external iliac lymph node metastasis and obturator lymph node metastasis

	PAN +ve (n=22)	PAN –ve (n=180)
Common and/or external iliac • Positive • Negative	20 2	6 174
	Sensitivity 0.91	Specificity 0.97
Obturator • Positive • Negative	14 8	6 174
	Sensitivity 0.64	Specificity 0.97

There were no clear complications caused by the surgery, with the exception of lymph cysts in 5 cases. The majority of patients had no symptoms and only a few patients complained of slight discomfort in the legs

Discussion

The metastasis to lymph nodes is a major prognostic factor among females with endometrial cancers. Therefore, careful assessment of the pathological nodal status is an integral part of the management of these patients. Some studies suggested that patients with lymphadenectomy had a significantly better prognosis than those without lymphadenectomy (13,14). These reports, however, focused only on whether lymphadenectomy should include PAN as well as pelvic lymph nodes. Yokoyama et al. reported that external iliac lymph nodes were the most commonly involved lymph nodes in endometrial cancer and that PAN metastasis spread via a route shared by the common iliac lymph nodes when tumor involves the cervix (14).

Some reports stated that PAN Lymphadenectomy did not improve prognosis, because the presence of PAN metastasis indicates systemic metastasis (6). The relative increased morbidity and the possibility that the outcome may not change made the omission of lymphadenectomy, therefore, more desirable when no metastasisis detected in the lymph node. In the present study, the common lymph node for metastasis is the obturator node (Table 2). However, the combination lymph nodes (external and/or common lymph nodes) were a more frequent site for metastasis than the obturator lymph nodes Panici et al (15) have studied 514 patients with stage I endometrial carcinoma. They were randomly assigned to undergo pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n =250). Both early and late postoperative complications occurred statistically significantly more frequently in patients who had received pelvic systematic lymphadenectomy (81 patients in the lymphadenectomy arm and 34 patients in the no-lymphadenectomy arm, P=.001). Pelvic systematic lymphadenectomy improved surgical staging as significantly more patients with lymph node metastases were found in the lymphadenectomy arm but this has not improved disease-free interval or overall survival.

If lymphadenectomy is to be proposed as part of treatment protocol, it might be restricted to internal and external iliac lymph nodes or even sampling of these nodes could be enough to give more information as a predictor of PAN metastasis. Table 3 shows that the sensitivity rate of the combination lymph nodes (91%) was higher than the obturator lymph nodes (14) .Matsumoto et al. (16) reported that PAN metastasis was significantly associated with common iliac lymph node metastasis. When we consider the results, it could be thought that metastasis may develop first at site of common and external iliac lymph nodes. These nodes are the key lymph nodes associated with PAN metastasis. Accordingly, lymphadenctomy of the external and common iliac lymph nodes should be done first. These data suggest that PAN dissection can be omitted when metastasis of the common iliac and external iliac lymph nodes is expected to be absent intra-operative or if this could be proven by frozen sections examination. There were 2 cases with spread to PAN without involvement of the pelvic lymph nodes. In one case the histology was clear cell carcinoma and the other was poorly differentiated carcinoma. In another series (17), one patient had PAN metastasis for metastasis than the obturator lymph nodes. If lymphadenectomy is to be proposed as part of treatment protocol, it might be restricted to internal and external iliac lymph nodes or even sampling of these nodes could be enough to give more information as a predictor of PAN metastasis. Table 3 shows that the sensitivity rate of the combination lymph nodes (91%) was higher than the obturator lymph nodes (14, 15). Matsumoto et al. reported that PAN metastasis was significantly associated with common iliac lymph node metastasis. When we consider the results, it could be thought that metastasis may develop first at site of common and external iliac lymph nodes. These nodes are the key lymph nodes associated with PAN metastasis. Accordingly, lymphadenectomy of the external and common iliac lymph nodes should be done first. These data suggest that PAN dissection can be omitted when metastasis of the common iliac and external iliac lymph nodes is expected to be absent intraoperatively or if this could be proven by frozen sections examination. There was 2 cases with spread to PAN without involvement of the pelvic lymph nodes. In one case the histology was clear cell carcinoma and the other was poorly differentiated carcinoma. In another series, one patient had PAN metastasis without pelvic wall lymph node metastasis. It was reported that endometrial cancer can directly metastasize to both pelvic and para-aortic lymph nodes with pelvic lymph nodes metastases being dominant, a distinct lymphatic spread pattern better viewed as being somewhere between cervical cancer and ovarian cancer (16). Aburustum et al isolated para-aortic nodal metastasis in the setting of negative pelvic nodes occurs in approximately 1% of surgically staged endometrial cancer cases. This low rate seems consistent for low- and high-grade lesions. Future studies looking at the incidence of isolated para-aortic nodal metastasis in the setting of negative sentinel pelvic nodes are warranted (17). It is necessary to perform LNE, particularly the removal of the para-aortic lymph node, in patients with endometrial cancers in order to improve postoperative therapy. Laparoscopy has similar surgical effects as laparotomy, but has a number of advantages (18).

The histological diagnosis of that case was also clear cell carcinoma. Prognosis is less favourable with clear cell carcinoma (19). Therefore, it might be necessary to perform PAN Lymphadenectomy in patients with clear cell carcinoma or very poorly differentiated carcinoma. Many studies have compared outcomes in women who have received systematic lymphadenectomy and those who have not, with some studies supporting lymphadenectomy for all grades of tumour (10, 20, 21) another supporting it for G3 tumours (12), and others suggesting that benefit depends on the number of lymph nodes removed (21). However these studies were non-randomised. ASTEC (A Study in the Treatment of Endometrial Cancer), a randomised multi-center study was designed to assess the therapeutic benefit of lymphadenectomy in endometrial cancer, independent of the effect of adjuvant radiotherapy in Europe. ASTEC consisted of two trials with separate randomisations that were designed to answer a surgical and a radiotherapy question. The surgical trial investigated whether pelvic lymphadenectomy could improve survival of women with endometrial cancer, which was thought preoperatively to be confined to the corpus. The radiotherapy trial addressed whether adjuvant external-beam radiotherapy (EBRT) could improve survival of women with intermediate-risk and high-risk early-stage endometrial cancer.

In conclusion, the present study revealed that in absence of metastasis in the common iliac and external iliac lymph nodes it would be very unlikely to have PAN metastasis and removing them is better avoided. Till we have the results of a randomised study it would be mandatory in some cases to have lymphadenectomy or sampling of external and common iliac lymph nodes.

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NEWS AND VIEWS

- **Folic acid supplementation and IVF pregnancy outcome in women with unexplained infertility. Reproductive BioMedicine Online, 03/24/2014**

Murto T, et al. – This study evaluated folic acid supplement use and folate status in women with unexplained infertility in relation to pregnancy outcome. Folic acid supplementation or good folate status did not have a positive effect on pregnancy outcome following infertility treatment in women with unexplained infertility. In addition, use of folic acid supplements and folate status were compared between women with unexplained infertility and fertile, nonpregnant control women. Women with unexplained infertility used significantly more folic acid supplements and had higher median total folic acid intake from supplements compared with fertile control women (both P<0.001). Women with unexplained infertility also had significantly higher median plasmafolate and lower median plasma homocysteine concentrations than fertile women (both P<0.001), but folic acid supplementation or folate status were not related to pregnancy outcome in women with unexplained infertility.

- **Reproductive performance after conservative surgical treatment of postpartum hemorrhage International Journal of Gynecology & Obstetrics, 01/09/2014**

Rasheed SM, et al. – This study aims to evaluate the impact of bilateral internal iliac artery ligation (BIL), bilateral uterine artery ligation (BUAL), step–wise uterine devascularization (SWUD), and B–Lynch on infertility, ovarian reserve, and pregnancy outcome. Of the 4 procedures, BIL had the least deleterious effect on reproductive performance; SWUD increased the risk of premature ovarian failure, and B–Lynch increased the risks of endometriosis, intrauterine adhesions, placenta previa, and preterm labor. The study included 168 infertile or pregnant patients–recruited at outpatient clinics in Egypt–who had previously undergone uterine–sparing surgery (BIL [group I], n=59; SWUD [group II], n=65); BUAL [group III], n=2; and B–Lynch [group IV], n=42).
Groups II and IV had the highest prevalences of infertility. The ovarian reserve was significantly lower in group II. Unexplained infertility was the predominant cause of infertility in group I, anovulation and premature ovarian failure in group II, and endometriosis and intrauterine adhesions in group IV. The frequency of obstetric complications, particularly placenta previa and preterm labor, was high in group IV.

- **Role of hysteroscopy and endometrial biopsy in women with unexplained infertility**
- **Archives of Gynecology and Obstetrics, 01/22/2014 Clinical Article**

Makled AK, et al. – This study was designed to evaluate the role of hysteroscopy and endometrial biopsy in women with unexplained infertility. Routine hysteroscopy and endometrial biopsy should be used as a basic part of the work–up for women with unexplained infertility.
Women with unexplained infertility were included in this prospective study, evaluated with transvaginal sonography and diagnostic hysteroscopy. Diagnostic hysteroscopy was performed between the 7th and 11th day of the cycle. The criteria for hysteroscopic findings were based on the cervical canal, uterine cavity, endometrium, visualization of the ostium tubae and lesions of the utero–tubal junction. After the hysteroscopic examination, endometrial biopsy was performed using a Pipelle® endometrial suction curette. Patients were classified according to the hysteroscopy results into four groups: patients with no abnormality detected (14), patients with cervical abnormalities (six), patients with endometrial abnormalities (73) and patients with uterine abnormalities (seven).
One hundred women with unexplained infertility were included. All patients underwent diagnostic hysteroscopy, except for seven patients: six patients had stenotic external or internal cervical ostium and one had inadequate visualization as the uterine cavity was filled with blood. Based on hysteroscopic findings, 31 patients were finally diagnosed with endometrial polyps; 14 endometritis; 15 endometrial hyperplasia; six submucous myomas; seven intrauterine synechiae (73 cases = endometrial abnormalities group); seven congenital uterine anomalies (uterine abnormalities group), six cervical stenosis (cervical abnormalities group) and 14 women without any uterine abnormalities (no abnormalities group). Analysis of samples obtained using the Pipelle® endometrial suction curette was non–diagnostic in 16 cases; the most common endometrial pathological feature detected by this analysis was endometritis (15 %).

- **Letrozole versus clomiphene citrate for unexplained infertility: A systematic review and meta-analysis Journal of Obstetrics and Gynaecology Research, 05/02/2014**

Liu A, et al. – In this study, authors investigate and compare letrozole with clomiphene in women with unexplained infertility. They conclude that letrozole is as

effective as clomiphene in women with unexplained infertility and letrozole at a dose of 2.5 mg seems more effective. They point out that further high–quality studies assessing the possible effectiveness of letrozole in selected groups of patients are warranted. MEDLINE, EMBASE, CENTRAL, CNKI and CBMdisc databases were searched up to March 2013.
Randomized controlled trials comparing letrozole with clomiphene in women with unexplained infertility were included. Pooled relative risk, mean difference and 95% confidence intervals were calculated. Authors found that there are no differences in pregnancy, miscarriage and multiple pregnancy rates, incidence rate of adverse events, number of dominant follicles (>18 mm) and endometrial thickness at hCG day in women with unexplained infertility between letrozole and clomiphene regimens.
The mean (±standard deviation) concentration of serum E2 on hCG day was lower in those treated with letrozole than those with clomiphene. The subgroup of 2.5 mg letrozole displayed a statistically significant higher rate of clinical pregnancy as compared with 100 mg of clomiphene.

- **Fertile discovery Queen's University Health News, 08/13/2014**

Queen's University researcher Richard Oko and his co–investigators have come up with a promising method of treating male infertility using a synthetic version of the sperm–originated protein known as PAWP. They found this protein is sufficient and required to initiate the fertilization process. Dr. Oko's research promises to diagnose and treat cases of male factor infertility where a patient's sperm is unable to initiate or induce activation of the egg to form an early embryo. The results of this study highlight the potential clinical applications of sperm PAWP as a predictor of infertility treatment. Since most human infertility treatments are now done by injecting a single sperm directly into an egg, supplementation of human sperm with PAWP protein may potentially be used to improve the success rate of infertility treatments in the future.

- **Risk factors for ectopic pregnancy in women with planned pregnancy: A case-control study European Journal of Obstetrics & Gynecology and Reproductive Biology, 08/25/2014**

Li C, et al. – In this study, authors want to explore the risk factors for ectopic pregnancy (EP) in women with planned pregnancy. Besides well–acknowledged risk factors for EP, attention should be paid to women with planned pregnancy who have a history of infertility and/or IVF treatment, to prevent complications from EP.
This case–control study was conducted in women with planned pregnancy and included 900 women diagnosed with EP (case group) and 889 women with intrauterine pregnancy (IUP) as the control group matched in terms of age and gestational week.
Socio–demographic characteristics, reproductive history, gynecological and surgical history, previous contraceptive use, and history of infertility were compared between the two groups. Blood samples were collected from all the participants to detect serum chlamydia trachomatis (CT) IgG antibody.
The odds ratio (OR) with its 95% confidential interval (CI) of each variable was calculated by univariable conditional logistic regression analysis. Factors significantly different between both groups, as revealed by univariable analysis, were entered into a multivariable logistic regression model by stepwise selection. The risk of EP was associated with previous adnexal surgery (adjusted OR=3.99, 95% CI: 2.40–6.63), uncertainty of previous pelvic inflammatory disease (adjusted OR=6.89, 95% CI: 3.29–14.41), and positive CT IgG serology (adjusted OR=5.26, 95% CI: 3.94–7.04). A history of infertility including tubal infertility (adjusted OR=3.62, 95% CI: 1.52–8.63), non–tubal infertility (adjusted OR=3.34, 95% CI: 1.60–6.93), and in vitro fertilization (IVF) treatment (adjusted OR=5.96, 95% CI: 1.68–21.21) were correlated with the risk of EP. Women who had previously used condoms were less likely to have EP during the current cycle (adjusted OR=0.27, 95% CI: 0.21–0.36).

- **Doppler study of uterine hemodynamics in women with unexplained infertility European Journal of Obstetrics & Gynecology and Reproductive Biology, 10/03/2013**

El–Mazny A et al. – This study aims to evaluate uterine artery blood flow using pulsed Doppler, and endometrial and subendometrial microvascularization using three–dimensional (3D) power Doppler, in women with unexplained infertility. Peri–implantation endometrial perfusion is impaired in women with unexplained infertility: Doppler study of uterine hemodynamics should therefore be considered in infertility work–up.

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