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Reference: 1. Muraro, A., et al., EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy, 2014. 69(5): p.590-601. **2.** Tang, M., et al., Hypo-antigenic and immune modulatory properties of a partially hydrolyzed cow's milk formula supplemented with prebiotic oligosaccharides EAACI, 2014 (Abstract number 1929). **3.** Van Esch, B.C., et al., In vivo and vitro evaluation of the residual allergenicity of partially hydrolyzed infant formulas. Toxicol Lett, 2011. 201(3): p.264-269. **4.** Van Esch, B.C., et al., Interlaboratory evaluation of a cow's milk allergy mouse model assess the allergenicity of hydrolyzed cow's milk based infant formulas. Toxicol Lett, 2013, 220(1): p.95-102. **5.** Arslanoglu, S., et al., Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr, 2008. 138(6): p.1091-1095. **6.** Arslanoglu, S., et al., Early neutral prebiotic oligosaccharide supplementation reduces the incidence of some allergic manifestations in the first 5 years of life. J Biol Regul Homeost Agents, 2012. 26(3 Suppl): p.49-59. **7.** Moro, G., et al., A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child, 2006. 91(10): p.814-819. **8.** Gruber, C., et al., Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. J Allergy Clin Immunol, 2010. 126(4): p.791-797. **9.** Haarman, M. and J. Knol, Quantitative real-time PCR assays to identify and quantify fecal Bifidobacterium species in infants receiving a prebiotic infant formula. Appl Environ Microbiol, 2005. 71(5): p.2318-2324. **10.** Martin, R., et al., Early life: gut microbiota and immune development in infancy. Benef Microbes, 2010. 1(4): p. 367-382. **11.** Jeurink, P.V., et al., Human milk: a source of more life than we imagine. Benef Microbes, 2013. 4(1): p.17-30.

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OF

GYNAECOLOGY, OBSTETRICS & MIDWIFERY

January 2016, Volume 16, Number 1

EDITORIAL

ORIGINAL ARTICLES (OBSTETRICS)

ORIGINAL ARTICLES (GYNAECOLOGY)

MIDWIFERY

Vagifem® 10µg – ultra low dose for vaginal atrophy[1]

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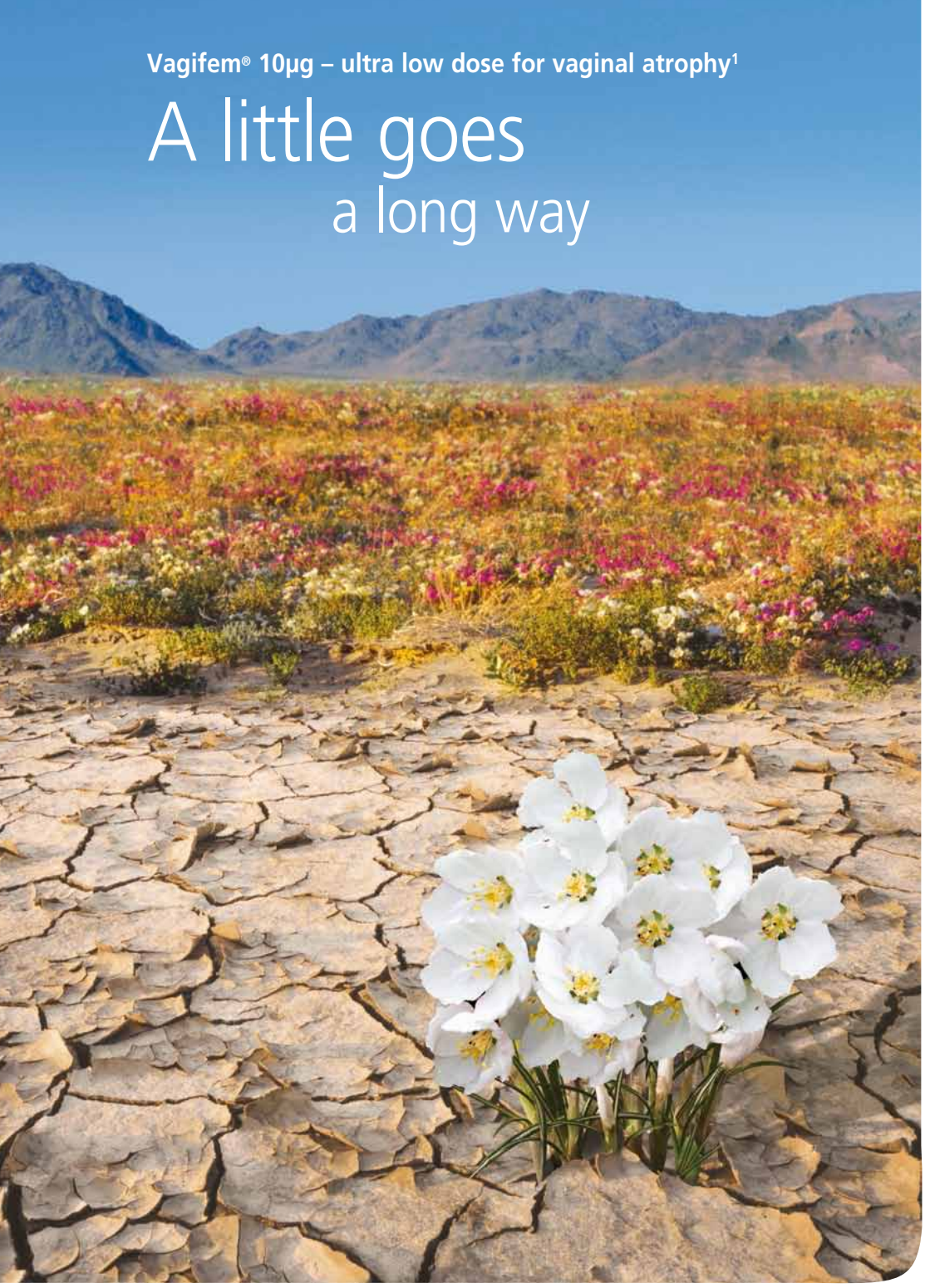

Abbreviated Prescribing Information Vagifem® 10 micrograms Vaginal Tablets. Refer to the Summary of Product Characteristics before prescribing. **Qualitative and quantitative composition:** Each tablet contains estradiol hemihydrate equivalent to 10 micrograms of estradiol. **Therapeutic indication:** Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women. **Contraindications:** Known, past or suspected breast cancer, known, past or suspected oestrogen dependent malignant tumours (e.g. endometrial cancer), undiagnosed genital bleeding, untreated endometrial hyperplasia, previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism), known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency), active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction), acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal, known hypersensitivity to the active substances or to any of the excipients, porphyria. **Special warnings:** The dose of 17β-estradiol is very low and the treatment is local; however, minimal absorption may be seen, especially during the first two weeks of treatment. **Pregnancy and lactation:** Vagifem® 10 micrograms is not indicated during pregnancy and lactation. **Dosage and administration:** Vagifem® 10 micrograms is administered into the vagina, using the applicator. **Initial dose:** One vaginal tablet a day for two weeks. **Maintenance dose:** One vaginal tablet twice a week. Treatment may be started on any convenient day. **Side effects:** The most commonly reported adverse events are headache, abdominal pain, vaginal haemorrhage, vaginal discharge or vaginal discomfort. **Legal category:** Only available on prescription. For further information please contact Novo Nordisk FemCare AG, Thurgauerstrasse 36/38, CH-8050 Zurich, Switzerland or the local Novo Nordisk subsidiary. Vagifem® is a registered trademark of Novo Nordisk FemCare AG.

Date of preparation: September 2012.

Reference:
1. Simon J et al. *Obstet Gynecol* 2008;112(5):1053–1060. **2.** Vagifem® 25µg Summary of Product Characteristics; October 2012. **3.** Vagifem® 10µg Summary of Product Characteristics; January 2012. **4.** Rioux JE et al. *Menopause* 2000;7(3):156–161. **5.** Dugal R et al. *Acta Obstet Gynecol Scand* 2000;79:293–297.

* of local 17β-estradiol

ID 4536, November 2012

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3. Introduction to the Cord Tissue Market and Cord Tissue-Derived Mesenchymal Stem Cells (CT-MSCs™), BIOINFORMANT, Jun 2015

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The *Hong Kong Journal of Gynaecology, Obstetrics & Midwifery* publishes peer-reviewed articles on all aspects of gynaecology, obstetrics, midwifery and related fields, including original basic and clinical studies, review articles, case reports and abstracts or reports presented at scientific meetings or seminars.

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- Abbreviate titles of periodicals according to the style of the *Index Medicus*. Follow the format (arrangement, punctuation) shown below:

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1. Fuchs AR, Fuchs F, Husslein P, et al. Oxytocin receptors in the human uterus during pregnancy and parturition. *Am J Obstet Gynecol* 1984; 150:734-41.

Books edited by other authors of the article

2. Redwine DB, Perez JJ. Pelvic pain syndrome: endometriosis and mid-line dysmenorrhea. In: Arregui MW, Fitzgibbons RJ, Katkhouda N, McKerman JB, Reich H, editors. Principles of Laparoscopic Surgery – Basic and Advanced Techniques. *New York: Springer Verlag*; 1995: 545-58.

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3. Varney H. Nurse Midwifery. *Boston: Blackwell Scientific Publications*; 1987: 23-32.

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Name of the Medicinal Product: CERVARIX®. Qualitative And Quantitative Composition: 1 dose (0.5 ml) contains 20 micrograms Human Papillomavirus type 16 L1 protein; 20 micrograms Human Papillomavirus type 18 L1 protein. Therapeutic indications: Cervarix® is a vaccine for use from the age of 9 years for the prevention of premalignant genital lesions, cervical and vaginal (lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. The use of Cervarix® should be in accordance with official recommendations. Posology: The vaccination schedule (spacing) on the age of the subject. For subject age at first vaccination 14 years at the time of the first injection, the recommended vaccination schedule is 0 and 6 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 5 month and 7 months after the first dose. For subject from 15 years and above at the time of the first injection, the recommended vaccination schedule is 0, 1, 6 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose. If at any age the second vaccine dose is administered before the 5th month after the first dose, the third dose should always be administered. The need for a booster dose has not been established. It is recommended that subjects who receive a first dose of Cervarix® complete the 3-dose vaccination course with Cervarix®. Paediatric population: Cervarix® is not recommended for use in girls below 9 years of age due to lack of data on safety and immunogenicity in this age group. Method of administration: Cervarix® is for intramuscular injection in the deltoid region. Contraindications: Hypersensitivity to the active substances or to any of the excipients. Administration of Cervarix® should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation. Special warnings and precautions for use: The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine. Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that precautions are in place to avoid injury from falls. Cervarix® should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Cervarix®. As with other vaccines administered intramuscularly, Cervarix® should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects. As with any vaccine, a protective immune response may not be elicited in all vaccinees. Cervarix® will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types. Therefore, appropriate precautions against sexually transmitted disease should continue to be used. Cervarix® is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Cervarix® has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer or cervical intraepithelial neoplasia (CIN). It is also not intended to prevent progression of other established HPV-related lesions or existing HPV infections with vaccine or non-vaccine types. Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Cervarix® will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains clinically important and should follow local recommendations. Duration of protection has not fully been established. Timing and need of booster dose(s) has not been established. Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available, there are no data on the use of Cervarix® in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals. There are no safety, immunogenicity or efficacy data to support interchangeability of Cervarix® with other HPV vaccines. Interaction with other medicinal products and other forms of interaction: In all clinical trials individuals who had received immunoglobulin or blood products within 3 months prior to the first vaccine dose were excluded. Use with other vaccines: Cervarix® may be administered concomitantly with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis (acellular) (pa) with or without inactivated poliomyelitis (IPV), (dTpa-IPV vaccines), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by Cervarix® one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to Cervarix® alone. The clinical relevance of this observation is not known. Cervarix® may be administered concomitantly with a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (Twinrix™) or with hepatitis B (rDNA) vaccine (Engerix™ B). Administration of Cervarix® at the same time as Twinrix™ has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-Hbs geometric mean antibody concentrations were significantly lower on co-administration, but the clinical relevance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-Hbs ≥ 10mIU/ml was 88.3% for concomitant vaccination and 100% for Twinrix™ given alone. Similar results were observed when Cervarix® was given concomitantly with Engerix™-B with 57.9% of subjects reaching anti-Hbs ≥ 10mIU/ml compared to 100% for Engerix™-B given alone. If Cervarix® is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. Use with hormonal contraceptive: In clinical efficacy studies, approximately 80% of women who received Cervarix® used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of Cervarix®. Use with systemic immunosuppressive medicinal products: As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment, an adequate response may not be elicited. Fertility, pregnancy and lactation: Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of 10,476 pregnancies were reported including 5,387 in women who had received Cervarix®. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infant including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonic/foetal development, parturition or post-natal development. These data are insufficient to recommend use of Cervarix® during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy. The effect on breast-fed infants of the administration of Cervarix® to their mothers has not been evaluated in clinical studies. Cervarix® should only be used during breast-feeding when the possible advantages outweigh the possible risks. No fertility data are available. Undesirable effects: Infections and infestations including upper respiratory tract infection; Nervous system disorders including headache; dizziness; Gastrointestinal disorders including nausea, vomiting, diarrhoea and abdominal pain; Skin and subcutaneous tissue disorders including itching/pruritus, rash, urticaria; Musculoskeletal and connective tissue disorders including myalgia, arthralgia; General disorders and administration site conditions including pain, redness, swelling at injection site, fatigue, fever (≥38°C). Other injection site reactions such as induration, local paraesthesia. Post marketing surveillance: Blood and lymphatic system disorders including Lymphadenopathy; Immune system disorders including Allergic reactions (including anaphylactic and anaphylactoid reactions); angioedema; Nervous system disorders including Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements; Hypoaesthesia. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Special precautions for disposal and other handling: A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration. The content of the syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. The vaccine should be well shaken before use. Instructions for administration of the vaccine presented in pre-filled syringe: 1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise. 2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. 3. Remove the needle protector, which on occasion can be a little stiff. 4. Administer the vaccine. Any unused product or waste material should be disposed of in accordance with local requirements.

Please read the full prescribing information prior to administration. Full prescribing information is available on request from: GlaxoSmithKline Ltd., 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information prepared in April 2014 based on GDS 22 (EU-44).

* In an analysis of CIN3+ lesions, combined irrespective of HPV type, Cervarix® showed 93% efficacy (95% CI: 76.9-98.7).[1,2]

** TVC HPV-naïve cohort: Representative of young girls and women (15-25 years) prior to the onset of sexual activity with no evidence of high-risk HPV infection at baseline (secondary endpoint). Women who received 3 one vaccine dose, with normal cytology, HPV DNA negative for 14 high-risk HPV types and HPV 16/18 seronegative (end of study analysis).[1,2]

\# In the control group (TVC naïve), 61.2% of CIN3+ lesions were associated with HPV 16/18.[1]

\#\# 93% efficacy against CIN3+, irrespective of type can be translated, in the context of the PATRICIA trial, to a potential prevention of 8 out of 10 CIN3+ lesions irrespective of HPV type (TVC naïve).[1]

~ Efficacy is inferred from immunobridging studies in girls 9-14 years of age.[1]

References:

1. Lehtinen M, Paavonen J, Wheeler CM et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012; 13: 89–99.
2. Cervarix® – Hong Kong Prescribing Information (Dec 2014).

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Editorial
From the Editor-in-Chief

I am most delighted to introduce this printed issue of the Journal as the first issue of 2016.

As in the past two issues, I am confident you will agree that the papers presented in this issue once again cover key developments in our specialty.

Preterm delivery is well known to be associated with major perinatal mortality and morbidity, and prediction of preterm labour has always been a key research topic worldwide. The pilot study on the use of rapid phosphorylated insulin-like growth factor binding protein in our local population to predict preterm delivery offers an exciting prospect[1]. Postpartum haemorrhage continues to be a major source of morbidity in our obstetric patients and in rare unfortunate incidences, a source of maternal mortality as well. The comparison of the maternal outcome of Caesarean and postpartum hysterectomy demonstrates the dire need for very vigilant and timely care for severe postpartum haemorrhage[2]. Fetal renal pelvic dilatation is one of the most commonly detected abnormalities during mid-trimester morphology scanning, and data to show the association between antenatal features and postnatal urological outcome should provide very valuable reference figures for the obstetrician involved in counselling these mothers during the antenatal period[3]. Screening for asymptomatic bacteriuria is apparently still not universal practice in all local obstetric protocols, and the prospective observational study that confirms the association of asymptomatic bacteriuria with a higher risk of adverse pregnancy outcome should provide strong evidence to support the incorporation of such screening into our protocols[4].

When dealing with patients with subfertility problems, we often tend to focus on the clinical aspects and easily overlook the psychiatric morbidity of these patients. The survey of psychiatric morbidity in infertile Chinese women in Hong Kong serves as a good reminder to all of us of the important need to assess and cater for the psychological wellbeing of these patients[5]. As robotic surgery becomes more and more commonly adopted in gynaecological surgery, there is indeed a need to compare the outcome between robotic surgery and conventional gynaecological surgery. The retrospective study to compare the surgical outcomes of robotic-assisted laparoscopic, laparoscopic and abdominal myomectomy is an excellent demonstration of such efforts[6]. Then there is the knowledge, attitudes, and practice survey of emergency contraception that informs us that despite the availability of various emergency contraception methods in Hong Kong, there remains a need to enhance the awareness and knowledge of our patients[7]. As medical treatment for ectopic pregnancy with methotrexate becomes more widely adopted as a standard alternative in our practice, it is indeed the appropriate moment to review and define the predictors of success for such treatment[8]. Going on to urogynaecology, as our experience in the use of tension-free vaginal tapes continues to accumulate, one starts to wonder whether there are better techniques to position the tape other than conventional blind placement. I leave the reader to judge whether transperineal ultrasound offers a solution[9]. Finally, as our Caesarean section rate continues to escalate, the prospective study comparing postnatal quality of life in women who delivered by normal vaginal delivery or Caesarean section seems most timely and appropriate[10].

I hope you will all continue to enjoy and cherish the journal as a platform for both scientific exchanges as well as for sharing new ideas and developments.

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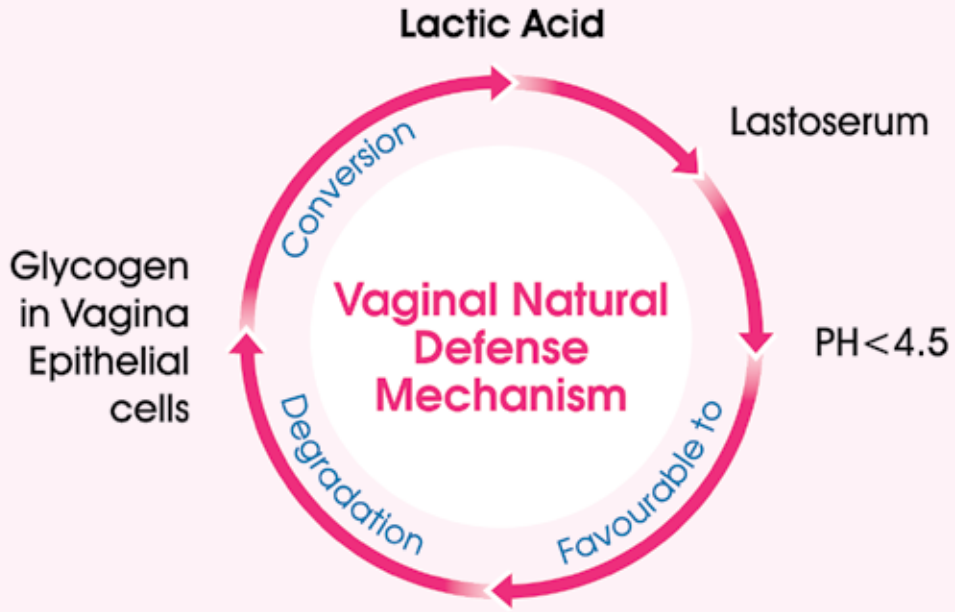

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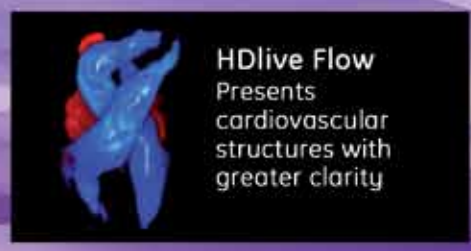

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Prediction of Preterm Delivery: A Pilot Study on the Use of Rapid Phosphorylated Insulin-like Growth Factor-binding Protein 1 Test

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Objective: This was a pilot study to determine whether the rapid phosphorylated insulin-like growth factor-binding protein 1 (phIGFBP-1) bedside test can help to predict preterm delivery in women who presented with symptoms of threatened preterm labour in our local population in Hong Kong.
Methods: This prospective cohort study was conducted in a tertiary obstetrics and gynaecology unit. Pregnant women with a singleton pregnancy and intact membrane who presented with symptoms of threatened preterm labour between 24 and 34 weeks' gestation, from July 2013 to May 2014, were recruited. Cervical samples were taken for rapid phIGFBP-1 bedside testing from eligible consenting patients. Sensitivity, specificity, negative predictive value, and positive predictive value of the rapid phIGFBP-1 bedside test to predict preterm delivery within 48 hours, 7 days, 14 days, as well as at <34 and <37 weeks' gestation were measured.
Results: A total of 39 women were recruited. Of 19 (49%) who had a positive result for the phIGFBP-1 test, three (16%) delivered within 7 days. A negative phIGFBP-1 test was confirmed in 20 (51%) women of whom two delivered within 7 days and one within 48 hours. The negative predictive value for predicting delivery within 7 days and 48 hours was 90% and 95%, respectively. The delivery outcome for women with a positive and those with a negative phIGFBP-1 result showed no statistical difference.
Conclusion: The high negative predictive value in this pilot study was similar to that in other studies.
Hong Kong J Gynaecol Obstet Midwifery 2016; 16(1):15-20

Keywords: Insulin-like growth factor binding protein 1; Obstetric labor, premature; Predictive value of tests

Introduction

Preterm delivery (PTD) is a serious pregnancy complication that can lead to significant perinatal morbidity and mortality[1]. It occurs in approximately 5% to 13% of all deliveries[2-4]. Prediction of PTD is difficult even in symptomatic women. Only about 20% of women who present with symptoms of threatened preterm labour (TPL) will deliver preterm[5]. If the accuracy of predicting PTD can be improved, there is a possibility that treatment to reduce neonatal morbidity and mortality, such as use of antenatal corticosteroids, tocolytics and neonatal support, can be reserved for those women at high risk of PTD and thus avoid unnecessary treatment for those at low risk.

Insulin-like growth factor-binding protein 1 (IGFBP-1) is abundant in amniotic fluid, but less so in other body fluids. It is synthesised in the decidua and liver and has different phosphorylation isoforms. Decidual cells and the human liver secrete predominantly phosphorylated forms of IGFBP-1 (phIGFBP-1), whereas amniotic fluid, fetal serum and maternal plasma contain a substantial amount of non-phIGFBP-1[6]. When delivery is approaching, fetal membranes begin to detach from the decidua parietalis. As decidual cells are damaged, phIGFBP-1 leaks into cervical secretions. Previous studies showed that a phIGFBP-1 level of ≥10 μg/L was considered elevated after 22 weeks' gestation and associated with an increased risk of PTD[7,8]. phIGFBP-1 in cervical fluid has been studied as a biochemical marker to predict PTD among symptomatic women (presenting with uterine contractions) between 23 and 37 weeks of gestation. A sensitivity of 40% to 80% and negative predictive value (NPV) of 86% to 99% in prediction of PTD has been shown in previous studies[9-12].

The detection of phIGFBP-1 in cervical fluid is possible using a bedside immunochromatographic

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rapid dipstick test (Actim Partus, Medix Biochemica, Kauniainen, Finland). It is based on highly unique monoclonal antibodies, and there is no effect from semen or urine[6]. It can be used from week 22 of pregnancy until term. A concentration of phIGFBP-1 in the extracted sample >25 μg/L is a positive result. Some overseas studies have suggested that a negative phIGFBP-1 test using this bedside kit can exclude imminent delivery within 7 days in about 90% to 95% of patients[13-17]. Nonetheless to date no local study has been performed in Hong Kong to address this issue. This pilot study aimed to determine whether a bedside rapid phIGFBP-1 test could predict PTD in symptomatic women in our locality.

Methods

This was a prospective cohort study carried out in the Department of Obstetrics and Gynaecology, Princess Margaret Hospital, Hong Kong from July 2013 to May 2014. The study was approved by the Kowloon West Cluster Research Ethics Committee, Hospital Authority (KW/FR-13-012[62-16]).

Patients with a viable singleton pregnancy and intact membranes who presented with symptoms of TPL, defined as having regular intermittent painful contractions occurring at least once in 10 minutes with regular uterine activity on cardiotocographic monitoring, between 24 and 34 weeks of gestation were recruited.

Patients with a multiple pregnancy, ruptured membranes, cervical dilatation, antepartum haemorrhage, chorioamnionitis, intrauterine growth restriction, pre-eclampsia, or major fetal or genital tract anomaly were excluded from the study.

The gestational age of the pregnancy was calculated using the first day of the last menstrual period (LMP) and confirmed by either a first- or second-trimester ultrasound scan. The gestational age was adjusted where there was a discrepancy >7 days or 14 days between the LMP and the first-trimester or second-trimester scan, respectively. PTD was defined as delivery after 24 and before 37 weeks of gestation.

Eligible patients were invited to participate in the study and written consent was obtained. Consenting women were treated according to the hospital protocol, with the addition of a cervical swab taken to detect the presence of cervical phIGFBP-1. Each patient admitted with symptoms of preterm labour underwent sterile speculum examination to assess the length and dilatation of the cervix. A cervical swab was taken from the cervical os using a polyester swab that came with the bedside kit (Actim Partus). It was held in place for 10 to 15 seconds. The swab was then placed in the Specimen Extraction Solution provided with the bedside kit and swirled vigorously for 10 seconds. The dipstick in the kit was placed in the Specimen Extraction Solution until the liquid front reached the result area. The result of the test was regarded as positive if two blue lines were visible. The test was read as negative if only one blue line was visible after 5 minutes. The result of the phIGFBP-1 test was read and documented by a midwife on a pre-printed form. The forms were immediately filed in a designated folder away from the patients' hospital record. The patients and managing obstetrician were thus blinded to the result and subsequent patient care was provided based on individual clinical situations according to our departmental protocol for management of TPL, irrespective of the test result. Transvaginal measurement of cervical length was then performed by obstetricians who had the Hospital Authority Obstetric and Gynaecological Ultrasonography qualification according to the standard described by the Fetal Medicine Foundation. The patient emptied her bladder prior to the ultrasound. She was then placed in the dorsal lithotomy position and the ultrasound probe (Philips HD11 XE C8-4V, California, US; or Esaote EC123, Florence, Italy) introduced into the vagina and directed at the anterior fornix. A sagittal view of the cervix was obtained. The endocervical mucus was used to guide the true position of the internal os. Calipers were used to measure the linear distance between the triangular area of echogenicity at the external os and the V-shaped notch at the internal os. Three measurements were taken and the shortest of three measurements was recorded.

Data Collection

A standardised data collection form was used. Demographic variables (age, gravidity, parity, gestational age, previous PTD, smoking) were retrieved from the antenatal record. The subsequent use of tocolytics, antenatal corticosteroids and pregnancy outcome were traced by the investigators and documented on the standardised data collection form. Phone follow-up was conducted to review the pregnancy outcome if the patient delivered outside our unit.

Statistical Analysis

All statistical analysis of data was done by PASW Statistics 18, release version 18.0.0 (SPSS, Inc., Chicago [IL], US). Fisher's exact test was used to analyse categorical data. For continuous data with normal distribution, independent-sample *t* test was used. For continuous data

with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

Results

Forty-three patients were considered suitable during the study period, but four refused consent so 39 patients were recruited. The mean (± standard deviation) maternal age was 28.8 ± 4.7 years. The median gestational age at recruitment was 30.4 (range, 28.7-32.7) weeks. The median gestational age at delivery was 38.5 (range, 37.1-39.4) weeks. Eight (20.5%) women delivered at <37 weeks, of whom five (12.8%) delivered before 34 weeks. Tocolytics were prescribed according to departmental protocol after admission to 38 (97.4%) women. A positive and negative phIGFBP-1 result was obtained in 19 (49%) and 20 (51%) women, respectively.

Table 1 shows the comparison of maternal demographics and obstetric characteristics between women with a positive and negative phIGFBP-1 test result. Their baseline characteristics were similar with no statistically significant difference.

The phIGFBP-1 result, delivery characteristics and outcome are shown in Table 2. Among the 19 women with a positive phIGFBP-1 result, five (26%) delivered before 37 weeks, of whom three delivered within 48 hours. All five patients had a spontaneous PTD. Fourteen (73.7%) patients did not have PTD. Among the 20 women with a negative phIGFBP-1 test result, 17 (85%) delivered after 37 weeks. PTD before 37 weeks occurred in three (15%) patients. One patient delivered within 24 hours of a negative phIGFBP-1 test result at 25 weeks and 1 day of gestation. The cervical length of that patient measured by transvaginal ultrasound was only 4 mm on admission. She was prescribed antenatal corticosteroids and atosiban as tocolytics before her delivery. Another woman was delivered by emergency lower segment Caesarean section 5 days after a negative phIGFBP-1 at 34 weeks' gestation because of a pathological fetal heart tracing on the cardiotogram without onset of labour. The third woman had a negative phIGFBP-1 test at 24 weeks and 2 days of gestation. She subsequently underwent spontaneous PTD at 36 weeks and 4 days. Although 15% of women with a negative phIGFBP-1 test result delivered before 37 weeks and 26% of women with positive phIGFBP-1 delivered preterm, the delivery outcome was not statistically different between the two groups.

The sensitivity, specificity, positive predictive value (PPV), and NPV of the phIGFBP-1 test are listed in Table

Table 1. Maternal demographics and obstetric characteristics of subjects*

Characteristic	Actim Partus–negative (n=20)	Actim Partus–positive (n=19)	p Value
Age (years)	29.7 ± 4.4	28.0 ± 4.9	0.28
Parity	0 (0-1)	0 (0-1)	0.66
Gravidity	2 (1-2)	2 (1-2)	0.81
Gestation (weeks)	31.3 (29.8-32.8)	29.3 (27.6-31.6)	0.13
Previous preterm			0.11
Yes	0	3 (16)	
No	20 (100)	16 (84)	
Smoking			1
Yes	1 (5)	1 (5)	
No	19 (95)	18 (95)	
Cervical length by transvaginal ultrasound (mm)	29.2 ± 9.9	29.4 ± 10.4	0.97
Steroids			0.49
Yes	20 (100)	18 (95)	
Tocolytics			0.49
Yes	20 (100)	18 (95)	
No	0	1 (5)	

* Data are shown as mean ± standard deviation, median (interquartile range), or No. (%)

3. A negative phIGFBP-1 test result was associated with a high NPV for delivery before 37 weeks. The NPV was 95% for delivery within 48 hours and remained as high as 90% for delivery within 14 days.

Discussion

This current study of 39 women with symptoms of TPL determined that the sensitivity, specificity, PPV, and NPV of phIGFBP-1 in predicting PTD <37 weeks was 62.5%, 54.8%, 26.3% and 85.0%, respectively. Respective values within 7 days were 60.0%, 52.9%, 15.8%, and 90.0%.

According to the Royal College of Obstetricians and Gynaecologists, antenatal corticosteroids are most effective in reducing neonatal respiratory distress syndrome in pregnancies that deliver between 24 hours and up to 7 days following administration of a second dose of antenatal corticosteroids[18]. The most common regimen of antenatal corticosteroids is two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart. Delivery within 48 hours and within 7 days were thus chosen as outcomes in this study.

Ting et al[10] carried out a prospective study of 94 women between 24 and 34 weeks of gestation with symptoms suggestive of PTD. The sensitivity, specificity, PPV and NPV of IFGBP-1 rapid test for PTD within 7 days was 69%, 78%, 39% and 92%, respectively. A recent larger prospective study published by Cooper et al1[2] that included 349 women with symptoms of PTD between 24 and 34 weeks found that the sensitivity, specificity, PPV and NPV of IFGBP-1 rapid test for PTD before 37 weeks were 39%, 76%, 24% and 86%, respectively.

The PPV of the test was low in our study, similar to

Table 2. Characteristics of delivery and outcome between patients with negative and positive results of phosphorylated insulin-like growth factor-binding protein 1 test*

Characteristic	Actim Partus–negative (n=20)	Actim Partus–positive (n=19)	p Value
Mode of delivery			0.24
Caesarean section	6 (30)	2 (11)	
Vaginal	14 (70)	17 (89)	
Gestation (weeks)	38.5 (37-39)	38.6 (34-40)	0.76
Cumulative delivery			
Within 24 hours	1 (5)	2 (11)	0.61
Within 48 hours	1 (5)	3 (16)	0.34
Within 7 days	2 (10)	3 (16)	0.66
Within 14 days	2 (10)	4 (21)	0.41
Delivery			
Before 37 weeks	3 (15)	5 (26)	0.45
Before 34 weeks	1 (5)	4 (21)	0.18

* Data are shown as mean ± standard deviation, median (interquartile range), or No. (%)

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value for phosphorylated insulin-like growth factor-binding protein 1 test*

	<24 Hours	<48 Hours	Within 7 days	Within 14 days	<34 Weeks	<37 Weeks
Sensitivity	66.7 (9.4-99.2)	75.0 (19.4-99.4)	60.0 (14.7-94.7)	66.7 (22.3-95.7)	80.0 (28.4-99.5)	62.5 (24.5-91.5)
Specificity	52.8 (35.5-69.6)	54.3 (36.6-71.2)	52.9 (35.1-70.2)	54.5 (36.4-71.9)	55.9 (37.9-72.8)	54.8 (36.0-72.7)
PPV	10.5 (1.3-33.1)	15.8 (3.4-39.6)	15.8 (3.4-39.6)	21.1 (6.1-45.6)	21.1 (6.1-45.6)	26.3 (9.1-51.2)
NPV	95.0 (75.1-99.9)	95.0 (75.1-99.9)	90.0 (68.3-98.8)	90.0 (68.3-98.8)	95.0 (75.1-99.9)	85.0 (62.1-96.8)

Abbreviations: NPV = negative predictive value; PPV = positive predictive value

* Data are shown in percentages (95% confidence intervals)

the findings of other published studies[10,12]. It is consequently deduced that a positive test should not be used as a sole indicator for PTD or used in isolation to decide on the need for initiating treatment that may prove to be unnecessary. It is worth mentioning that the commonly used tocolytics and repeated dose of steroids are not without adverse effects. Beta-agonists carry a risk of palpitations, tremor, nausea and vomiting, headache and pulmonary oedema[19] whereas the use of a calcium channel blocker has a risk of flushing, palpitations, and hypotension[20,21]. Although the side-effects of atosiban are fewer, mainly nausea[22], it is an expensive drug. The cost of a course of atosiban is about HK$6000 to HK$7000, thus unnecessary and repeated use of the medication in public hospitals will significantly drive up the overall public medical cost. A repeated dose of steroids is associated with decreased weight, length and head circumference of the fetus at birth[23]. A non-significant higher risk of cerebral palsy has also been reported among children exposed to multiple doses of steroids[24]. Therefore tocolytics and steroids should be used with caution.

Similar to other studies, the NPV in this study was as high as 90% for delivery within 7 days and 85% for delivery before 37 weeks. A negative test result should therefore be reassuring for obstetricians and pregnant women, and might avoid unnecessary use of steroids and tocolytics. Nonetheless there was no statistical difference in outcome between the positive and negative phIGFBP-1 groups. This may have been due to the small sample size, the main limitation of this pilot study. If a NPV were to be set at 85% with the margin of error being 0.05, which is the same as the present study, it is calculated that a sample size of 196 (assuming there is no dropout) or 245 (assuming there is a 20% dropout rate) would be required to have an adequately powered study to show a significant difference between the positive and negative phIGFBP-1 groups.

Although there was no statistical difference for outcome, there were differences in the absolute event rate for PTD between the negative and positive phIGBBP-1 groups (95% vs. 84% for not delivering within 48 hours; 95% vs. 79% for not delivering before 34 weeks; and 85% vs. 74% for not delivering before 37 weeks). Such data may have clinical implications or importance for the use of antenatal corticosteroids and tocolytics in women who present with symptoms of TPL, should a significant difference in pregnancy outcome be shown by a larger prospective study.

In this study, 100% of patients in the negative phIGFBP-1 group and 95% in the positive phIGFBP-1 group were prescribed antenatal corticosteroids and tocolytics. Of 20 women with a negative phIGFBP-1 result, only one (5%) delivered within 48 hours and before 34 weeks, but all received antenatal corticosteroids and tocolytics. The application of these medications might theoretically be avoided in 95% of the women. The one patient who delivered within 48 hours and before 34 weeks of gestation had a cervical length of 4 mm measured by transvaginal ultrasound. Therefore, the addition of cervical length measurement may be of value and help to predict PTD. This needs to be addressed in a future larger prospective study.

Although the study by Cooper et al[12] showed a high NPV, it has been argued that the application of such a test result is not clinically important due to the minimal change in pre- and post-test negative probability from 84% (292/349) to 86% (95% confidence interval [CI], 82%-91%). In this current study, the pre-test and post-test negative probability was 79.5% (31/39) and 85% (95% CI, 62.1%-96.8%) respectively for delivering preterm before 37 weeks. The difference in pre-test negative probability between the current study and the one by Copper et al[12] might be due to the use of different inclusion criteria: in the latter study[12] PTD was defined as symptoms of uterine activity judged by the assessing physician to be indicative of PTD, whereas in our study an objective assessment of uterine activity defined as regular intermittent painful contractions occurring at least once in 10 minutes with regular uterine activity on cardiotocographic monitoring was used. Nevertheless despite the small difference in the estimated pre-test negative probability, the post-test negative probability strongly supports Cooper et al's data[12] and this current study.

In conclusion, the high NPV found in this pilot study is similar to that in other studies. The clinical implications for use of tocolytics and antenatal steroids in women with a negative phIGFBP-1 test result need to be addressed in a larger prospective study.

Declaration

The Actim Partus bedside kits were provided by Nordep Healthtech.

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Peripartum Hysterectomy: Comparison of the Outcome of Caesarean and Postpartum Hysterectomy

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Objective: To compare the risk factors and complications of Caesarean hysterectomy (CH) and postpartum hysterectomy (PH) in a single obstetric unit over the last 15 years.
Methods: A retrospective review was made of 48 cases of peripartum hysterectomy performed from 1999 to 2014 (15 years). Cases were classified as CH or PH group. Epidemiological data, indications for hysterectomy, total blood loss, complications, and re-laparotomy rate were analysed and compared between the two groups.
Results: The Caesarean section rate was 20.2% among the 68,211 deliveries during the study period. The incidence of hysterectomy following Caesarean deliveries was 0.25% (n=35), that following vaginal delivery was 0.023% (n=13). The most common indication for CH was placenta praevia, that for PH was uterine atony. Total blood loss was comparable between the two groups but a significantly higher proportion in the PH group had disseminated intravascular coagulopathy (DIC) [85% vs. 49%] and required more units of blood transfusion compared with the CH group. Within the entire cohort, eight (17%) cases required re-laparotomy due to re-bleeding, and these cases had a significant higher risk of postoperative complications, longer length of intensive care unit stay, and need for ventilatory support.
Conclusion: Uterine atony and placenta praevia were the most common indications for peripartum hysterectomy. There were no major significant differences in the clinical outcome between CH and PH patients, but the incidence of DIC was apparently higher in the PH group compared with the CH group.
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Keywords: Cesarean section; Hysterectomy; Postpartum hemorrhage

Introduction

Peripartum hysterectomy is the definitive procedure for management of intractable postpartum haemorrhage and is often associated with significant maternal morbidity and mortality. The incidence of peripartum hysterectomy has been observed to be increasing over time[1], with reported rates varying from 0.41/1000 in the UK[2] to 1.3/1000 in Taiwan[3]. In general, Caesarean hysterectomy (CH) is performed during the same surgery shortly following a Caesarean delivery, while a postpartum hysterectomy (PH) is shortly after a vaginal delivery[1].

Previous studies have shown that the indications for PH have changed over time with intractable uterine atony and placenta accreta becoming more important indications, while the incidence of uterine rupture has decreased significantly over the past decades[4,5]. The incidence of placenta accreta is closely associated with Caesarean section rate[6]. Similar to the worldwide trend, the overall Caesarean section rate in Hong Kong has increased from 22.5% in 1994[7] to 36.9% in 2009[8]. It is therefore relevant to evaluate the impact of such an increase in Caesarean section rate on peripartum hysterectomy rates. The progressive development of conservative surgical management of severe postpartum haemorrhage, including the use of compression sutures, balloon tamponade and radiological embolisation, was also postulated to have an impact on the overall incidence and indications for peripartum hysterectomy[9,10]. The last review of peripartum hysterectomy in our locality was performed over 15 years ago[11]. This current retrospective study aimed to evaluate the differences in incidence, indications, risk factors, and complications of CH and PH in the last 10 years.

Methods

A retrospective analysis was performed of all women who underwent emergency peripartum hysterectomy over a period of 15 years in a tertiary regional obstetric unit. A comprehensive obstetric database and the Labour Ward registry were used to search for all women who had emergency peripartum hysterectomy performed

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between July 1999 and June 2014. Emergency peripartum hysterectomy was defined as hysterectomy performed within 72 hours of the time of delivery, and CH was referred to as peripartum hysterectomy following Caesarean section and PH as hysterectomy following vaginal delivery. Cases of elective incidental hysterectomy at the time of Caesarean section, for example that for ovarian or cervical malignancies, were excluded from this analysis. A total of 48 cases were identified according to the above criteria and all were included in the analysis. The complete hospital records of these patients, including clinical notes, operation records, anaesthetic records, laboratory results and blood transfusion records were retrieved and reviewed.

The cases were divided into the CH group versus PH group for comparison. The epidemiological data for maternal age, parity, previous Caesarean section, multiple pregnancies, antepartum haemorrhage, gestational diabetes mellitus, use of prostaglandins, gestation at delivery, birth weight, and mode of delivery were extracted and entered into a specifically designed proforma for major postpartum haemorrhage. In addition, the indications for hysterectomy, use of second-line surgical procedures before hysterectomy, operative blood loss, number of units of blood products transfused, documented disseminated intravascular coagulopathy (DIC), postoperative complications, and re-laparotomy rates were evaluated. Total blood loss was calculated by adding the intraoperative blood loss and the estimated blood loss post-delivery or postoperatively. The total number of units transfused was calculated from the total volume of blood products transfused during the entire delivery episode and DIC was defined as the presence of prolonged prothrombin and activated partial thromboplastin time together with thrombocytopenia based on laboratory haematological results. A secondary comparison was also performed in the same cohort to compare the outcome of those who required re-laparotomy because of bleeding versus those without re-laparotomy. Re-laparotomy was defined as any subsequent surgical exploration for control of haemorrhage during the same delivery episode.

Statistical analysis was performed using the Statistical Package for the Social Sciences Windows version 21.0 (SPSS Inc, Chicago [IL], US). Student's *t* test was used to assess means between groups for continuous variables, while Chi-square test or Fisher's exact test were used for proportions. Clinical significance was set at p value of <0.05.

Results

During the study period, there were 68,211 deliveries in our hospital, of which 13,831 were by Caesarean section, giving an overall Caesarean section rate of 20.2%. There were 48 cases of peripartum hysterectomy in this period that fulfilled our selection criteria, giving an overall incidence of 0.07%. None of the hysterectomies was performed electively for malignancy or other incidental pathology. All decisions for hysterectomy were made in the presence of a consultant. There were 35 CH, constituting 0.25% of all Caesarean sections, and 13 PH, constituting 0.023% of all vaginal deliveries. The incidence of peripartum hysterectomy was significantly lower following vaginal delivery than following Caesarean section (relative risk 10.5, $p<0.001$). There was one case of maternal mortality due to severe postpartum haemorrhage with placenta praevia/accreta in this cohort.

A comparison of the basic pregnancy characteristics between CH and PH groups showed no major differences in the demographic characteristics, including age, parity, number of previous Caesarean sections, or multiple pregnancies (Table 1). Nonetheless there were more women with antepartum haemorrhage, and more delivering preterm with lower birth weight in the CH group than the PH group. This was most likely because all except one of the placenta praevia/accreta cases (n=19, 54%) were all clustered in the CH group. Although there was a higher incidence of previous Caesarean section in the CH group compared with the PH group (40% vs. 15%), the difference was not statistically significant probably because of the small number of cases. The two cases of previous Caesarean section in the PH group were both for term singletons in women who opted for a vaginal birth after Caesarean (VBAC). Hysterectomy was performed for uterine atony and amniotic fluid embolism with DIC, respectively. There were no cases with more than one previous Caesarean section in the PH group as we would not offer VBAC to these patients in our unit. More women in the PH group had gestational diabetes mellitus than the CH group (6/13, 46% vs. 3/35, 9%). Of the six cases in the PH group, four had uterine atony, one had placenta accreta, and one had vaginal lacerations. The three women with gestational diabetes in the CH group underwent hysterectomy for placenta praevia (twin pregnancy), placenta abruption, and uterine atony, respectively. As the indications for peripartum hysterectomy were not directly related to gestational diabetes or its complications in these cases, the association was most likely incidental (Table 1).

Comparison of indications for peripartum hysterectomy revealed that the primary cause of PH was uterine atony (77%) and in the CH group, placenta praevia/

Table 1. Group comparisons of basic pregnancy characteristics*

	CH group (n=35)	PH group (n=13)	p Value; MD; 95% CI
Age (years)	34.5 ± 5.12	35 ± 4	0.77; -0.5; -3.63 to 2.72
Parity			
Nulliparous	16 (46)	8 (62)	0.51
Multiparous	19 (54)	5 (38)	
Previous Caesarean section	14 (40)	2 (15)	0.17
Had ≥2 previous Caesarean sections	6 (17)	0	0.11
Multiple pregnancy	4 (11)	0	0.20
Antepartum haemorrhage	8 (23)	0	0.04
Gestational diabetes mellitus	3 (9)	6 (46)	0.003
Other significant antenatal medical complications	4 (11)	2 (15)	0.71
Gestation at delivery (weeks)	36.2 ± 3.4	39.5 ± 0.9	0.001; -3.3; -5.22 to -1.33
Birth weight (g)	2850 ± 869	3299 ± 309	0.01; -449; -792 to -107
Mode of delivery			
NSD	0	8 (62)	
VE/LF	0	5 (38)	
Elective/emergency LSCS	8/26 (97)	0	
Classical Caesarean section	1 (3)	0	

Abbreviations: CH = Caesarean hysterectomy; CI = confidence interval; LSCS = lower-segment Caesarean section; MD = mean difference; NSD = normal spontaneous delivery; PH = peripartum hysterectomy; VE/LF = vacuum extraction/ low forceps

* Data are shown as mean ± standard deviation or No. (%), unless otherwise specified

accreta (54%) was the primary indication. There was one case of placenta accreta in the PH group, in a para 2 patient with no previous Caesarean section. She presented with uterine atony after delivery and the final pathology confirmed the presence of placenta accreta. There were no cases of uterine rupture leading to PH during this study period. All but two peripartum hysterectomies were performed within 24 hours of delivery, the one in the CH group being performed 26 hours after the primary Caesarean section and the one in the PH group performed 29 hours after normal vaginal delivery (Table 2).

The total blood loss and blood loss at decision for hysterectomy was similar for both groups although a higher proportion of patients in the PH groups suffered from DIC and required transfusion of significantly more blood products. As a large proportion of CH patients had bleeding from a low lying placenta, none underwent subtotal hysterectomy contrary to 31% in the PH group. Overall, over 40% (21/48) of patients had second-line procedures prior to hysterectomy. The use of compression sutures was higher in the CH group (31% vs. 8%) while use of balloon tamponade was higher in the PH group (15% vs. 9%). There were also no significant differences regarding postoperative complications, or re-laparotomy rates or length of intensive care unit (ICU) stay between the two groups (Table 3). The single case of maternal mortality occurred in a woman with one previous Caesarean section and current unpredicted placenta accreta. She had brisk bleeding of around 4000 ml at the time of emergency Caesarean section followed by cardiac arrest on the table, and succumbed despite intensive advanced resuscitation and immediate resort to hysterectomy.

There were eight women who required re-laparotomy because of re-bleeding, six (75%) following CH. Nonetheless mode of delivery did not appear to have a statistically significant predicative value in discriminating which patients were at risk of re-laparotomy, probably because of the small number of patients involved. Among antenatal risk factors, multiple pregnancy was apparently more common in those who required re-laparotomy, while antepartum haemorrhage, gestational diabetes, or previous Caesarean section were not associated with

Table 2. Group comparisons of operative details at peripartum hysterectomy*

	CH group (n=35)	PH group (n=13)	p Value; MD; 95% CI
Cause of postpartum haemorrhage			
Placenta praevia/accreta	19 (54)	1 (8)	0.001
Uterine atony	16 (46)	10 (77)	
Amniotic fluid embolisation	0	1 (8)	
Vaginal lacerations	0	1 (8)	
Blood loss at decision for hysterectomy (ml)	2448 ± 750	2640 ± 953	0.51; 192; -399 to 783
Total blood loss (ml)	6805 ± 5499	6904 ± 3533	0.95; 100; -3408 to 3209
Type of hysterectomy			
Total	35 (100)	9 (69)	<0.001
Subtotal	0	4 (31)	
Documented DIC	17 (49)	11 (85)	0.02
Transfusion			
Whole blood or packed cells units	10.8 ± 8	16 ± 7	0.02; -5.20; -11.1 to 0.97
Fresh frozen plasma	26 (74) [4-20]	12 (92) [4-24]	0.17
Cryoprecipitate	10 (29) [4-12]	6 (46) [4-22)	0.25
Platelets	22 (63) [2-20]	11 (85) [4-16)	0.14
Factor VIIa	3 (9)	2 (15)	0.49
Delayed hysterectomy >24 hours	1 (3)	1 (8)	0.45
Use of haemabate or other prostaglandins as oxytoxics	16 (46)	8 (62)	0.32
Second-line procedures before hysterectomy			
Compression sutures	11 (31)	1 (8)	
Balloon tamponade	3 (9)	2 (15)	0.27
Internal iliac ligation	1 (3)	0	
Radiological uterine embolisation	3 (9)	0	

Abbreviations: CH = Caesarean hysterectomy; CI = confidence interval; DIC = disseminated intravascular coagulopathy; MD = mean difference; PH = peripartum hysterectomy

* Data are shown as No. (%) [range] or mean ± standard deviation, unless otherwise specified

Table 3. Comparison of complications at peripartum hysterectomy*

	CH group (n=35)	PH group (n=13)	p Value; MD; 95% CI
Complications			
Vault/wound haematoma	6 (17)	4 (31)	0.10
Acute renal failure	0	1 (8)	
Peripartum cardiomyopathy	1 (3)	1 (8)	
Bladder injury	3 (9)	0	
Bowel injury/obstruction	0	1 (8)	
Re-laparotomy	6 (17)	2 (15)	0.88
ICU stay (days)	3.05 ± 0.89	2.96 ± 0.77	0.73; 0.09; -0.46 to 0.66
Ventilatory support (days)	1.45 ± 0.92	1.80 ± 0.85	0.23; -0.35; -0.94 to 0.24
Maternal mortality	1 (3)	0	0.53

Abbreviations: CH = Caesarean hysterectomy; CI = confidence interval; ICU = intensive care unit; MD = mean difference; PH = peripartum hysterectomy

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

an increased risk (Table 4). The amount of blood loss at decision for hysterectomy did not differ between the two groups although total amount of blood loss, incidence of DIC, and total units of blood transfused were significantly higher in those who required re-laparotomy. Postoperative complications, including length of ICU stay and the need for ventilatory support, were also higher in the re-laparotomy group (Table 5).

A logistic regression model was constructed and significant factors associated with need for re-laparotomy were entered into the model in a stepwise fashion. None of the factors that were found to be significant on univariate analysis were significant in the regression model, again due to the small number of cases who required re-laparotomy.

Discussion

The incidence of peripartum hysterectomy was 0.7/1000 in our study, and is comparable with other reports across different centres worldwide[2,3]. Although there were no major significant differences in the clinical outcome for those with CH compared with those with PH, the incidence of DIC was apparently higher in the PH group. The overall re-laparotomy rate was 17% in this cohort with a significantly increased risk of morbidity. Nonetheless re-laparotomy rate was not significantly higher in the CH group compared with the PH group.

As evident in other studies, placenta praevia has become a progressively more important risk factor for CH than uterine atony[2]. The increasing rates of primary Caesarean section have no doubt led to an increased incidence of previous Caesarean section, and thus placenta praevia/accreta in subsequent pregnancies[12]. While placenta praevia is readily recognisable on antenatal ultrasound examination, the risk of CH is greatly increased in the presence of a major previa[13]. On the contrary, uterine atony remains to be the primary risk factor for PH, and evidence from placental pathology has suggested that such intractable uterine atony can be associated with clinical and pathologic findings consistent with acute inflammation and infection[14]. There is evidence from population-based surveillance that the incidence of severe postpartum haemorrhage due to uterine atony has been progressively increasing over the last 15 years[15], although the factors associated with this trend could not be clearly identified.

Table 4. Comparison of pregnancy characteristics between those with and without re-laparotomy*

	No re-laparotomy (n=40)	Re-laparotomy (n=8)	p Value; MD; 95% CI
Age (years)	34.4 ± 4.4	35.6 ± 6.80	0.54; 1.2; -2.62 to 4.92
Parity			
Nulliparous	20 (50)	4 (50)	1.0
Multiparous	20 (50)	4 (50)	
Previous CS	12 (30)	4 (50)	0.27
Had ≥2 previous CS	4 (10)	2 (25)	0.24
Multiple pregnancy	2 (5)	2 (25)	0.06
Antepartum haemorrhage	6 (15)	2 (25)	0.61
Gestational diabetes mellitus	7 (18)	2 (25)	0.61
Other significant antenatal medical complications	6 (15)	2 (25)	0.48
Gestation at delivery (weeks)	37.1 ± 3.5	37.2 ± 2.3	0.92; 0.1; -2.46 to 2.71
Birth weight (g)	3026 ± 793	2697 ± 707	0.28; -329; -938 to 279
Mode of delivery			
NSD	6 (15)	2 (25)	0.88
VE/LF	5 (13)	0	
Elective/emergency LSCS	8/20 (70)	0/6 (75)	
Classical CS	1 (3)	0	

Abbreviations: CI = confidence interval; CS = Caesarean section; LSCS = lower-segment Caesarean section; MD = mean difference; NSD = normal spontaneous delivery; VE/LF = vacuum extraction/low forceps

* Data are shown as mean ± standard deviation or No. (%), unless otherwise specified

Table 5. Comparison of operative details at hysterectomy between those with and without re-laparotomy*

	No re-laparotomy (n=40)	Re-laparotomy (n=8)	p Value; MD; 95% CI
Cause of postpartum haemorrhage			
Placenta praevia	17 (43)	2 (25)	0.35
Uterine atony	22 (55)	5 (63)	
Amniotic fluid embolisation with DIC	0	1 (13)	
Vaginal laceration	1 (2)	0	
Blood loss at decision for hysterectomy (ml)	2617 ± 937	2441 ± 710	0.61; -176; -883 to 530
Total blood loss (ml)	6046 ± 4546	10,760 ± 5657	0.01; 4714; 1024-8403
Type of hysterectomy			
Total	37 (92)	7 (88)	0.64
Subtotal	3 (8)	1 (13)	
Duration of operation (mins)	254 ± 244	231 ± 213	0.89; -24; -423 to 368
Documented DIC	20 (50)	8 (100)	0.008
Transfusion (range of units given)			
Whole blood or packed cell units	10.5 ± 6.6	22.2 ± 8.4	0.001; 11.7; 6.28-17.1
Fresh frozen plasma	30 (4-20) [75]	8 (8-24) [100]	0.07
Cryoprecipitate	12 (4-8) [30]	4 (4-20) [50]	<0.001
Platelets	25 (2-16) [63]	8 (2-20) [100]	0.03
Factor VIIa	3 (8)	2 (25)	0.01
Delayed hysterectomy >24 hours	1 (3)	1 (13)	0.19
Prostaglandins as oxytoxics	22 (55)	2 (25)	0.12
Second-line procedures before hysterectomy			
Compression sutures	10 (25)	2 (25)	1
Balloon tamponade	3 (8)	2 (25)	0.89
Internal iliac ligation	1 (3)	0	0.65
Complications			
Vault/wound haematoma	7 (18)	3 (38)	0.01
Acute renal failure	1 (3)	0	
Peripartum cardiomyopathy	1 (3)	1 (13)	
Bladder injury	2 (5)	1 (13)	
Bowel injury/obstruction	0	1 (13)	
ICU stay (days)	2.76 ± 0.64	4.37 ± 0.35	<0.001; 1.61; 1.14-2.08
Ventilatory support (days)	1.36 ± 0.81	2.5 ± 0.75	0.001; 1.14; 0.50-1.76
Maternal mortality	1 (3)	0	0.65

Abbreviations: CI = confidence interval; DIC = disseminated intravascular coagulopathy; ICU = intensive care unit; MD = mean difference

* Data are shown as No. (%) [range] or mean ± standard deviation, unless otherwise specified. Because of rounding, not all percentages total 100

Uterine rupture used to be a more significant indication for peripartum hysterectomy[4] but no such cases presented during our study period. This may be due to the cautious use of oxytocin, direct Caesarean section in cases with two previous Caesarean sections, and the decreased number of grand multiparous women (0.45%) in our locality[8]. An overall reduction in the incidence of vaginal birth after previous Caesarean section could also contribute to very low rates of previous Caesarean scar dehiscence in recent cohorts[2].

With regard to type of hysterectomy to be performed, there was no attempt to control bleeding by subtotal hysterectomy in the CH in this cohort. This is understandable as bleeding in placenta praevia will likely involve the cervix and a total hysterectomy will be required. Nonetheless in PH, the primary risk factor is uterine atony and subtotal hysterectomy alone will control the bleeding. Indeed, it would be technically more difficult to perform a total hysterectomy when the cervix has been fully dilated in a postpartum case. Previous studies showed no differences regarding operative time or blood transfusion rate between the two types of hysterectomy[11]. In this cohort, the type of hysterectomy was also unrelated to the need for re-exploration. Although there were more bladder injuries in the CH group, such direct trauma was likely due to adhesions from previous Caesarean section or from placenta accreta/percreta rather than the procedure for hysterectomy alone[16].

The rate of DIC in our study was 49% in the CH group and 85% in the PH group. This is significantly higher than the 33.3% quoted in Lau et al[11], although the total blood loss quoted appeared to be similar. In addition, in our current cohort, despite a similar total blood loss in the CH and PH group, there was a significantly higher rate of DIC and units of blood transfused in the PH group. Possible explanations included delays in prophylactic transfusion of blood products and coagulation factors during the resuscitation of PH patients compared with patients delivered by Caesarean section for whom earlier input and intervention by an obstetric anaesthetist was likely, who would also more readily initiate earlier transfusion of blood products. There could also be more underestimation of blood loss in the labour ward by midwives in PH patients compared with CH patients where blood loss documentation in the operating theatre might be more precise. An overall higher incidence of DIC in the current cohort than in previous local data[11] could indicate more vigilant detection of DIC in current obstetric practice, with more ready resort to urgent laboratory tests to confirm coagulopathy[17].

Second-line procedures to control haemorrhage and avoid peripartum hysterectomy are being increasingly adopted and are more common in our current postpartum haemorrhage protocols[18-20]. This was particularly evident when comparing the cases managed in the earlier years within the study period to the more recent cases, when balloon tamponade or compression sutures were more commonly used. The PH group had a lower incidence of second-line procedures before proceeding to direct hysterectomy (3/13, 23%) compared with the CH group (18/35, 52%), although the difference was not statistically significant (p=0.32, Fisher's exact test). There was evidence that the appropriate use of such second-line procedures could reduce the need for hysterectomy[10,21], thereby decreasing total blood loss and morbidity from associated complications such as DIC[22].

The total blood loss in the re-laparotomy group was significantly higher compared with those without need for re-laparotomy. From our data, it was obvious that if haemorrhage could be controlled earlier, the associated morbidity and risks should be correspondingly reduced[23]. Nonetheless due to the small number of patients who required re-laparotomy, we were not able to identify any particular risk factors for such re-laparotomy. Early resort to second-line procedures to avoid hysterectomy and to reduce massive blood loss should be a significant factor that reduces the risk of re-laparotomy and associated morbidity.

Our findings confirmed an almost 10-fold increase in the incidence of emergency peripartum hysterectomy in those with Caesarean delivery compared with vaginal delivery[24,25]. Although the indications for hysterectomy differed significantly in the two groups, as in similar studies in the past, we were unable to find major differences in terms of the operative outcome and associated morbidity[11,25]. While early recognition of severe postpartum haemorrhage of >1000 ml[20] and prompt management with the use of conservative surgical procedures will reduce blood loss, risk of DIC, and the need for hysterectomy, it is clear that peripartum hysterectomy remains a life-threatening obstetric emergency that can be life-saving. At the same time though it is associated with potentially devastating consequences. All major obstetric services should continue to conduct detailed surveillance of the trends in peripartum hysterectomy and associated morbidity.

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A Local Study on Maternal and Fetal Characteristics of Isolated Antenatal Hydronephrosis, and Fetal Renal Pelvis Anteroposterior Diameter in Prediction of Postnatal Urological Outcomes

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Objectives: To describe the maternal and fetal characteristics of isolated antenatal hydronephrosis (ANH), to address parental concerns by providing local data based on the fetal renal pelvis anteroposterior diameter (APD), and to determine the most effective APD cutoff in the second and third trimester for prediction of postnatal urological outcome.
Methods: A retrospective review of all cases referred to the prenatal diagnostic clinic over a 21-month period from 1 January 2013 to 30 September 2014 was performed. All the 4010 ultrasound examination reports were retrieved and those diagnostic of ANH were identified. Antenatal hydronephrosis was defined by the system based on the APD proposed by the Society for Fetal Urology. Maternal and fetal characteristics were studied. Postnatal uropathy and surgery were the events of interest.
Results: Overall, 90.8% of kidneys with isolated ANH detected in the third trimester were found to have normal anatomy after birth. Of the 153 fetuses studied, eight were identified to have postnatal uropathy of whom four underwent surgical intervention. Fetuses with second-trimester APD of >10 mm were at increased risk of postnatal uropathy (odds ratio=10.35; 95% confidence interval, 1.80-59.60; p=0.01), whereas third-trimester APD of ≥9 mm also demonstrated a significant risk (odds ratio=8.56; 95% confidence interval, 1.03-71.30; p=0.04). Third-trimester APD better predicted both postnatal uropathy and need for surgical intervention than second-trimester APD (p≤0.001). The respective best cutoff above which postnatal uropathy and surgery was anticipated were 7.3 mm and 9.6 mm in the third trimester (sensitivity 75% and specificity 76.7% for postnatal uropathy, 100% and 93.3% for surgery).
Conclusion: Fetal renal pelvis APD, particularly when measured during the third trimester, serves as a good predictor of postnatal uropathy and need for surgical intervention. Measurement of the APD remains the most important factor in predicting fetal urological outcome.
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Keywords: Hydronephrosis; Kidney pelvis; Prenatal diagnosis; Ultrasonography; Urethral obstruction

Introduction

Antenatal hydronephrosis (ANH), also known as fetal pyelectasis or dilatation of the fetal renal collecting system, is one of the most common abnormalities detected on antenatal ultrasound examination. Depending on the diagnostic criteria used to define ANH, it is reported in approximately 1% to 5% of all pregnancies[1]. ANH is twice as common in male fetuses as female[2]. It is proposed that the increased voiding pressure in male fetuses in utero causes the higher prevalence of ANH[3]. Isolated ANH has been suggested to have association with Down syndrome and most other chromosomal abnormalities[4,5], especially when additional sonographic markers are present[6]. Therefore, in fetuses with other structural abnormalities or soft markers of aneuploidy, the option of fetal karyotyping should be considered[4-7].

A variety of physiological changes in pregnancy may influence the fetal renal pelvis. ANH is 6 times more likely to occur in fetuses of mothers who themselves demonstrate hydronephrosis[7]. The relaxant effect of progesterone on the smooth muscle of the urinary tract is considered a cause for maternal hydronephrosis in pregnancy, and the same hormonal effect is likely to influence the fetal urinary tract[2]. Maternal hydration signified by maternal bladder

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fullness was found to be associated with larger fetal renal diameter by Babcook et al[8]. A study of 18 women showed that in nearly one-third of mild ANH cases, the fetal renal pelvis diameter varied according to the bladder volume, suggesting variability in the fetal renal pelvis during a bladder filling cycle[9]. Although the majority of ANH cases (41%-88%) are transient hydronephrosis with no obstructive pathology identified, ANH may signify an underlying urinary obstructive disease, such as pelvi-ureteric junction obstruction (PUJO) in 10% to 30%, vesicoureteral reflux (VUR) in 10% to 20%, or urethral obstruction or megaureters in 5% to 10% of cases[1]. Prognosis depends on a variety of factors, including the degree of ANH, amniotic fluid volume, and the presence of bilateral lesions. Evaluation and treatment of uropathy after delivery can be extensive. The diagnosis of ANH may cause significant parental anxiety[1,10].

Clinical practice varies widely regarding the evaluation of ANH fetuses. There is no uniform definition or grading for ANH in the antenatal or postnatal period. The most widely used objective parameter in current literature is the measurement of the fetal renal pelvis anteroposterior diameter (APD)[1,3,7,11,12]. Because of its simplicity, APD is favoured by 91% of maternal-fetal medicine (MFM) specialists for evaluation of ANH[13]. Several APD cutoffs above which uropathy is suspected have been considered in the literature. The majority of these vary between 4 mm and 10 mm in the second trimester and between 7 mm and 10 mm in the third trimester, with APD >10 to 15 mm being highly suggestive of significant urinary tract pathology[3]. A grading system based on APD was published by the Society of Fetal Urology (SFU) in 2010. During the second trimester, the SFU system defines ANH as mild for APD of 4 to <7 mm, moderate for 7 to 10 mm, and severe for >10 mm. During the third trimester, mild ANH is defined as APD of 7 to <9 mm, moderate as 9 to 15 mm, and severe as >15 mm. According to a large meta-analysis, the risks of having postnatal uropathy are 11.9% for mild, 45.1% for moderate, and 88.3% for severe ANH[14].

There were three main objectives of our study. Firstly, we aimed to describe the maternal and fetal characteristics of isolated ANH cases. Secondly, we wanted to be able to address parental concerns by providing local data on the antenatal and postnatal outcomes once ANH is diagnosed, based on the SFU APD system, to compensate for the paucity of local data. Lastly, our study tried to determine the most effective APD cutoff value in the second and third trimester to predict postnatal uropathy and the need for urological surgery.

Methods

The prenatal diagnosis clinic (PDC) in the study hospital receives referrals from both the private sector and the antenatal clinic of our obstetric unit. The PDC has a well-established MFM team led by MFM subspecialist consultants with standard follow-up protocols. Once a case is referred to the PDC for ANH, detailed follow-up ultrasound scans in the second and third trimester are arranged. The maximum renal pelvis APD is measured in a transverse mid-abdominal plane showing the fetal kidneys. The fetal size, amniotic fluid index, and any other abnormalities in the fetal urinary tract are recorded. Fetuses with bilateral or unilateral APD of >7 mm in the third trimester are referred to the paediatrician for assessment in the postnatal nursery after delivery. Ultrasound of the urinary tract will be arranged by the paediatrician on postnatal day 3 to confirm the diagnosis and determine the severity of hydronephrosis, and avoid the false-negative effect due to physiological dehydration and oliguria[15,16]. The diagnoses of postnatal ultrasounds performed in the Department of Diagnostic Radiology were recorded. Additional diagnostic tests such as micturating cystourethrogram were performed according to paediatric protocols to identify postnatal uropathy. When APDs were <4 mm in the second trimester and <7 mm in the third trimester, ANH was considered resolved. The urological outcome for these fetuses were also retrieved for review.

A retrospective review of all cases referred to the PDC over a 21-month period from 1 January 2013 to 30 September 2014 was performed. All ultrasound examination reports at the PDC during the study period were retrieved and those specifically referred for ANH were identified. All other cases, especially those referred for amniotic fluid volume and fetal urological abnormalities, were reviewed in detail and those found to have ANH were also included in the study. The SFU APD system was adopted to define ANH in the current study. Cases diagnosed to have multicystic kidney dysplasia were excluded.

Postnatal uropathy was selected as the main event of interest because the management of uropathy can be extensive, may include surgery, and causes significant anxiety to parents[10], and only conservative management is needed once normal urological anatomy is verified after delivery. The degree of worry that parents experience concerning the prognosis of uropathy is observed to be much more than that regarding conservative management in cases of normal anatomy. Fetuses referred for scan in the third trimester were studied. Maternal characteristics including age, body mass index (BMI), parity, smoking

history, history of ANH in previous pregnancies, Down syndrome screening result, as well as presence of gestational diabetes mellitus (GDM) were recorded. If Down syndrome screening showed a high risk of chromosomal abnormality, the results of confirmatory tests were retrieved. The APDs in both second and third trimester were traced in order to determine the effectiveness of APD in prediction of postnatal urological outcome. Unilateral or bilateral involvement, which kidney was involved, ANH grading, fetal sex, fetal size, and amniotic fluid volume were also studied and compared.

There is considerable variation among different studies with respect to methodology and study design. Contrary to some studies in which the larger APD was used if ANH was bilateral[11], we adopted a 'renal unit' comprising a kidney with the ipsilateral ureter down to the level of vesicoureteric junction as the basis of study, so that the clinical course of the kidneys could be better assessed, as in some other studies[7,13,17-22].

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (Windows version 22.0, SPSS Inc., Chicago [IL], US). For continuous variables, descriptive statistics were presented as mean with standard deviation. Differences in means of groups were compared using independent *t* test. Categorical variables were reported as percentages and were analysed with Pearson Chi-square test and Fisher's exact test. Multiple logistic regression was used with verification of collinearity among variables. Adjustment for confounders was carried out. Odds ratio (OR) with 95% confidence interval were calculated to determine the relationship between the APD and uropathy. Receiver operating characteristic (ROC) curves were used to assess the performance of APD in the second and third trimester in the prediction of postnatal uropathy and the need of surgical intervention. Area under the curve (AUC), sensitivity, and specificity of different APD cutoffs were calculated. Statistical significance was established for p value of <0.05.

Results

All 4010 ultrasound examination reports issued by the PDC during the 21-month study period were retrieved and studied carefully. Four fetuses were found to have multicystic kidney dysplasia and were excluded from the analysis. A total of 146 fetuses with 291 renal units were referred to the PDC for follow-up scans for ANH in the third trimester, together with another seven new referrals. The outcome for these 153 fetuses with 305 renal units scanned are shown in Figure 1. Among these 153 fetuses, nine were lost to follow-up and hence excluded from subsequent statistical analysis. The 287 kidneys from the remaining 144 fetuses were studied. ANH was detected in 36 fetuses unilaterally and 31 fetuses bilaterally in 67 fetuses, giving rise to 98 renal units for analysis.

Although the majority of kidneys with ANH (89/98, 90.8%) were found to have normal anatomy after birth, nine (9.2%) of these 98 kidneys in eight infants exhibited postnatal uropathy. Among these eight infants, three who had unilateral ANH in the third-trimester scan were also found to have uropathy in the contralateral kidney after delivery, accounting for three (1.6%) false-negative cases in these 189 kidneys scanned normal before. Therefore, 12 kidneys in eight fetuses in total were identified to have postnatal uropathy in our study.

Comparison of maternal age, BMI, parity, smoking history, history of ANH in previous pregnancies, and presence of GDM revealed no significant differences between the two groups. All fetuses diagnosed to be high risk on Down syndrome screening underwent confirmatory tests in the current study and all were confirmed to have a normal karyotype. Down syndrome screening results did not differ much in both groups (Table 1).

Bilateral involvement and male gender did not show a significant increase in risk (OR=0.85; p=0.82 and OR=0.36; p=0.19, respectively). The APDs in the second and third trimester were studied. The distribution of kidneys with different ANH grades in both trimesters is shown in Table 1. Multivariate analysis with adjustment of confounding factors showed that fetuses with second-trimester severe ANH, i.e. APD of >10 mm, were at increased risk of postnatal uropathy (OR=10.35; p=0.01). Concerning the third-trimester ANH grading, only the moderate/severe ANH group, i.e. APD of ≥9 mm, demonstrated a significant risk of postnatal uropathy (OR=8.56; p=0.04).

Increase in APD in the second trimester did not predict postnatal uropathy well (OR=1.09; p=0.55) although increase in the third trimester significantly increased the risk (OR=1.91; p<0.001). The ROC curves for the APD in the second and third trimester in predicting postnatal uropathy and need for surgical intervention are displayed in Figures 2 and 3. The AUC of each ROC curve was calculated. Of note, the AUC can be interpreted as the probability that a randomly selected individual from the positive group has a larger APD than whom from the negative group. The AUC for APD in the second trimester as an indicator for postnatal uropathy was 0.647 (p=0.12)

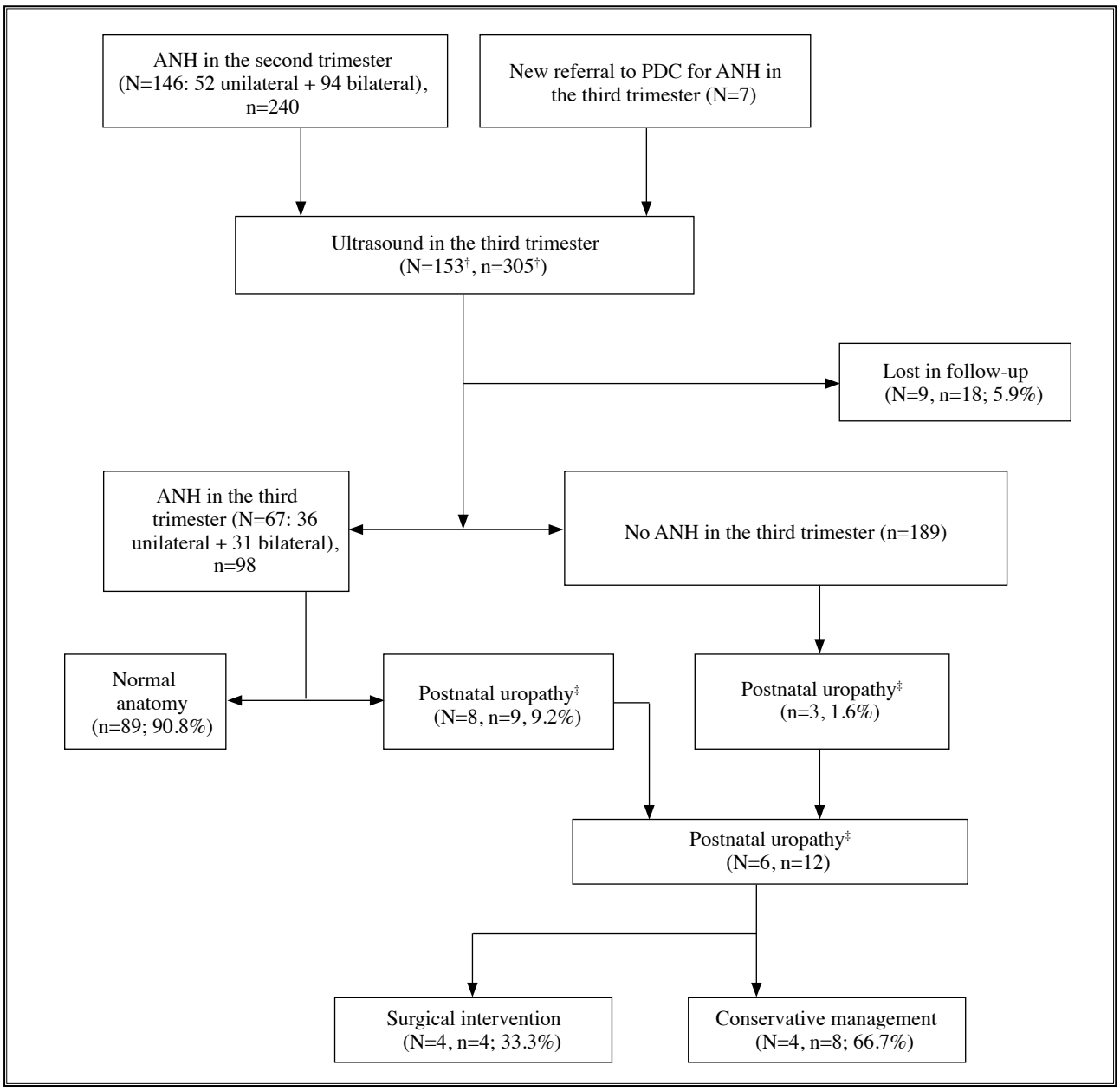

*Figure 1. Flowchart of the outcomes of fetuses and renal units**

Abbreviations: ANH = antenatal hydronephrosis; N = number of fetuses; n = number of renal units; PDC = prenatal diagnostic clinic.

* Percentages are calculated based on renal units

† One fetus had unilateral renal agenesis and ANH in the contralateral side

‡ Three kidneys with uropathy were found in the 189 renal units with no ANH in the third-trimester scan, the contralateral kidneys with ANH were detected already, giving rise to 8 fetuses with 12 pathological renal units in total (details are shown in Table 3)

while that in the third trimester was 0.843 ($p<0.001$). The AUC for APD in the second trimester as an indicator for postnatal surgery was 0.682 ($p=0.21$) while that in the third trimester was 0.986 ($p=0.001$). The third-trimester APD performed better in prediction of both postnatal uropathy and need for surgical intervention than the second trimester APD ($p\leq0.001$). The best APD cutoffs for prediction of postnatal uropathy and postnatal surgery were determined by maximising the sensitivity, i.e. true-positive rate together with specificity, i.e. true-negative rate. The best cutoffs above which postnatal uropathy and surgery can be anticipated were 6.9 mm and 10 mm respectively in the second trimester, and 7.3 mm and 9.6 mm respectively in the third trimester. The sensitivity and specificity of

Table 1. Comparison of maternal and fetal characteristics of third-trimester ANH cases with postnatal uropathy*

	Normal anatomy (n=89)	Uropathy identified (n=9)	p Value	Odd ratio (95% confidence interval)	p Value
Maternal age at booking visit (years)	30.29 ± 4.30	30.33 ± 5.61	0.98	1.01 (0.83-1.23)	0.91
BMI at booking visit (kg/m^2)	22.39 ± 3.30	21.26 ± 2.45	0.33	0.97 (0.72-1.30)	0.82
Parity			0.49	0.32 (0.05-2.04)	0.23
0	37 (42)	5 (56)			
≥1	52 (58)	4 (44)			
Smoking history			1.00	-	-
Non-smoker	83 (93)	9 (100)			
Ex-smoker / current smoker	6 (7)	0			
History of ANH in previous pregnancy			1.00	-	-
No	85 (96)	9 (100)			
Yes	4 (4)	0			
NT (MoM)	1.02 ± 0.26	0.84 ± 0.42	0.26	0.23 (0.02-2.92)	0.26
AFP (MoM)	1.13 ± 0.21	0.69 ± 0.00	0.16	0.00 (0.00-0.01)	0.99
bHCG (MoM)	1.13 ± 0.61	5.76 ± 10.94	0.001	1.96 (0.83-4.63)	0.13
PAPP-A (MoM)	0.97 ± 0.49	1.41 ± 1.93	0.16	1.71 (0.75-3.92)	0.20
Down syndrome screening result			0.31	5.38 (0.32-89.41)	0.24
Low risk	71 (80)	6 (67)			
High risk	3 (3)	1 (11)			
Not done	15 (17)	2 (22)			
GDM			0.05	1.66 (0.25-11.00)	0.60
Yes	76 (85)	5 (56)			
No	13 (15)	4 (44)			
Gestational age at scan (days)	241.81 ± 10.74	251.56 ± 9.55	0.01	1.15 (1.06-1.24)	0.001
Laterality in third trimester			0.82	0.85 (0.21-3.34)	0.82
Bilateral	53 (60)	5 (56)			
Unilateral	36 (40)	4 (44)			
Kidney side			0.73	1.66 (0.41-6.78)	0.48
Left	49 (55)	4 (44)			
Right	40 (45)	5 (56)			
APD in second trimester (mm)	6.58 ± 2.20	7.10 ± 3.89	0.56	1.09 (0.81-1.47)	0.55
ANH grading in second trimester					
Normal	1 (1)	1 (11)	0.12	1.00†	†
Mild	45 (51)	2 (22)	0.07	0.26 (0.05-1.42)	0.12
Moderate	24 (27)	2 (22)	1.00	0.83 (0.15-4.61)	0.84
Severe	5 (6)	3 (33)	0.03	10.35 (1.80-59.60)	0.01
Missing APD	14 (16)	1 (11)	-	-	-

Abbreviations: AFP = alpha fetoprotein; AGA = appropriate for gestational age; ANH = antenatal hydronephrosis; APD = anteroposterior diameter; bHCG = beta human chorionic gonadotropin; BMI = body mass index; GDM = gestational diabetes mellitus; LGA = large for gestational age; MoM = multiple of median; NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A; SGA = small for gestational age

* Data are shown as mean ± standard deviation or No. (%)

† Fetuses with normal APD were selected as the reference group

‡ Moderate and severe ANH groups were combined because of presence of zero cell count

Table 1. (cont'd)

	Normal anatomy (n=89)	Uropathy identified (n=9)	p Value	Odd ratio (95% confidence interval)	p Value
APD in third trimester (mm)	8.73 ± 1.67	13.22 ± 3.49	0.000	1.91 (1.38-2.65)	0.000
ANH grading in third trimester					
Mild	46 (52)	1 (11)	0.03	0.12 (0.01-0.97)	0.05
Moderate	43 (48)	5 (56)	0.74	8.56 (1.03-71.30)‡	0.04‡
Severe	0	3 (33)	0.001	‡	‡
Fetal sex			0.37	0.36 (0.08-1.67)	0.19
Male	73 (82)	6 (67)			
Female	16 (18)	3 (33)			
Fetal size			0.59		
AGA	78 (88)	9 (100)		-	-
SGA	0	0		-	-
LGA	11 (12)	0		-	-
Liquor volume			1.00		
Normal	87 (98)	9 (100)		-	-
Decreased	0	0		-	-
Increased	2 (2)	0		-	-

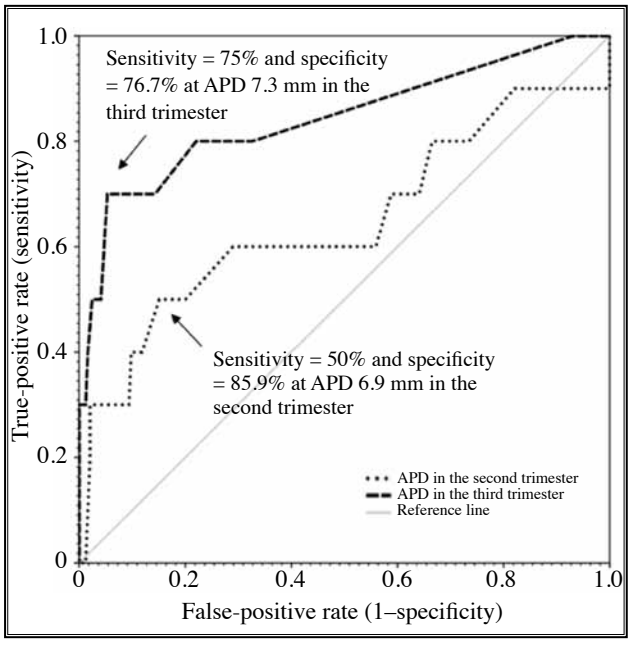

Figure 2. Renal pelvis anteroposterior diameter (APD) to predict postnatal uropathy

Area under the curve for APD in the second trimester was 0.647 (95% confidence interval, 0.430-0.863, p=0.12), and that in the third trimester was 0.843 (95% confidence interval, 0.685-1.000, p<0.001)

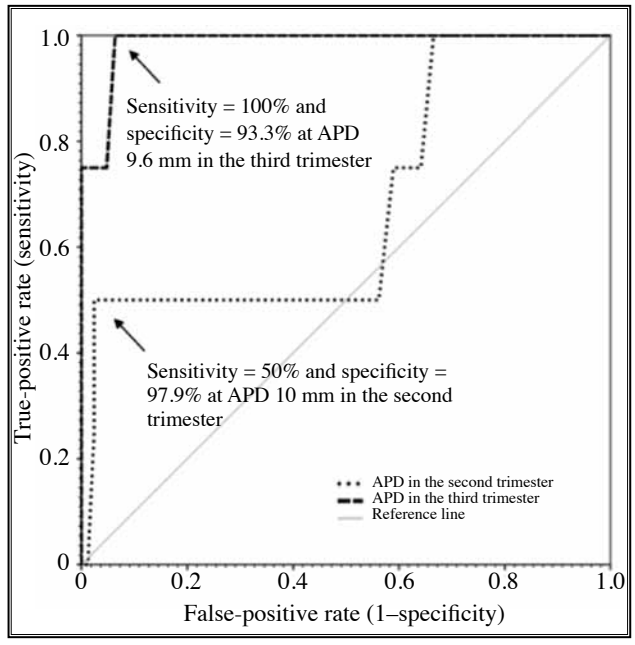

Figure 3. Renal pelvis anteroposterior diameter (APD) to predict postnatal surgical intervention

Area under the curve for APD in the second trimester was 0.682 (95% confidence interval, 0.388-0.977, p=0.21), and that in the third trimester was 0.986 (95% confidence interval, 0.961-1.000, p=0.001)

different APD cutoffs are shown in Table 2 and Figures 2 and 3.

Discussion

The current definition of ANH is variable and management shows diversity among different centres. There is little agreement on the best protocol for follow-up. Over decades different diagnostic systems have been proposed to establish a threshold value to distinguish normal fetal renal pelvis dilatation from pathological cases. The SFU proposed a five-grade system in 1993 based on the ultrasound appearance of the renal parenchyma and pelvicalyceal system[1]. This SFU system has been shown to have good intra-rater, but fair inter-rater reliability[23]. While Zhan et al[24] used an ultrasound scoring system comprising renal pelvic dilatation together with parenchymal thickness and pelvicalyceal morphology for 158 Chinese fetuses, Leung et al[25] from a local tertiary centre advocated a different fetal hydronephrosis index with incorporation of the volume of fetal urinary bladder, so eliminating the confounding effect of a full bladder. Both showed promising results. Recently in mid-2014, a multidisciplinary panel produced a consensus on the classification of prenatal and postnatal urinary tract dilatation in order to promote effective and accurate communication between different specialists[26]. Apart from the SFU definition of ANH based on APD, additional sonographic features of fetal renal parenchyma, bladder and ureters were included in the risk stratification. Extensive evaluation will be required to assess its effectiveness in predicting fetal outcome in the future. To date, APD remains the most widely used parameter in the management of ANH. Corteville et al[27] recommended an APD of >4 mm before 33 weeks of gestation, and >7 mm after 33 weeks of gestation to warrant postnatal follow-up. Some authors proposed that the risk of significant postnatal uropathy would be minimal if APD was <10 mm in the third trimester[17], whereas Gotoh et al[28] suggested that surgery would not be necessary if APD was <20 mm between 30 and 40 weeks of gestation.

The diagnosis of ANH causes significant parental anxiety and obstetrician's uncertainty in management. Counselling of parents is often based on the obstetrician's personal knowledge and belief[1,10,18]. Our data showed that the vast majority of ANH cases in the third trimester turned out to have normal urological anatomy (89/98, 90.8%).

Table 2. Efficacy of different renal pelvis APDs in predicting postnatal urological outcomes*

APD (mm)	Prediction of postnatal uropathy				Prediction of postnatal surgery			
	Second trimester		Third trimester		Second trimester		Third trimester	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
≥3	92.9	16.1	1.00	1.5	100	16.4	100	1.3
≥4	85.7	29.3	1.00	4.1	100	30.6	100	4.0
≥5	64.3	61.8	1.00	7.8	50.0	61.2	100	7.3
≥6	50.0	81.1	75.0	66.7	50.0	80.4	100	65.7
≥7	42.9	89.2	75.0	76.3	50.0	88.6	100	75.3
≥8	35.7	93.6	56.3	83.7	50.0	93.2	100	83.7
≥9	28.6	96.4	56.3	94.1	50.0	96.1	100	93.0
≥10	21.4	98.0	37.5	95.6	50.0	97.9	75.0	95.0
≥11	0.00	98.8	37.5	97.4	0.00	98.9	75.0	96.7
≥12	0.00	99.2	31.3	98.5	0.00	99.3	75.0	98.0
≥13	0.00	100	25.0	98.9	0.00	100	75.0	98.7
≥14	NA	NA	25.0	100	NA	NA	75.0	99.7
≥15	NA	NA	18.8	100	NA	NA	50.0	99.7
≥16	NA	NA	12.5	100	NA	NA	50.0	100
≥17	NA	NA	6.3	100	NA	NA	25.0	100
≥18	NA	NA	0.00	100	NA	NA	0.00	100

Abbreviations: APD = anteroposterior diameter; TPR = true-positive rate; TNR = true-negative rate; NA = not available

* Data are shown as TPR (sensitivity) or TNR (specificity) in percentages

Compliance with postnatal follow-up is all that is needed for these cases.

Although the left kidney has been shown to be more likely to develop ANH[29], our study did not confirm a prevalence of ANH and uropathy in the left kidney, and side of kidney involvement was unrelated to clinical outcome (OR=1.66; p=0.48). Male fetuses are more likely to be affected by ANH, in accordance with a male predominance of various postnatal uropathies[3,30,31]. Bilateral hydronephrosis is of greater concern particularly in a male fetus with abnormal amniotic fluid volume[32,33]. Both bilateral involvement and male gender were not shown to have a significant risk for developing uropathy in the current study (OR=0.85; p=0.82 and OR=0.36; p=0.19 respectively). One reason might be the relatively small incidence of the outcome of interest, i.e. postnatal uropathy in our study.

Studies that have quantified the risk of postnatal uropathy for different ANH grades are limited, especially when APD is used for grading severity of ANH. Lee et al[14] summarised the risk of postnatal uropathy as 11.9% for mild, 45.1% for moderate, and 88.3% for severe ANH. ORs were used in the current study to express risk of adverse fetal urological outcome. When only second-trimester APD was considered, severe ANH, i.e. APD of >10 mm, had an upsurge in postnatal uropathy (OR=10.35; p=0.01). There was a more than 8-fold increase in the risk of postnatal uropathy for the moderate/severe ANH group in the third trimester when APD was ≥9 mm (OR=8.56; p=0.04). These findings support the suggestion according to the review issued by a multidisciplinary panel that moderate and severe ANH warrant an ultrasound evaluation to determine progression of urinary tract dilatation[26]. These data are beneficial in providing information to facilitate prenatal counselling.

The statistical significance of high AUC for third-trimester APD (Figures 2 and 3) shows that APD in the third trimester is useful to predict both postnatal uropathy and need for surgical intervention. It was consistent with the comment by Bouzada et al[12] that APD after 28 weeks of gestation is a simple and efficient tool to screen for possible significant uropathy and the AUC quoted was 0.900. The best APD cutoff for prediction of postnatal uropathy in our study was 7.3 mm in the third trimester, when we tried to maximise the sensitivity but not deprive the specificity much, hence giving a higher true-positive rate and a lower false-negative rate. These findings are comparable with those of Corteville et al[27] who recommended a cutoff at 7 mm in the third trimester. A systematic review by Ismaili et al[34] also proposed the cutoff at 7 mm. The recommendation by Corteville et al[27] was criticised for the high false-positive rate, APD ≥4 mm prior to 33 weeks of gestation and ≥7 mm after 33 weeks showed a sensitivity of 100% and false-positive rates of 30% to 80%[3], similar to the finding of Bouzada et al[12] that the sensitivity and specificity for the best cutoff at 7.5 mm was 97.9% and 40.6%, respectively. On the contrary, the third-trimester APD of 7.3 mm from our analysis achieved a balance between sensitivity and specificity in predicting postnatal uropathy and need for surgery (sensitivity 75% and specificity 76.7%). The sensitivity and specificity of the APD at 7 mm as the best cutoff in a study of similar sample size to ours was 87% and 85%, respectively[35].

Different cutoff values are chosen in different centres, depending on the sensitivity and specificity required. The best cutoff for need for surgical intervention is more variable among different studies, ranging mostly from 10 mm to 15 mm[7,11,12,20,36], possibly because the need for postnatal surgery may be influenced by a variety of factors such as pathology, postnatal renal function, difference in the surgeon's practice, and parental preference. The APD cutoff for prediction of the need for postnatal surgery at 9.6 mm in our study showed high sensitivity of 100% and specificity of 93.3%. In view of the good predictive value of third-trimester APD as shown by various studies and our analysis, an institute may consider delaying the follow-up scan to the third trimester when a fetus is referred for ANH at an earlier gestation, especially when ANH is mild. The reduced frequency of investigations decreases parental anxiety[10], and perhaps also allows better allocation of manpower and resources in a busy PDC. Further research will help to verify the best time of evaluation for ANH cases.

Eight infants with 12 renal units were found to have postnatal uropathology in our study (Table 3). Consistent with the prevalence in the current literature, PUJO and VUR remained the most common pathologies. Postnatal uropathy was chosen as the major outcome of interest in our analysis as the need to undergo surgical intervention may be influenced by a variety of factors. In addition, most postnatal uropathy can be detected in early infancy. Other limitations of our study include those common to most other retrospective studies. The retrospective nature of data collection may lead to incompleteness of data for analysis. Larger-scale study and longer follow-up are preferable. Postnatal events such as urinary tract infection[37-39] take time to develop, and the need for surgical intervention may

Table 3. Summary of the eight infants with postnatal uropathy

Case No.	Sex	Renal pelvis anteroposterior diameter (mm)				Postnatal uropathy (12 renal units)	Management
		Second trimester		Third trimester			
		Left	Right	Left	Right		
1	Male	4	3	6*	12†	Bilateral grade 5 VURs	Conservative
2	Male	NA	NA	6*	16†	Left grade 2 VUR Right grade 3 VUR	Conservative
3	Male	9.1	10.6	9	14†	Right PUJO	Right pyeloplasty
4	Male	4.8	8.1	17†	6	Left distal ureteric stricture	Resection of stricture
5	Female	10	7.9	11†	8†	Left grade 4 VUR Right grade 3 VUR	Conservative
6	Male	11	5.8	15†	8	Left PUJO	Left pyeloplasty
7	Male	6	11	6*	13†	Bilateral ureteroceles	Conservative
8	Female	4.5	4.8	10†	10	Left megaureter	Insertion of J-J stent

Abbreviations: NA = not available; PUJO = pelvi-ureteric junction obstruction; VUR = vesicoureteric reflux

* Three false-negative cases in the 189 renal units with no antenatal hydronephrosis identified in the third-trimester scan

† Nine true-positive cases in the 98 renal units with antenatal hydronephrosis identified in the third-trimester scan

evolve in later infancy, thus longer observation might be needed. The subjective nature of antenatal and postnatal ultrasound examinations may be a confounder. Data on features of renal parenchyma, calyces and ureters were not consistently obtained, and they might reflect more severe obstructive uropathy.

The strength of our study is that all fetuses were followed up in a single antenatal ultrasound unit with good standard and consistency in definition and care of ANH throughout. We had a low proportion of cases lost to follow-up compared with some other studies (Figure 1). Lee et al[14] reported in a meta-analysis that 246 (15%) of 1678 patients with ANH were lost to follow-up. Last but not least, our study helps in the provision of local data on ANH. We hope the results of this analysis will be useful in our prenatal counselling and relief of parental anxiety.

In conclusion, fetal renal pelvis APD, particularly when measured in the third trimester, serves as a good predictor of postnatal uropathy and need for surgical intervention. Anteroposterior diameter measurement remains the most important factor in predicting fetal urological outcome. The best APD cutoff in the prediction of postnatal urological outcome depends on the choice of sensitivity and specificity of the test.

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Obstetric Outcome for Pregnant Women with Asymptomatic Bacteriuria in Hong Kong

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Objective: To determine the prevalence of asymptomatic bacteriuria (ASB) and its effects on the obstetric outcome in Hong Kong pregnant women.
Methods: This was a 6-month prospective observational study carried out in a local obstetric unit, from December 2011 to June 2012. Singleton pregnant women who attended their first antenatal visit during the first trimester, and without symptoms of urinary tract infection (UTI) were recruited. Midstream urine was collected. ASB was defined as a positive culture of $>10^5$ colony forming units per ml (CFU/ml) in the absence of white blood cells on microscopy. Treatment was given as appropriate. Their obstetric outcome was evaluated by statistical analysis using odds ratio, t test, and Chi-square test to determine significance.
Results: The incidence of ASB and UTI was 1.7% and 1.6%, respectively. For ASB, the most commonly isolated bacteria was *Escherichia coli* (38.1%) followed by *Streptococcus agalactiae* (19.0%). Compared with the control group, the maternal age was younger in the ASB group, but no differences were found in the other characteristics. There was significantly higher risk of neonatal intensive care unit admission and pre-eclampsia with respective odds ratio of 4.2 and 6.8 in the ASB group, but no significant difference was noted in the other outcomes. There was significantly higher risk of low-birth-weight baby (<1500 g) in the borderline bacterial count ($\geq 10^4$ and $<10^5$ CFU/ml) group with an odds ratio of 5.9.
Conclusion: There was a higher risk of adverse obstetric outcome in Hong Kong pregnant women with ASB detected during the first trimester.
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Keywords: Bacteriuria; Infant, low birth weight; Infant, premature; Pyelonephritis

Introduction

Asymptomatic bacteriuria (ASB) is defined as the presence of a significant quantity of bacteria in a properly collected urine specimen from a person without symptoms or signs of urinary tract infection (UTI)[1]. Being asymptomatic, this condition cannot be detected without a screening test. The prevalence of ASB during pregnancy ranges from 2% to 15% in worldwide literature reports[2-5]. A recent local study conducted by our group, which included all pregnant women attending their first antenatal visit in all trimesters, showed that 8.2% and 2.0% of the Hong Kong pregnant population had ASB of 104 colony forming units per ml (CFU/ml) and 105 CFU/ml in the culture of midstream urine (MSU), respectively[6].

The current literature on this topic was inconclusive in establishing the relationship between ASB and adverse pregnancy outcome. A prospective study showed that 75% of young women had spontaneous clearance of asymptomatic bacteriuria[7]. Meta-analysis showed that non-bacteriuric patients had half the risk of preterm delivery and two-thirds the risk of low birth weight when compared with bacteriuric patients[8]. Nonetheless multivariate analysis in a study in Wales showed that bacteriuria was not significantly associated with spontaneous preterm birth[9]. In the Cochrane review meta-analysis, antibiotic treatment for ASB during pregnancy could reduce the risk of pyelonephritis and low birth weight but not the risk of preterm delivery or subsequent morbidities[10].

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There are lack of local data for determining the prevalence and the obstetric complications in women with ASB and currently no standardised screening of MSU for ASB in Hong Kong[11]. Furthermore, there was also discrepancy in the definition of ASB in different literature reports. The most common reported definition was the presence of bacterial count of $\geq 10^5$ CFU/ml for urine cultured in the laboratory[1,3]. Nonetheless some reports also used $\geq 10^4$ CFU/ml as significant for young women[4,12]. Despite the reported figures, the standard of laboratory practice, including days of culture and types of culture medium used, would also vary in different centres. This explains the importance of performing this study in our local standardised laboratory in order to determine a reasonable outcome for our population. We postulate that if ASB is associated with adverse pregnancy outcome, the detection and hence treatment of women with ASB may reduce the associated morbidities and perinatal mortality.

Methods

This prospective observational study was carried out in a local tertiary obstetric referral centre. The study protocol was approved by the Research Ethics Committee (Kowloon Central / Kowloon East) of Hospital Authority (KC/KE-11-0157/ER-1). All pregnant women who attended their first visit in the antenatal clinic during the first trimester from December 2011 to June 2012 were recruited and informed consent was obtained before all study procedures. Screening for ASB was performed during their first visit in the first trimester[13]. Due to manpower limitations in our single local centre, women who had their first antenatal visit after the first trimester were not recruited, nor were those with the following characteristics: unable to give an informed consent for any reason, refused to give an informed consent, second trimester or later, presented with dysuria at the first antenatal visit suggestive of possible underlying UTI, and multiple pregnancy (Figure).

Women were instructed by investigators to collect their MSU sample in a sterile boric acid container. They were advised to clean the perineum prior to collection of urine to reduce the chance of contamination or false-positive result. Twenty ml of fresh-voided MSU was saved in each case. The sample was sent for processing on the same day in the laboratory accredited by the National Association of Testing Authorities, Australia (NATA) / Royal College of Pathologists of Australasia (RCPA) [No. 14238].

Women were diagnosed with ASB by pure laboratory criteria defined as a urine sample that showed

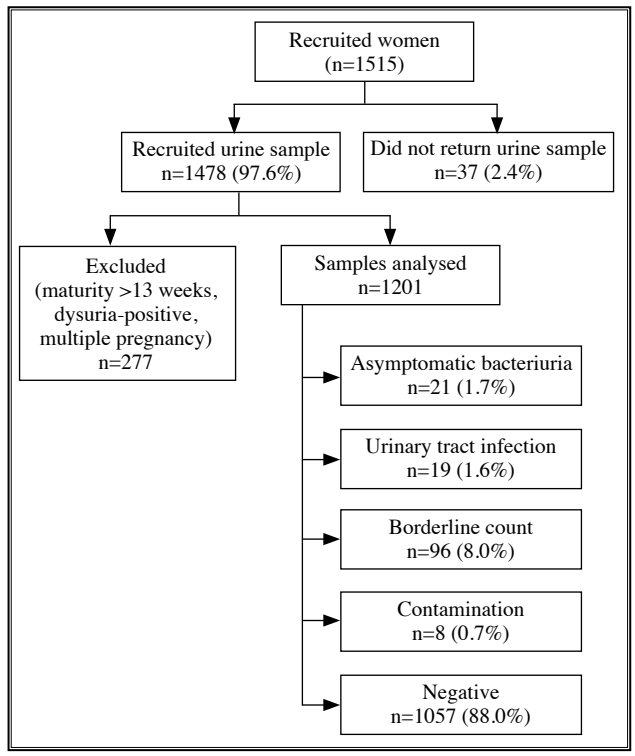

Figure. Procedure for case recruitment and midstream urine sample saving

no white blood cells on microscopy and yielded growth of ≥105 CFU/ml in the culture medium.

If the urine samples showed presence of white cells on microscopy and yielded culture growth of an organism, they were managed as having UTI and a course of antibiotics was prescribed according to the culture sensitivity to prevent complications of ascending UTI and sepsis. Post-treatment MSU was sent for culture and microscopy to confirm bacterial clearance. When women were found to have ASB, which was defined as a positive urinary bacterial count $\geq 10^5$ CFU/ml, they were notified. Counselling was given in the out-patient setting and the potential consequences of ASB in pregnancy from literature reports were explained to the patient in detail. We then advised a course of antibiotics according to the culture and sensitivity result. If they declined antibiotic treatment, an alternative of repeating the MSU for microscopy and culture would be offered as literature reports have shown that there is a possibility of spontaneous clearance of ASB without treatment in young women[7]. Even though these women completed the study process, their future MSU results would be monitored and they would be counselled during the subsequent antenatal visit as these reports were filed in their antenatal record. Those women with an MSU containing bacterial count of $\geq 10^4$ and $<10^5$ CFU/ml were considered to have a borderline count. Antibiotic treatment was not routinely given because of the possibility

of contamination[4]. Nonetheless if urinary symptoms developed, or if the woman was worried and requested treatment, or if subsequent MSU showed significant bacterial count of $\geq 10^5$ CFU/ml, antibiotics were offered. Women with a urine sample that revealed no white cells on microscopy and yielded no growth on culture were considered to have a negative result and served as a control group.

The pregnancy outcomes for the successfully recruited women were retrieved from the electronic patient obstetric records of our tertiary referral obstetric centre. The primary outcome studied was the preterm delivery rate (i.e. before 37 weeks of gestation). Secondary outcomes included the rate of maternal UTI during pregnancy and within 6 weeks of delivery (defined as a positive urine culture with presence of white blood cells on microscopy), pyelonephritis (defined as presence of fever, loin pain and a positive urine culture with presence of white blood cells on microscopy), and pre-eclampsia (defined as blood pressure of ≥140/90 mm Hg on a minimum of two occasions 4 hours apart, together with presence of proteinuria [≥ 0.3 g per day during 24-hour urine collection or >0.3 g of protein per gram of creatinine in the spot urine protein-to-creatinine ratio]), birth weight of the baby, Apgar score at 1 and 5 minutes of life, and the rate of admission to the neonatal intensive care unit.

Data were analysed with the Statistical Package for the Social Sciences (SPSS) 22.0 for Mac. Demographic data were described by descriptive statistics in terms of mean, and statistical analysis was performed using t test for continuous variables and Chi-square test for categorical variables. Univariate analysis logistic regression model was used to determine the correlation between the ASB and the possible associated adverse pregnancy outcome and odds ratio (OR) of 95% confidence interval (CI) was used to deduce the correlation. A $p<0.05$ was considered to be statistically significant for all statistical analyses.

Results

Characteristics of the Study Population

Of the 1515 women recruited, 1478 (97.6%) urine samples were collected. Urine samples were not returned by 37 women giving a default rate of 2.4%. After excluding women who were in the second trimester of pregnancy or later, those with dysuria and those with a multiple pregnancy (Figure), 1201 samples were identified and analysed. Using presence of a bacterial count of $\geq 10^5$ CFU/ml as the cutoff level, 21 (1.7%) women yielded a positive growth in their urine culture with no white blood cells on microscopy, and were considered to have ASB. A positive urinary culture and positive white cell count on microscopy was present in 19 (1.6%) women who were considered to have a UTI. A borderline count of $\geq 10^4$ but $<10^5$ CFU/ml was present in 96 (8.0%) women and eight (0.7%) had a positive growth of $<10^5$ CFU/ml with negative white blood cell count on microscopy. The latter refused a repeat urine sample and was therefore considered to be contaminated. In all, 1057 (88.0%) women yielded no growth in their urine culture (Figure).

All 19 women with UTI were prescribed antibiotics. Among the 21 women with ASB, five (23.8%) agreed to take a course of antibiotics and 14 (66.7%) requested after counselling to repeat their MSU sample. Among these 14 women, 12 (85.7%) yielded negative results on the subsequent MSU sample and the remaining two (14.2%) had contamination of the urine sample and refused further investigation or treatment. Two (9.5%) women were unable to be contacted.

Of the 1201 women who had saved their MSU sample, 887 (73.9%) subsequently delivered in our unit and the outcome of their pregnancy was retrieved from the electronic patient obstetric record. Thirty-one (2.6%) women suffered a miscarriage during the first trimester and one (0.1%) had a miscarriage during the second trimester. Termination of pregnancy was performed in 12 (1.0%) women due to various reasons including trisomies, fetal structural abnormalities, and maternal anxiety. A further 101 (8.4%) delivered at another hospital and 169 (14.1%) defaulted from follow-up. The outcome of their pregnancy could not be traced.

Among the 887 women who delivered in our unit, 779 (87.8%) had a negative culture of urine and served as controls, 16 (1.8%) had ASB, 12 (1.4%) had UTI, 69 (7.7%) had a borderline bacterial count, and 11 (0.8%) had a contaminated MSU sample.

The demographics of the women with ASB and the control group were analysed (Table 1). There was no significant difference between the two groups in the gestational age at time of urine saving, parity, education level, or history of UTI (Table 1). The mean maternal age of the ASB group was younger than the controls (28.7 years vs. 31.3 years, p=0.03).

Bacteriology

In all urine samples (n=135) with a positive culture (including women with ASB, UTI and borderline bacterial

count), *Staphylococcus* species was the most commonly isolated bacteria (n=44, 30.6%) followed by *Streptococcus* species (n=25, 17.4%) [Table 2].

Escherichia coli was the most commonly isolated bacteria in the ASB group (8/21 samples, 38.1%), followed by *Streptococcus agalactiae* (group B streptococcus [GBS]) [4/21 samples, 19.0%].

Obstetric Outcomes

Of these 887 women, 885 (99.8%) had a live birth in our unit. There were two cases of intrauterine death (2/779, 0.3%) in the control group and no cases in the ASB group. The intrauterine deaths occurred at 25 and 38 weeks of gestation and no cause was identified in either case. There was a significantly higher proportion of neonatal intensive care unit admission in the ASB group than in the control

Table 1. Comparison of demographics between pregnant women with asymptomatic bacteriuria and the controls*

Characteristic	Asymptomatic bacteriuria (n=16)	Controls (n=779)	p Value
Maternal age (years)	28.7 ± 4.3	31.1 ± 4.5	0.03
Gestational age at time of urine saving (weeks)	10.3 ± 0.9	10.1 ± 1.2	0.7
Parity			0.6
Nulliparous	11 (69)	454 (58)	
Multiparous	5 (31)	325 (42)	
History of urinary tract infection	5 (31)	337 (43)	0.9
Education level			0.09
Primary	0	11 (1)	
Secondary	6 (38)	447 (57)	
College	4 (25)	65 (8)	
University	6 (38)	256 (33)	

* Data are shown as mean ± standard deviation or No. (%) of women

Table 2. Isolated bacteria species present in midstream urine samples among women with asymptomatic bacteriuria and among all positive urine samples*

Species	Asymptomatic bacteriuria with count ≥105 (n=21)	All positive urine samples (n=144)
Staphylococcus species	0	44 (30.6)
Streptococcus species	0	25 (17.4)
Enterococcus species	1 (4.8)	13 (9.0)
Escherichia coli	8 (38.1)	12 (8.3)
Streptococcus agalactiae	4 (19.0)	10 (6.9)
Coliform organisms	1 (4.8)	7 (4.9)
Staphylococcus aureus	1 (4.8)	7 (4.9)
Coagulase-negative *Staphylococcus aureus*	0	6 (4.2)
Gram-negative bacilli	0	4 (2.8)
Candida species	0	4 (2.8)
Klebsiella species	2 (9.5)	3 (2.1)
Lactobacillus	2 (9.5)	3 (2.1)
Candida albicans	0	2 (1.4)
Acinetobacter	0	1 (0.7)
Beta-haemolytic *Streptococcus*	0	1 (0.7)
Non-haemolytic *Staphylococcus*	1 (4.8)	1 (0.7)
Non-haemolytic *Streptococcus*	1 (4.8)	1 (0.7)

* Data are shown as No. (%). Some samples may yield >1 strain of bacteria

group (25% vs. 7%, OR=4.2, 95% CI, 1.3-13.5) [Table 3]. Of the four cases who required neonatal intensive care unit admission, only one case was related to preterm delivery at 35 weeks due to pre-eclampsia. There was no other difference in the proportion of birth weight of <2500 grams, delivery before 37 weeks, before 34 weeks, before 28 weeks, or Apgar score of <7 at 1 minute and at 5 minutes of life between the ASB group and the controls.

Asymptomatic Bacteriuria

For maternal outcome, there was a significantly higher proportion of women with pre-eclampsia in the ASB group than in the controls (13% vs. 2%, OR=6.8, 95% CI, 1.4-32.5) [Table 3]. No significant difference was found in the risk of UTI and no case of pyelonephritis in either group.

Borderline Bacterial Count

Compared with the control group, women with a borderline bacterial count in their MSU sample had a significantly higher risk of low birth weight baby (<1500 g) with OR of 5.9 (95% CI, 1.1-32.6) [Table 4]. There were no differences in other outcomes.

Group B streptococcus

The incidence of ASB and UTI due to GBS was 0.8% only (9/1201 women) and seven (77.8%) of whom delivered at our unit. All these seven women carried to term (i.e. gestational age ≥37 weeks) and delivered a baby within the normal range of birth weight (>2500 g). Only

Table 3. Comparison of obstetric outcomes between asymptomatic bacteriuric group and the controls*

Variable	Asymptomatic bacteriuria (n=16)	Controls (n=777)	Odds ratio	95% Confidence interval
Delivery before 37 weeks	1 (6)	46 (6)	1.1	0.1-8.2
Delivery before 34 weeks	0	11 (1)	-	-
Delivery before 28 weeks	0	2 (0.3)	-	-
Birth weight <2500 g	1 (6)	52 (7)	0.9	0.1-7.1
Birth weight <1500 g	0	4 (1)	-	-
Apgar score <7 at 1 minute	1 (6)	17 (2)	3.0	0.4-23.9
Apgar score <7 at 5 minutes	0	4 (1)	-	-
Admission to neonatal intensive care unit	4 (25)	57 (7)	4.2	1.3-13.5†
Maternal urinary tract infection	0	20/779 (3)	-	-
Pre-eclampsia	2 (13)	16/779 (2)	6.8	1.4-32.5†

* Data are shown as No. (%) of women
† Statistically significant

Table 4. Comparison of obstetric outcomes between women with borderline bacteria count in midstream urine culture (count ≥10^4 and <10^5 CFU/ml) and the controls*

Variable	Borderline (n=69)	Controls (n=777)	Odds ratio	95% Confidence interval
Delivery before 37 weeks	6 (9)	46 (6)	1.5	0.6-3.7
Delivery before 34 weeks	2 (3)	11 (1)	2.0	0.5-9.6
Delivery before 28 weeks	1 (1)	2 (0.3)	5.7	0.5-63.7
Birth weight <2500 g	5 (7)	52 (7)	1.1	0.4-2.8
Birth weight <1500 g	2 (3)	4 (1)	5.9	1.1-32.6†
Apgar score <7 at 1 minute	3 (4)	17 (2)	2.0	0.6-7.1
Apgar score <7 at 5 minutes	1 (1)	4 (1)	2.8	0.3-25.8
Admission to neonatal intensive care unit	6 (9)	57 (7)	1.2	0.5-2.9
Maternal urinary tract infection	4 (6)	20/779 (3)	2.3	0.8-7.0
Pre-eclampsia	2 (3)	16/779 (2)	1.4	0.3-6.3

* Data are shown as No. (%) of women
† Statistically significant

one baby required admission to the neonatal intensive care unit due to transient tachypnoea of newborn.

Discussion

The incidence of ASB in this cohort was 1.7%, lower than in previous worldwide literature reports[2-5]. Consistent with a previous local study in 1970[14], the incidence of ASB in Chinese pregnant women was lower than that reported from other countries. This study may be criticised by the possible selection bias caused by exclusion of cases booked after the first trimester of pregnancy. Nonetheless the number of women excluded was 277 (18.7%) and only 158 (10.7%) were excluded due to late booking at second trimester, constituting a relatively small proportion of the total number of cases evaluated. Second, the prevalence of ASB and UTI will vary in different geographical areas since ethnicity, bacteriology, and socioeconomic status also vary in different countries and this may explain the possible relatively low prevalence of ASB in our local population.

The incidence of UTI in the first trimester was 1.6%. No subsequent risk of maternal UTI was identified in the ASB group. This was probably because of the small sample size. The incidence of UTI among all women was 2.2% (20/887 women). This incidence was relatively low compared with the incidence of UTI in non-pregnant women in the local population[15]. The lower incidence of UTI may be related to the low incidence of ASB.

Staphylococcus species and *Streptococcus* species were the most commonly isolated bacteria in women with a positive urine culture but neither was present in the ASB group. There may have been possible contamination by skin commensals due to the difficulty experienced by pregnant women in cleaning the genital region properly prior to urine saving[3].

Escherichia coli was the most commonly isolated bacteria in the MSU culture in the ASB group. The result was consistent with a local study of non-pregnant Hong Kong women[16] and also consistent with most other reported studies around the world[4,17,18]. Among the 12 samples that yielded *Escherichia coli*, two (16.7%) were positive for extended-spectrum beta-lactamases (ESBL), likewise a similar result of 14.3% reported in a local study[19]. In these two cases, both ESBL strains were sensitive to Augmentin which allows treatment by offering a course of oral antibiotics.

The incidence of ASB and UTI due to GBS was 0.8% only (9/1201 women). Isolation of GBS from the urine of pregnant women signifies heavy vaginal colonisation and the Royal College of Obstetricians and Gynaecologists guideline recommends intrapartum antibiotics to prevent early-onset GBS infection in neonates[20]. The incidence of GBS colonisation in MSU samples was much lower than that found in the lower vagina and rectum (10.4%) in another local study[21], or around 24% in universal prenatal screening. One possible reason for the low incidence could be due to the insensitivity of the cutoff level for diagnosis of GBS infection[22]. Our study only included MSU samples collected during the first trimester. With the low prevalence of GBS bacteriuria, the first-trimester MSU sample may not improve the identification of GBS colonisation above our current universal screening at 35 to 37 weeks' gestation in public hospitals.

There was no significant increase in the risk of preterm birth in the ASB group (OR=1.1, 95% CI, 0.1-8.2). There were no cases of preterm birth before 28 and 34 weeks in the ASB group. Nonetheless the risk of neonatal intensive care unit admission was significantly higher in the ASB group. This is contrary to previous literature reports that revealed no significant difference in the incidence of neonatal intensive care unit admission[1]. Of the four cases that required neonatal intensive care unit admission, only one case was related to preterm delivery at 35 weeks due to pre-eclampsia.

There was an increased risk of pre-eclampsia in women with ASB (OR=6.8, 95% CI, 1.4-32.5), consistent with other reported studies[23,24]. To date, the aetiology of pre-eclampsia has been well defined although literature reports are quite controversial[25]. Although the sample size of this study was relatively small, the high OR signifies the necessity of further investigation in this area and it may help to improve the maternal and fetal outcomes with earlier prediction of its occurrence.

Since some literature reports used a bacterial count of 10^4 CFU/ml as the cutoff for defining ASB[4,12], results of the borderline count and the control group were also studied (Table 4). There was a significantly higher risk of low birth weight of <1500 g in the borderline culture group compared with the control group. Repeating the study using a larger sample would be required to establish the relationship with outcome and to decide the appropriate cutoff level.

To our knowledge, this is the first prospective study to investigate the routine screening for ASB during the first trimester in the Hong Kong pregnant population and the

obstetric outcome. Nonetheless our study was limited by a relatively small sample size in a single centre. Further studies with multiple centres and a larger sample size including all pregnant women are suggested for further delineation of the relationship between ASB and important obstetric outcomes such as preterm birth, neonatal intensive care unit admission rate, and appropriate cutoff level for bacterial count in MSU.

Conclusion

Our study demonstrated a higher risk of pre-eclampsia and neonatal intensive care unit admission in Hong Kong pregnant women with ASB during the first trimester. In addition, there was a significantly higher risk of low birth weight (<1500 g) in the borderline culture group than the control group. Further studies are required to decide the appropriate cutoff for ASB.

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A Two-centre Study of Psychiatric Morbidity among Infertile Chinese Women in Hong Kong

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Objectives: To study the psychiatric morbidity of infertile females versus fertile females in Hong Kong using validated psychometric tests and to investigate the intrinsic demographic factors related to psychological morbidity that arises from infertility.
Methods: A two-centre cross-sectional observational study was conducted of consecutive infertile patients who attended an infertility clinic and fertile controls who attended the nurse-led smear clinic from 1 June 2014 to 30 November 2014. Socio-demographic and clinical data were collected. Psychometric status was assessed by a 12-item General Health Questionnaire, Beck Depression Inventory, and State-Trait Anxiety Inventory (STAI).
Results: Analysis of 245 valid questionnaires revealed a significantly higher median STAI score in infertile women compared with their fertile counterparts (58 vs. 50, p=0.001). More infertile women had tertiary education or above (37.4% vs. 14.3%, p=0.01) and more were in full-time employment compared with fertile controls (71.6% vs. 41.0%, p=0.002). The prevalence of housewives was double among the controls (46.2% vs. 20.6%, p=0.002). More infertile women lived in private housing compared with controls (75.5% vs. 50.0%, p=0.001). Subgroup analyses revealed that infertile housewives and those living in private housing scored significantly higher in STAI than their fertile counterparts (p=0.03 and p=0.04, respectively).
Conclusion: Infertile women have a higher predisposition to anxiety disorders and were more career-oriented. Subgroup analyses of possible confounding factors revealed that infertile housewives and private-housing occupants were significantly more prone to anxiety than their fertile counterparts.
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Keywords: Anxiety; Depressive disorder; Infertility, female

Introduction

Fertility has been viewed as the link between generations and the tie for many to immortality. Infertility is defined as a woman of reproductive age who has not conceived after 1 year of unprotected sexual intercourse[1]. It is a public health issue, with a 10% global prevalence. In Hong Kong, an estimated one in six couples have difficulty conceiving for a variety of reasons[2]. With its emotionally stressful nature and high socio-economic burden, infertility is a life crisis for both men and women. It is not only a gynaecological illness but also a biopsychosocial health problem[3].

Psychiatric Morbidity Associated with Infertility

Much previous research has focused on the psychological distress associated with infertility. Descriptive reports suggest that the experience of infertility can be devastating[3]. Across many cultures, individuals perceive their childlessness as a sign of diminished status, defectiveness, and incompetence. Some women hide their distress from health care providers because of the fear of being stigmatised and criticised[4]. It has been reported that high rates of clinically significant symptoms of depression and anxiety, suicidal tendency, and a strong conceptualisation of grief affect people with infertility[5]. Intimate partner violence and sexual violence have also been associated with infertility[5]. Another difficult emotional consequence of infertility is the loss of control over one's life[6]. This loss of control may begin prior to a formal diagnosis of infertility; difficulty with conception can challenge a couple's notion that they are in charge of their own reproduction. Since an important part of the

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adult identity is to be capable of reproduction[7,8], infertility becomes the focal point of daily discourse, often to the exclusion of other important aspects of life.

Psychiatric Morbidity and Infertility in Chinese

Distress associated with infertility can be complex, multidimensional, and strongly influenced by sociocultural values. As many Chinese societies are influenced by Confucian teaching where barrenness is regarded as an unfilial offence, infertility can be exceedingly stigmatising and traumatic. In a psychological survey performed in Beijing[9], more than 80% of couples had been tormented by various psychological stresses caused by infertility, and half of the infertile women rated infertility as the most stressful event in their lives. This was viewed as being even more stressful than marital dissolution or the death of a close relative. A local study by Lok et al[10] revealed that 33% of patients who attended an assisted reproductive technology clinic reported a significant level of psychological stress and 8% exhibited moderate to severe symptoms of depression.

A number of previous publications have addressed the psychological impact of infertility and its treatment or treatment failure on infertile women. This current study was designed to investigate the psychological impact of the diagnosis of infertility on infertile women and compare their level of psychiatric morbidity with that of their fertile counterparts in Hong Kong. Our objective was to assess the severity of psychological morbidity among these women using validated psychometric tests and to identify the associated intrinsic demographic factors. A better understanding of the psychological impact of infertility in Hong Kong women will enable the formulation of a more tailored psychological intervention.

Methods and Materials

Subjects and Controls

In Hong Kong, reproductive technology techniques can be provided only to partners who are married[11]. In our study, infertile Chinese women who attended the infertility clinic at the Pamela Youde Nethersole Eastern Hospital (PYNEH) and the Prince of Wales Hospital (PWH) were recruited. The PYNEH is a regional hospital that serves Hong Kong Island East and offers level 2 infertility treatment such as ovulation induction and intrauterine insemination. The PWH is a university-affiliated hospital that serves the New Territories in Hong Kong and provides level 3 infertility treatment including in-vitro fertilisation. Patients seen at the infertility clinics are largely referred by primary care physicians, private sector specialists, and the Family Planning Association. Patients who were non-Chinese, unwilling to participate, or who had a history of psychiatric or chronic disease(s) were excluded from the study.

Healthy married fertile women who attended the nurse-led smear clinic at the PWH served as controls. These women had treated cervical pathology and were currently stable and attending regular Pap smear surveillance at the nurse-led smear clinic. Those who were non-Chinese, unwilling to participate, or who had a history of infertility or psychiatric or chronic disease(s) were excluded from the study.

Study Design

This was a cross-sectional observational study. After obtaining institutional review board approval at both PYNEH and PWH, patients were given an explanation of the aim and process of the study, including all psychometric tests and interviews to be conducted. Written informed consent was obtained. All participants were requested to complete a set of questionnaires that requested socio-demographic and clinical data (Appendix) and three psychometric self-rating scales: 12-item General Health Questionnaire (GHQ-12), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI). The results were compared among the two groups.

The socio-demographic data (age, years of marriage, education level, employment status and family income) and clinical data (type, cause and duration of infertility, history of fertility treatment received, obstetric history and history of psychiatric illness) were collected.

General Health Questionnaire

The GHQ is an extensively used self-reported questionnaire for the detection and measurement of psychiatric morbidity in a general clinical setting[12]. The GHQ-12 is the shortest version and comprises only 12 questions. The questionnaire focuses on two major areas: inability to carry out normal functions and the appearance of new and distressing phenomena. The caseness threshold is 4 for the GHQ-12. The validated Chinese version of GHQ-12 was used[13].

Beck Depression Inventory

The 21-item BDI is one of the most widely used and reliable questionnaires for detecting depression as well as its intensity in normal populations[14]. A score of ≥12 is associated with depression. The validated Chinese version was used[15].

State-Trait Anxiety Inventory

The STAI has been widely applied to assess a patient's vulnerability to be anxious (Trait Anxiety scale) and current anxiety level (State Anxiety scale)[16]. A total score of ≥39 for the State Anxiety scale has been suggested to detect clinically significant symptoms. The Chinese validated version was used[17].

Sample Size Calculation

Based on a local study published in 2002[10], 33% of infertile Hong Kong Chinese women who attended an ART clinic scored above an arbitrary cutoff in the GHQ. Assuming half of these high scorers fulfilled the appropriate diagnosis of a psychiatric disorder, the anticipated prevalence was 16.5%. If the anticipated rate is 4 times higher than that of the normal fertile controls as described in previous literature[18], with a case-to-control ratio of 4:1, 152 subjects and 38 controls were required with a 80% power at a 5% significance level.

Two-sample Proportion Test

The sample size for subject (n0) and control group (n1) were calculated based on the formula:

$$n_0 = \frac{(z_{\alpha/2} + z_{1-\beta})^2[kp_1(1-p_1) + p_2(1-p_2)]}{k(p_1 - p_2)^2}$$

where α denotes the significance level (0.05); β as 1-power (assuming the power being 80%); n1 as k (control-to-case ratio, 1:4) x n_0; p_1 as sample prevalence rate of the subject group (16.5%); and p2 as sample prevalence rate of the control group (16.5% / 4 = 4.125%). With power of 80% and the case-to-control ratio of 4:1, the total required sample size was 190 (i.e. 152 subjects and 38 controls).

Statistical Analyses

All statistical analyses were performed using PASW Statistics 18, release version 18.0.0 (SPSS Inc., Chicago [IL], US). For categorical data, the Chi-square test and Fisher's exact test were used according to the data pattern. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

Correlation analyses of demographic variables in psychometric test scores were done. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Spearman's rho correlation test) was used. Spearman's rho correlation coefficient of >0.4 in the absolute value and a p value of <0.05 was regarded as statistically significant.

Subgroup analyses of potential confounding demographic factors were performed to eliminate their effect on psychometric test scores. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

Results

A total of 245 valid questionnaires were collected during the period 1 June 2014 to 30 November 2014. The Figure shows the recruitment of participants in this study. In the infertile arm, 58 women attending the PYNEH infertility clinic and 178 attending the PWH infertility clinic were approached, of whom 22 did not satisfy the inclusion criteria and nine refused to participate as they

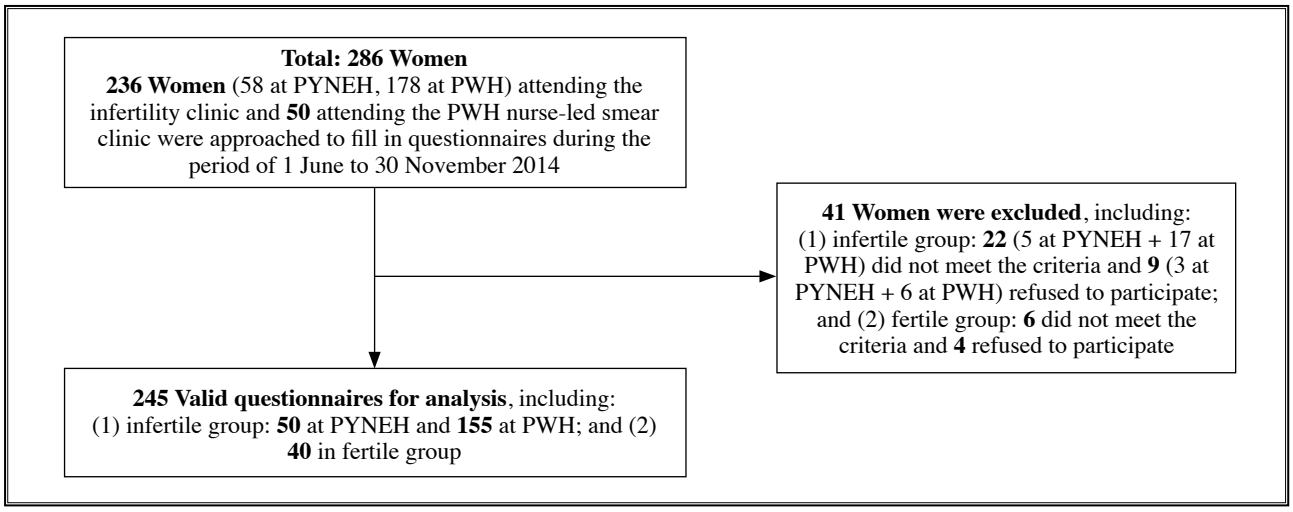

Figure. Recruitment of participants

Abbreviations: PWH = Prince of Wales Hospital; PYNEH = Pamela Youde Nethersole Eastern Hospital

were unwilling to disclose personal information to the researchers. A final total of 205 infertile women were thus recruited. In the fertile arm, 50 fertile women attending the nurse-led smear clinic at PWH were approached, of whom six did not satisfy the inclusion criteria and four refused to participate as they were unwilling to disclose personal information to the researchers. A total of 40 fertile controls were thus recruited. Table 1 shows the women's socio-demographic and clinical data. The median age was 34 years in infertile women and 35 years in the control group; no statistical difference in age was noted between the two groups (p=0.78). Approximately 93% of the infertile women were nulliparous and 85% of the fertile controls had at least one child (p<0.001). A history of termination of pregnancy was present in six of the nulliparous controls. The rate of miscarriages was similar between the two

Table 1. Demographic characteristics of participants*

Characteristic	Infertile group (n=205)	Control group (n=40)	p Value
Age (years)	34 (32-37)	35 (32-37)	0.78
Parity			<0.001
0	190 (92.7)	6 (15.0)	
1	15 (7.3)	17 (42.5)	
2	0	15 (37.5)	
≥3	0	2 (5.0)	
No. of previous miscarriage			0.90
0	172 (83.9)	34 (85.0)	
1	22 (10.7)	4 (10.0)	
2	8 (3.9)	1 (2.5)	
≥3	3 (1.5)	1 (2.5)	
No. of previous abortion			<0.001
0	179 (87.3)	17 (42.5)	
1	18 (8.8)	10 (25.0)	
2	6 (2.9)	11 (27.5)	
≥3	2 (1.0)	2 (5.0)	
Family income (HK$)	25,000 (15,000-40,000)	21,500 (14,750-30,000)	0.18
Missing data	18	10	
Education level			0.01
Primary	6 (3.0)	3 (8.6)	
Secondary	118 (59.6)	27 (77.1)	
Tertiary or above	74 (37.4)	5 (14.3)	
Missing data	7	5	
Employment status			0.002
Full-time	146 (71.6)	16 (41.0)	
Part-time	8 (3.9)	3 (7.7)	
Unemployed	8 (3.9)	2 (5.1)	
Housewife	42 (20.6)	18 (46.2)	
Missing data	1	1	
Living place			0.001
Public housing	49 (24.5)	19 (50.0)	
Private	151 (75.5)	19 (50.0)	
Missing data	5	2	

* Continuous variables are shown as median (interquartile range) and analysed by Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test

Table 2. Comparisons of psychometric assessment between infertile and fertile women*

	Infertile group (n=205)	Control group (n=40)	p Value
GHQ-12			
Total score	1 (0-3)	2 (0-4)	0.21
Score <4	153/202 (76)	29 (72)	0.66
Score ≥4	49/202 (24)	11 (28)	
Missing data	3	-	
BDI			
Total score	5 (1-11)	6 (0-17)	0.75
Score <12	152/193 (79)	25/39 (64)	0.05
Score ≥12	41/193 (21)	14/39 (36)	
Missing data	12	1	
STAI			
Total score	58 (51-65)	50 (46-57)	0.001
Score <39	4/198 (2)	2 (5)	0.25
Score ≥39	194/198 (98)	36 (95)	
Missing data	7	2	

Abbreviations: BDI = Beck Depression Inventory; GHQ-12 = 12-item General Health Questionnaire; STAI = State-Trait Anxiety Inventory

* Continuous variables are shown as median (interquartile range) and analysed by Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test. Percentages were calculated with exclusion of missing data

groups: 16.1% of infertile women and 15% of the controls (p=0.90). A history of previous termination was present in 12.7% of the infertile women, significantly less compared with 57.5% of the controls (p<0.001). Family income was comparable between the two groups with a median of HK$25,000 per month in infertile subjects compared with HK$21,500 in the controls.

The majority of the women from the two groups scored below the cutoff value of GHQ-12 and BDI (GHQ-12 score <4: 76% in the infertile group vs. 72% in the controls; BDI score <12: 79% vs. 64%), and were not statistically different (Table 2).

Up to 98% of infertile women scored above the STAI cutoff value of 39, indicating presence of clinically significant anxiety symptoms. A significantly higher STAI median (interquartile range) score was noted compared with the controls (58 [51-65] vs. 50 [46-57], p=0.001) [Table 2].

Correlation analyses of demographic variables and STAI scores were performed. The results are presented as Spearman's rho correlation coefficient and shown in Table 3. Since none of the demographic variables were positively or negatively correlated with the STAI score to a statistically significant level, subgroup analyses were performed after matching for education level, occupational status, and housing arrangement between the infertile and fertile groups to eliminate the effect of these factors on the STAI score.

The infertile women were more highly educated with 37.4% having a tertiary education compared with 14.3% in the control group (p=0.01, Table 1). Participants with only primary level education (n=9) were excluded because the sample size was too small. Subgroup analysis of education level–matched participants showed no

Table 3. Correlations between State-Trait Anxiety Inventory scores and continuous variables

Variable	Score
Age	r= –0.049 (p=0.45, n=236)
Parity	r= –0.171 (p=0.01, n=236)
No. of previous miscarriage	r= –0.031 (p=0.63, n=236)
No. of previous abortion	r= –0.225 (p<0.001, n=236)
Family income	r=0.147 (p=0.03, n=210)
Education level	r=0.159 (p=0.02, n=226)

significant difference in the median STAI score among the two groups (p=0.11, Table 4). Although no statistical difference was demonstrated between the median STAI scores, the infertile group, regardless of their education level, scored higher in STAI when compared with the controls.

Employment was also statistically different between the two groups (p=0.002); the majority of the infertile subjects had a full-time job compared with the control group (71.6% vs. 41.0%) whilst the controls were mostly housewives (46.2% vs. 20.6% in the infertile group). Subgroup analysis in the full-time employed participants showed no significant difference in the median (interquartile range) STAI score (57.5 [51-64.25] in the infertile group vs. 53.5 [47-57.75] in the control group, p=0.10). Nonetheless analysis of the housewife population revealed that infertile housewives had significantly more anxiety than fertile housewives (59 [51-66.75] in the infertile group vs. 50 [46.5-66] in the control group, p=0.03) [Table 4]. Subgroup analysis of the part-time employed (n=11) and unemployed participants (n=10) was excluded because their sample size was too small. The types of housing arrangement were statistically different between the infertile and control groups. Significantly more infertile women lived in private housing (75.5%) than public housing (24.5%). This is in contrast to the 50% split in the fertile controls (p=0.001) that is consistent with the normal distribution for the general population of Hong Kong[19]. The median (interquartile range) STAI score was significantly higher in the infertile private housing occupants than their fertile counterparts (58 [51-65] in the infertile group vs. 50 [47-57.5] in the control group, p=0.04) [Table 4].

Discussion

In this study, we analysed the psychiatric morbidity of infertile women using three validated psychometric tests. We used the GHQ-12, BDI, and STAI to assess the level of psychiatric stress, depression tendency and anxiety symptoms. No significant difference was noted between the two groups for GHQ-12 and BDI; thus our study cannot demonstrate a positive association between infertility and depression. That depression is not always recognised in infertile patients possibly because they are reluctant to report depressive symptoms to their clinician. It has been reported that these patients prefer to appear well-adjusted, presumably because they fear that fertility treatment will be denied or postponed if psychiatric problems are revealed[20,21].

Up to 98% of infertile participants scored above the cutoff value of STAI revealing that they were displaying clinically significant anxiety symptoms. This finding is in line with previous studies that showed infertility to be associated with anxiety[22,23]. With this high STAI score in both groups, our results showed that Hong Kong women of

Table 4. Subgroup analysis of State-Trait Anxiety Inventory scores*

	Infertile group	Control group	p Value
Education level			
Secondary	(n=118)	(n=27)	
	57 (50.75-64)	50 (46.75-58.25)	0.06
Tertiary	(n=74)	(n=5)	
	60 (53.5-66.5)	53 (44-61)	0.11
Employment			
Housewife	(n=42)	(n=18)	
	59 (51-66.75)	50 (46.5-66)	0.03
Full-time	(n=146)	(n=16)	
	57.5 (51-64.25)	53.5 (47-57.75)	0.10
Living place			
Public housing	(n=49)	(n=19)	
	56 (50.75-63)	50 (46-59)	0.11
Private housing	(n=151)	(n=19)	
	58 (51-65)	50 (47-57.5)	0.04

* Continuous variables are shown as median (interquartile range) and analysed by Mann-Whitney *U* test

reproductive age are vulnerable to psychological morbidity, especially anxiety. The reason behind this observation is nonetheless beyond the scope of this study. The finding that clinically significant anxiety is very common in women of reproductive age encouraged us to consider the incorporation of STAI as an essential assessment tool for infertility patients to identify those patients at risk. Links have been suggested between anxiety, depression, the hypothalamic-pituitary-adrenal axis (e.g. anxiety-induced hyperprolactinaemia) and failure to conceive; psychological intervention aimed at reducing anxiety might increase the likelihood of conception[24-26].

Comparison of infertile subjects with controls revealed a significantly higher median STAI score in the former. Nonetheless before we can conclude that infertility is a significant factor underlying increased anxiety, subgroup analysis was performed to correct three apparent confounding factors that differed significantly between the infertile and control groups. These were education level, employment status, and housing type. Our analysis of these matched cohorts also showed significant differences in the STAI levels, consolidating the concept that infertility is a stress-inducing condition.

Infertile women had a higher education level and a higher proportion were in full-time employment. Our findings are consistent with the widely observed global trend of infertile women being more career-oriented[27]. In our subgroup education level–matched cohort analysis, we did not demonstrate a statistically significant difference between the two groups; nonetheless the median STAI score in the infertile group tended to be higher. This observation agrees with the findings of previous studies that infertile patients are more anxious than the normal population[24,28].

As expected with more career-oriented women, the proportion of those in full-time employment was higher in the infertile group. In contrast, the control group comprised mostly housewives, followed by full-time, part-time, and then unemployed women. Subgroup analysis of all full-time employed participants showed no difference in the STAI median scores between the infertile women and controls. Donkor and Sandall[29] suggested that infertile women with high-level occupations use a problem-focused stress coping strategy, so they experience a lower infertility-related stress. This could explain why the full-time working infertile patients in our study did not show a significantly higher STAI score despite being confronted by an apparent life stressor. We postulate that although the nature of the stressor is very important, the stress-coping mechanism also plays a crucial role in determining the severity of stress manifested.

Subgroup analysis also showed that infertile housewives suffered significantly more anxiety symptoms than fertile housewives. A Japanese group and an Iran group have also demonstrated this phenomenon[24,30]; since housewives are generally expected to manage households and to procreate, it is easy to understand why they are more vulnerable to mental stress secondary to being infertile. Significantly more infertile women (75.5%) lived in private housing compared with the control group. Although they lived in different types of housing estates, the family income for the two groups was similar, and close to the Hong Kong average income[19]. This suggests that their social support and resources were not significantly different. Nonetheless with the astronomical housing price for both rental and private properties in Hong Kong, it is fair to hypothesise that the relative spending power and financial flexibility are lower for those living in private housing. To correct for this potential bias due to their financial flexibility, a subgroup analysis was required. This subgroup analysis showed a statistically significant difference when the median STAI score of private-housing–matched infertile women and controls was compared. This means that by matching the financial burden of the two groups, the difference in the observed median STAI score may be due to the infertility problem endured by the infertile women.

The strength of our study is that it was a two-centre study that involved 245 participants from a diverse background. This contributes to the generalisability of the study. Results generated from the current study can be extrapolated and applied to the population we are serving. Nonetheless there are several limitations. First, measurement of psychiatric morbidity was based on the use of psychometric assessment only. These psychometric tests function as a screening tool and assess the severity of symptoms in a patient with a previously diagnosed psychiatric disorder. Formal assessment is beyond the role of an obstetrician. A clinical psychologist or psychiatrist is required to clinically diagnose and manage individuals with genuine psychiatric disorders. We suggest referral to a clinical psychologist or psychiatrist for women who score above the cutoff level in the psychometric tests so that formal assessment using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders can be arranged with intervention planned when indicated. Second, although the initial power analysis (80%) deemed our study to have adequate subjects for overall assessment, a larger trial with more patients would allow us to perform

more subgroup analyses in a comprehensive manner since some subgroups could not be properly analysed due to their small case number, for example those with only primary school education (n=9), part-time employed (n=11), or unemployed (n=10). Third, the controls were recruited from one centre only. If a larger trial is to be considered in the future, liaisons with the Family Planning Association of Hong Kong and Maternal and Child Health Centres can be considered as it can enrich the diversity of the controls and be more representative of the general population. Fourth, the magnitude of the effect of infertility duration and previous treatment attempts and/or failure on psychiatric morbidity were beyond the scope of our study. It would be clinically useful to know whether they have an adverse effect on psychiatric wellbeing so that clinicians can identify infertile patients who are more vulnerable to psychiatric morbidity.

Conclusion

In a cohort matched for age, ethnicity, marital status, and family structure, infertile women had a higher predisposition to anxiety disorders than controls, based on the psychometric assessment using STAI. In our study, infertile women had a higher level of education, more were in full-time employment, and more lived in private housing. Correction of these confounding factors was achieved by performing matched subgroup analyses. Infertile housewives and those living in private housing were especially more prone to anxiety than their fertile counterparts. We suggest that a thorough history-taking that addresses these factors is prudent. Since STAI identified a large proportion of infertile patients at risk of clinically significant anxiety, we propose to incorporate STAI as an essential screening tool at the first infertility consultation with consequent referral to a clinical psychologist or psychiatrist if the STAI is abnormally elevated. Infertility is a disease of the body and mind so a holistic approach must be employed to help affected couples. Our aim as health care providers is to help them to endure this stressful experience and accept this harsh diagnosis while providing adequate support and information to enhance their understanding and compliance with the subsequent intense treatment.

Declaration

The authors declared no conflict of interest in this study.

Appendix

Additional material related to this article can be found on the HKJGOM website. Please go to <http://www.hkjgom.org/>, search for the appropriate article, and click on **Full Text (PDF)** following the title.

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A Retrospective Study to Compare the Surgical Outcomes of Robotic-assisted Laparoscopic, Laparoscopic, and Abdominal Myomectomies in a Hong Kong Community Hospital

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Objective: To compare the short-term operative and postoperative outcome of patients who underwent robotic-assisted laparoscopic (RALM), laparoscopic (LM), and abdominal (AM) myomectomies.
Methods: Patients who underwent RALM, LM and AM at Pamela Youde Nethersole Eastern Hospital from January 2007 to August 2014 were retrospectively reviewed.
Results: A total of 17 cases of RALM (9 with conventional technique, 8 with hybrid technique), 20 cases of LM, and 58 cases of AM were included. Patients were similar in age and body weight. The median weight of the fibroids removed in the AM group (286 g) was heavier than the LM group (205 g) and the RALM group (214 g) [p=0.002]. The median operating time of the RALM group was 240 minutes, and was significantly longer than that in the LM group (187.5 mins) and the AM group (69 mins) [p<0.001]. The median length of hospital stay (RALM 4 days, LM 3 days, AM 4 days; p=0.002) was shorter in the laparoscopic group. No significant differences were noted among the three groups for estimated blood loss, and operative and postoperative complications. Significantly more patient-controlled analgesia was used in AM (88%) than RALM (18%) and LM (5%) groups (p<0.001).
Conclusion: AM was more efficient to remove fibroids of heavier weight in a shorter operating time when compared with LM and RALM. Nonetheless patients who underwent RALM and LM had less postoperative pain when compared with AM. LM was associated with least postoperative pain and shortest postoperative hospital stay. RALM was not superior to LM but was at least as safe as other routes of myomectomy.
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Keywords: Laparoscopy; Robotics; Treatment outcome; Uterine myomectomy

Introduction

Uterine fibroid is the most commonly seen benign pelvic tumour in women of reproductive age. It is estimated that 20% to 40% of women of reproductive age have uterine fibroids1. Myomectomy is the standard surgical treatment for symptomatic women who wish to avoid hysterectomy, and thereby preserve fertility. Approximately 1800 myomectomies are carried out each year in Hong Kong[1]. The surgical techniques for myomectomy include laparotomy, laparoscopy, and recently robotic technique. The minimally invasive laparoscopic myomectomy offers less blood loss[2-4], minimal postoperative pain[4,5], shorter hospital stay[2], rapid convalescence[4], and reduced adhesion formation when compared with traditional open abdominal myomectomy. Nonetheless it may be limited by the size and number of fibroids reasonably removed[6]. It requires advanced laparoscopic skills to manoeuvre the rigid laparoscopic instruments that are fixed at the skin level by trocars, resulting in an overall reduction in degrees of freedom for dissection and suturing when compared with open surgery. The use of a remotely controlled robot has the potential to facilitate laparoscopic procedures and allows the surgeon to be seated comfortably while visualising the surgical field in a three-dimensional view. It also allows for increased dexterity and precision as it scales the surgeon's movements by varying increments and filters out unintentional tremors[7]. The primary disadvantages of robotics are increased cost[8-10], longer operating time[2,8,11-14], and lack of haptic feedback[7].

The optimal surgical technique for myomectomy remains debatable. There is currently no local study to compare the pros and cons of different routes of myomectomy. Pamela Youde Nethersole Eastern Hospital (PYNEH) is the local main public community hospital that offers robotic-assisted laparoscopic myomectomy (RALM).

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This study aimed to compare the operative and immediate postoperative outcomes of RALM, standard laparoscopic myomectomy (LM), and abdominal myomectomy (AM) performed at PYNEH, in order to provide local information about these three different routes of myomectomy.

Methods

All cases of RALM (n=19), LM (n=49), and AM (n=127) performed at PYNEH from 1 January 2007 to 31 August 2014 were identified by searching the operative record listing of the hospital clinical medical system. The details of the cases were studied via the electronic patient record on the clinical medical system and the handwritten medical record notes. Cases of myomectomy with only single or two small fibroids of <4 cm removed, adenomyoma requiring wedge resection, and those that required concurrent adnexal surgery were excluded from analysis. Cases of AM with uterine size ≥18 weeks were excluded in order to have a group with uterine size comparable with that of RALM and LM cases. One case of RALM and four cases of LM required conversion to laparotomy and were excluded. These cases needed to be converted to laparotomy due to intraoperative findings of a large stuck posterior fibroid, which itself explained the limited access of the minimally invasive approach for myomectomy. One case of LM for torsion of a pedunculated fibroid in a 22-week pregnant patient was also excluded.

The data abstracted comprised patient demographics and clinical characteristics including age, body weight, history of abdominal surgery, and symptoms arising from the fibroids. Peri-operative preparation including prophylactic antibiotics, bowel preparation and pitressin use were recorded. Operative details included uterine size, fibroid characteristics (number, size and location of fibroid), weight of fibroids removed, operating time, docking and console time for RALM, estimated blood loss, need for intraoperative blood transfusion, morcellator use, and need for minilaparotomy in LM and RALM, entry of uterine cavity and intraoperative complications. Immediate postoperative outcomes including length of hospital stay, patient controlled analgesia (intravenous morphine) use, haemoglobin drop, postoperative blood transfusion, and complications were also recorded.

The practice of RALM was commenced at PYNEH in June 2010 and was performed using the da Vinci robotic surgical system (Intuitive Surgical Inc., Sunnyvale [CA], US). Patients were placed in the dorsal lithotomy position and a Foley catheter was inserted. A uterine manipulator was used if necessary. Depending on the surgeon's preference, either a 3 or 4 arm robotic setup with two assistant ports was used. A midline or right-sided docking technique was used. Docking time was the time used to fasten the robotic arms to the inserted trocars and introduce the camera and the robotic endowrist instruments (Intuitive Surgical Inc., Sunnyvale [CA], US). Console time was defined as the total time on the console for robotic surgery. The left lower quadrant undocked 12-mm assistant port was used by the assistant as a conventional laparoscopic port for irrigation and suction, passage of needles, tissue retraction and morcellation. In standard robotic myomectomy, the serosa of the fibroid is infiltrated with a diluted pitressin (vasopressin) solution prior to uterine incision with ultrasonic or monopolar energy. The fibroid is enucleated and the uterine defect, based on the surgeon's preference, is closed in multiple layers with barbed delayed absorbable suture (polyglactin 910 vicryl) to the myometrium and unbarbed delayed absorbable suture (polydioxanone) or fine vicryl to the serosa. An adhesion barrier (Interceed; Ethicon, US, LLC) may be placed onto the closed uterine wound to prevent adhesion formation. At the end of the robotic part of the procedure, traditional laparoscopy is used for morcellation by laparoscopic power morcellators and extraction of the removed fibroids. In the hybrid robotic myomectomy technique, a conventional laparoscopic technique is used for fibroid enucleation and the robot is swiftly docked to accomplish the uterine repair. The advantages of hybrid technique are the preservation of tactile sensation that helps in dissection of the fibroid and the use of a rigid tenaculum that can exert significant effective pull without risk of equipment damage. Fibroids of >10 cm and are beyond the pelvis, deep intramural fibroids or highly vascular fibroids are therefore best approached by the hybrid method[15]. Nonetheless this technique entails a time lag used for docking before the operator can sit at the console to control the uterine bleeding and should be used only after the robotic team are familiar with the docking procedure. For LM, a 10-mm trocar is placed through the umbilicus for the camera and two to three extra trocars are placed in the lower abdomen. The uterus is infiltrated with pitressin and an incision made using the Harmonic scalpel or monopolar scissors. The fibroid is then dissected out with generous traction with a tenaculum. The uterine defect is closed in multilayers and suturing done with laparoscopic needle holders. A morcellator is used to remove the fibroid from the abdominal cavity. Traditional AM is performed by a standard procedure with a suprapubic transverse skin incision or subumbilical midline skin incision.

In our unit, we selected cases with uterine size <20 weeks and with small number of fibroids for myomectomy

using a minimally invasive technique. We did not apply strict selection criteria for robotic over laparoscopic approach. We initially allocated cases to RALM if they were considered difficult to dissect or suture laparoscopically, such as big intramural, lower pole, cervical or broad ligament fibroids, but the number of fibroids was restricted to three to four. The choice of hybrid robotic myomectomy technique was partly the surgeons' preference and was mostly adopted by surgeons more experienced with robotic surgery. Patients did not need to pay for the extra cost of robotic myomectomy but the use of this technique was also dependent on the availability of the robot system in the operating theatre.

All statistical analysis of data was done by PASW Statistics 18, release version 18.0.0 (SPSS, Inc., Chicago [IL], US). Concerning categorical data, the Chi-square test and Fisher's exact test were used according to the data pattern. For continuous data with a highly skewed distribution, non-parametric tests were used. Kruskal-Wallis *H* test and Mann-Whitney *U* test were adopted to analyse the continuous data of three groups and two groups, respectively. Bonferroni correction adjustment was applied when the comparison of two groups had been analysed. The critical level of statistical significance was set at 0.05.

The study protocol was approved by the Ethics Committee of the Hong Kong East Cluster. The requirement for informed consent was waived because of the retrospective nature of the study.

Results

After exclusion, a total of 95 cases, with 17 cases (18%) of RALM, 20 cases (21%) of LM, and 58 cases (61%) of AM, were included in the study (Figure). Patient demographics, clinical characteristics, and preoperative preparation for myomectomy are summarised in Table 1. The median age of the patients was 36 years in the RALM group, 38 years in the LM group and 37 years in the AM group, and was not statistically different (p=0.73). There was no significant difference among the three groups in body weight, previous abdominal surgery and symptoms arising from the fibroids, although the LM group (25%) and the AM group (19%) appeared to have a higher proportion of patients who had undergone previous abdominal surgery compared with the RALM group (6%). There was no routine protocol for the preoperative use of prophylactic antibiotics or bowel preparation for different routes of

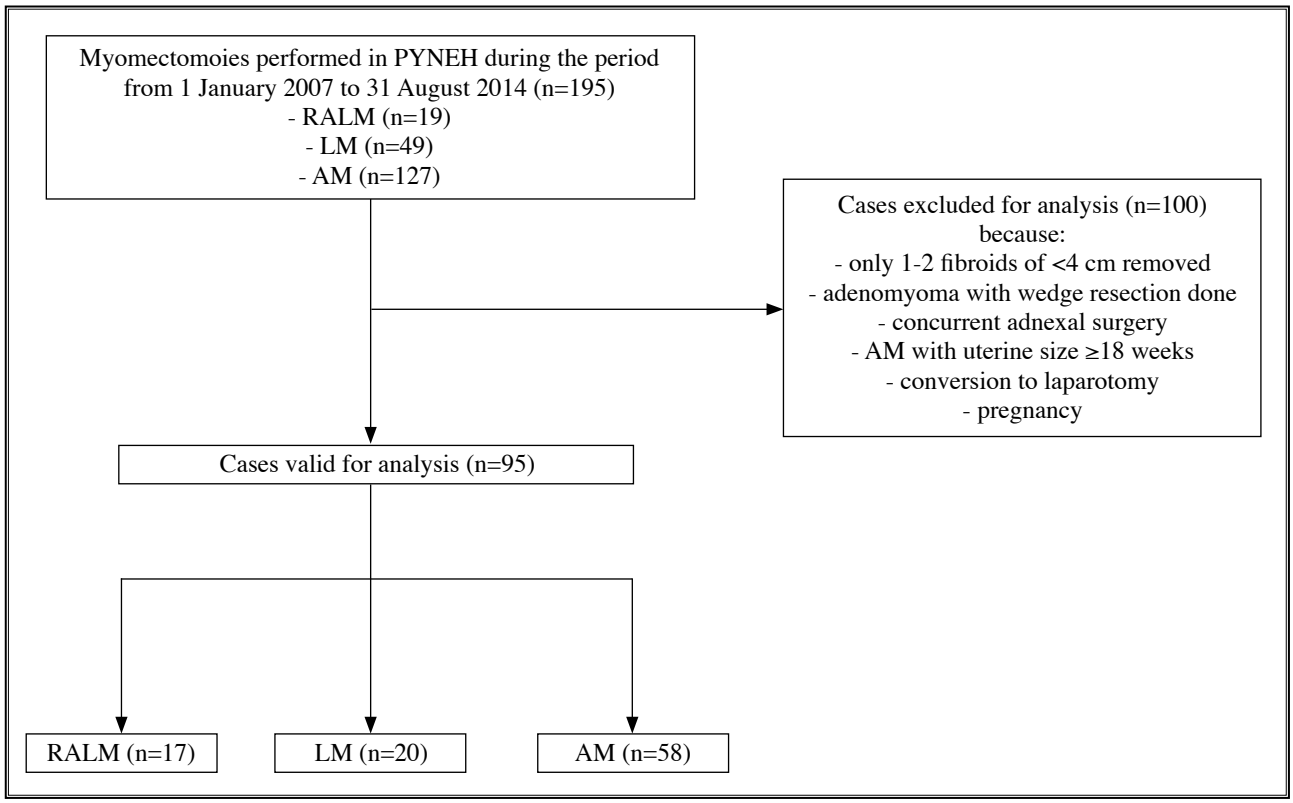

Figure. Recruitment of subjects in this study

Abbreviations: AM = abdominal myomectomy; LM = laparoscopic myomectomy; PYNEH = Pamela Youde Nethersole Eastern Hospital; RALM = robotic-assisted laparoscopic myomectomy

myomectomy and their use was totally dependent on the individual surgeon's practice. The use of prophylactic antibiotics before skin incision was statistically higher in the AM group (95%) than the RALM (82%) and LM (55%) groups (p<0.001). We specifically looked at the two techniques of robotic myomectomy and compared their demographics, clinical characteristics, and preoperative preparation (Table 1). Among the 17 cases of RALM, nine (53%) were performed with a conventional robotic technique while eight (47%) were performed using a hybrid robotic technique. The number, size, and location of fibroids did not differ significantly between the three types of myomectomy and the two techniques of robotic myomectomy (Table 2). The median uterine size of the patients in the RALM, LM, and AM groups was 12, 12 and 14 weeks gravid size, respectively (p=0.12). The median weight of the fibroids removed in the AM group (286 g) was heavier than the LM group (205 g) and the RALM group (214 g) [p=0.002]. The hybrid robotic technique apparently removed larger size and heavier fibroids than conventional robotic myomectomy. More fibroids and intramural fibroids were removed with the hybrid robotic technique when compared with the conventional technique, although none of these findings was statistically significant.

Table 3 shows the operative details of the three routes of myomectomy. The median operating time of the RALM group was 240 minutes, significantly longer than that of the LM group (187.5 mins) and the AM group (69 mins) [p<0.001]. The operating time for robotic surgery comprised the docking time and ranged from 3 to 20 minutes (median, 6 mins). The median console time was 131 minutes. The median estimated blood loss and the pitressin use were similar among the three groups. No intraoperative complications such as injury to the bowel, urinary bladder or ureter occurred. One case of RALM and one case of LM, but none of AM, required blood transfusion during operation. Fewer cases of RALM (6%) had the uterine cavity entered during operation when compared with LM (15%) and AM (26%) groups but the difference was not statistically significant (p=0.20). Conventional and hybrid robotic myomectomy techniques were comparable intraoperatively except for a significantly longer median operating time in the hybrid robotic group (275 mins vs. 205 mins, p=0.02).

Table 1. Comparison of demographics, clinical characteristics, and preoperative preparation among the study groups*

	RALM			LM (n=20)	AM (n=58)	p Value (A, B, C)‡
	Conventional (n=9)†	Hybrid (n=8)†	Total (n=17)			
Age (years)	38 (35-39)	34.5 (29.3-37.5)	36 (34-38)	38 (32.5-39)	37 (34.75-40)	0.73 (0.46, 0.47, 0.97)
Body weight (kg)	56.8 (51.4-66.8)	52.3 (50.7-56.9)	54.8 (50.9-58.8)	50.2 (44.6-57.4)	52.9 (48.7-56.6)	0.21 (0.12, 0.31, 0.20)
Previous abdominal surgery	1 (11)	0	1 (6)	5 (25)	11 (19)	0.31
Symptom						
Menorrhagia	4 (44)	5 (63)	9 (53)	12 (60)	34 (59)	0.90
Pressure symptoms/ pain/AROU	5 (56)	4 (50)	9 (53)	7 (35)	32 (55)	0.29
Subfertility	2 (22)	0	2 (12)	2 (10)	5 (9)	0.89
Asymptomatic	0	0	0	2 (10)	1 (2)	0.19
Others	0	0	0	1 (5)	2 (3)	1
Prophylactic antibiotic	6 (67)	8 (100)	14 (82)	11 (55)	55 (95)	<0.001
Bowel preparation	8 (89)	7 (88)	15 (88)	18 (90)	57 (98)	0.09

Abbreviations: AM = abdominal myomectomy; AROU = acute retention of urine; LM = laparoscopic myomectomy; RALM = robotic-assisted laparoscopic myomectomy

* Age and body weight are shown as median (interquartile range) and analysed by Kruskal-Wallis *H* test and Mann-Whitney *U* test. Categorical variables are expressed by No. (%) and analysed by Pearson Chi-square test or Fisher's exact test

† No statistically significant differences were found between conventional and hybrid technique for listed parameters

‡ A = RALM vs. LM; B = RALM vs. AM; C = LM vs. AM

Table 2. Comparison of fibroid characteristics among the study groups*

	RALM			LM (n=20)	AM (n=58)	p Value (A, B, C)‡
	Conventional (n=9)†	Hybrid (n=8)†	Total (n=17)			
Uterine size (weeks gravid size)	12 (10-14)	14 (12-16)	12 (12-15)	12 (10-14)	14 (12-16)	0.12 (0.37, 0.32, 0.05)
Size of largest fibroid (cm)	8 (6-10)	10 (8.5-11.5)	10 (7-10)	8 (6-9.75)	8 (6-9)	0.09 (0.09, 0.04, 0.80)
Specimen weight (g) [n=81]	(n=7) 192 (163-270)	(n=8) 287 (177.25-320.5)	(n=15) 214 (164-313)	(n=17) 205 (72.5-352.5)	(n=49) 286 (204-388)	0.002 (0.47, 0.11, 0.07)
No. of fibroid(s)						0.81
1	6 (67)	3 (38)	9 (53)	11 (55)	24 (41)	
2	1 (11)	0	1 (6)	2 (10)	8 (14)	
≥3	2 (22)	5 (62)	7 (41)	7 (35)	26 (45)	
Location of largest fibroid						0.09
Subserosal	6 (67)	3 (38)	9 (53)	5 (25)	18 (31)	
Intramural	2 (22)	4 (50)	6 (35)	10 (50)	34 (59)	
Submucosal	0	0	0	1 (5)	2 (3)	
Pedunculated	0	0	0	3 (15)	3 (5)	
Broad ligament	1 (11)	1 (13)	2 (12)	1 (5)	0	
Cervical	0	0	0	0	1 (2)	
Uterine wall largest fibroid originated						0.77
Anterior	2 (22)	3 (38)	5 (29)	5 (25)	22 (38)	
Posterior	5 (56)	3 (38)	8 (47)	10 (50)	20 (34)	
Fundal	2 (22)	1 (13)	3 (18)	5 (25)	12 (21)	
Lateral	0	1 (13)	1 (6)	0	4 (7)	

Abbreviations: AM = abdominal myomectomy; LM = laparoscopic myomectomy; RALM = robotic-assisted laparoscopic myomectomy

* Continuous variables are shown as median (interquartile range) and analysed by Kruskal-Wallis *H* test and Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test

† No statistically significant differences were found between conventional and hybrid techniques for listed parameters

‡ A = RALM vs. LM; B = RALM vs. AM; C = LM vs. AM

The postoperative outcomes of the three different types of myomectomy are shown in Table 4. The median length of postoperative hospital stay was shorter in the LM group (RALM 4 days, LM 3 days, AM 4 days, p=0.002). The median haemoglobin drop was also similar. The use of patient-controlled analgesia that released intravenous morphine was significantly more in the AM group (88%) than the RALM (18%) and LM (5%) groups (p<0.001). There was no significant difference in terms of postoperative complications among the three groups. The RALM group appeared to have more minor febrile morbidity that was managed with antibiotics. Two cases of AM were complicated by shock and haemoperitoneum, one of whom required repeat laparotomy for haemostasis. More cases of AM (10%) required postoperative blood transfusion than LM (5%) and RALM (6%) but the difference was not statistically significant (p=0.82). Conventional robotic myomectomy required a shorter median length of postoperative hospital stay than hybrid robotic myomectomy (2 days vs. 4 days, p=0.01). The two subgroups were otherwise not significantly different postoperatively (Table 4).

Discussion

Robotic-assisted surgery has become a worldwide trend recently. Since the da Vinci robotic surgical system

Table 3. Comparison of operative details among the study groups*

	RALM			LM (n=20)	AM (n=58)	p Value (A, B, C)†
	Conventional (n=9)	Hybrid (n=8)	Total (n=17)			
Operating time (mins)	205 (179.5-252.2)‡	275 (246.3-301.8)‡	240 (205-286)	187.5 (131.3-253.8)	69 (55-93.5)	<0.001 (0.03, <0.001, <0.001)
Docking time (mins)	5 (4-9.5)	6.5 (5-9.75)	6 (5-9.5)	-	-	-
Console time (mins)	127 (100-162.5)	135 (122.5-143.3)	131 (114.5-147.5)	-	-	-
Estimated blood loss (ml)	200 (100-325)	250 (62.5-375)	200 (100-350)	200 (50-525)	150 (77.5-300)	0.58 (0.52, 0.28, 0.92)
Pitressin	8 (89)	8 (100)	16 (94)	18 (90)	54 (93)	0.86
Morcellation (RALM and LM)	8 (89)	7 (88)	15 (88)	17 (85)	-	1
Minilaparotomy for fibroid removal (RALM and LM)	1 (11)	1 (13)	2 (12)	2 (10)	-	1
Intraoperative complications	0	0	0	0	0	-
Intraoperative transfusion	1 (11)	0	1 (6)	1 (5)	0	0.15
Enter uterine cavity	0	1 (13)	1 (6)	3 (15)	15 (26)	0.20

Abbreviations: AM = abdominal myomectomy; LM = laparoscopic myomectomy; RALM = robotic-assisted laparoscopic myomectomy

* Continuous variables are shown as median (interquartile range) and analysed by Kruskal-Wallis *H* test and Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test

† A = RALM vs. LM; B = RALM vs. AM; C = LM vs. AM

‡ The p value was 0.02 for comparison of operating time between conventional and hybrid techniques

(Intuitive Surgical Inc., Sunnyvale [CA], US) was first approved by the US Food and Drug Administration for gynaecological application in April 2005[16], a robotic system has been applied for benign and malignant gynaecological conditions including hysterectomy, pelvic and para-aortic lymphadenectomy, myomectomy, sacrocolpopexy, tubal ligation or re-anastomosis, salpingo-oophorectomy, and ovarian cystectomy[7,8]. Myomectomy is a particularly challenging procedure to be performed via a conventional laparoscopic approach due to the difficulties associated with the rigid instruments for dissecting the fibroid and suturing the fibroid bed. It was believed that robotic technology can overcome the limitations of conventional laparoscopy and enable myomectomy, which would otherwise require an open surgical approach, to be performed as a minimally invasive procedure.

The current study compared the outcome of the three different approaches of myomectomy. It suggests that AM is more efficient than LM and RALM when removal of a heavier weight fibroid in a shorter operating time is required. Barakat et al[2] reported a total 575 myomectomies including the comparison of robotic-assisted (n=89, 15.5%), laparoscopic (n=93, 16.2%), and abdominal (n=393, 68.3%) myomectomy. The actual surgical time was significantly longer in the robotic-assisted group (181 mins) than the laparoscopic group (155 mins) and the abdominal group (126 mins, p<0.01), and is in agreement with our finding. The additional operating time of RALM may be attributed to the docking and undocking procedure of the robot. In addition, the learning curve associated with acquiring the skills to perform robot-assisted surgery is approximately 50 practice cases[7]. In our study the 17 cases of RALM were shared by five different surgeons who may not have reached the peak of the learning curve. The longer operating time required in the hybrid robotic myomectomy may be due to the possibly larger and deeper uterine wound following fibroid enucleation that required extensive multilayered suturing. Barakat et al[2] showed that the abdominal group had a longer median hospital stay of 3 days, compared with 1 day in the laparoscopic group and 1 day in the robotic-assisted group (p<0.001). The

Table 4. Comparison of postoperative outcomes among the study groups*

	RALM			LM (n=20)	AM (n=58)	p Value (A, B, C)†
	Conventional (n=9)	Hybrid (n=8)	Total (n=17)			
Length of hospital stay (days)	2 (2-3)‡	4 (4-4.75)‡	4 (2-4)	3 (3-4)	4 (4-5)	0.002 (0.81, 0.02, 0.001)
Haemoglobin drop (g/dL) [n=92]	(n=8) 1.3 (0.77-2.38)	(n=8) 2.1 (0.53-3.88)	(n=16) 1.6 (0.63-3)	(n=18) 1.65 (1.15-2.55)	1.65 (0.7-2.63)	0.71 (0.68, 0.83, 0.40)
PCA IV morphine use	1 (11)	2 (25)	3 (18)	1 (5)	51 (88)	<0.00
Complications						
Fever	1 (11)	2 (25)	3 (18)	0	6 (10)	0.16
Wound infection	0	0	0	0	1 (2)	1
Urinary tract infection	0	0	0	2 (10)	2 (3)	0.33
Gastro-intestinal (upper gastro-intestinal bleeding, ileus)	1 (11)	0	1 (6)	1 (5)	1 (2)	0.34
Myomectomy wound haematoma	1 (11)	0	1 (6)	0	5 (9)	0.43
Shock/subrectal haematoma/ haemoperitoneum	0	0	0	0	2 (3)	1
Fever	1 (11)	2 (25)	3 (18)	0	6 (10)	0.16
Wound infection	0	0	0	0	1 (2)	1
Urinary tract infection	0	0	0	2 (10)	2 (3)	0.33
Gastro-intestinal (upper gastro-intestinal bleeding, ileus)	1 (11)	0	1 (6)	1 (5)	1 (2)	0.34
Myomectomy wound haematoma	1 (11)	0	1 (6)	0	5 (9)	0.43
Shock/subrectal haematoma/ haemoperitoneum	0	0	0	0	2 (3)	1
Re-laparotomy	0	0	0	0	1 (2)	1
Blood transfusion	0	1 (13)	1 (6)	1 (5)	6 (10)	0.82

Abbreviations: AM = abdominal myomectomy; LM = laparoscopic myomectomy; PCA IV = intravenous patient-controlled analgesia; RALM = robotic-assisted laparoscopic myomectomy

* Continuous variables are shown as median (interquartile range) and analysed by Kruskal-Wallis *H* test and Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test

† A = RALM vs. LM; B = RALM vs. AM; C = LM vs. AM

‡ The p value was 0.01 for comparison of length of hospital stay between conventional and hybrid techniques

prolonged operating time and increased operative cost of robotic-assisted myomectomy may be offset by the shorter hospital stay. Gobern et al[17] showed similar findings in a retrospective study to evaluate the operative outcome of robotic (n=66, 21.4%), laparoscopic (n=73, 23.7%), and abdominal (n=169, 54.9%) myomectomies conducted at a community hospital. Median operating time of robotic surgery (140 mins) was significantly longer compared with laparoscopic (70 mins) and abdominal myomectomies (72 mins, p<0.01). Robotic and laparoscopic myomectomies required significantly shorter hospital stay compared with abdominal myomectomies. Our study did not show a shorter postoperative hospital stay in the robotic myomectomy group as a whole, but the conventional robotic myomectomy group had a shorter postoperative hospital stay than the hybrid robotic myomectomy group. We do not know whether this was due to the surgeon's preference or other reasons. Nonetheless patients who underwent

RALM and LM experienced less postoperative pain as reflected by the lower intravenous morphine use when compared with AM. Nash et al[13] compared RALM (n=27) and AM (n=106) stratified by uterine size. Intravenous hydromorphone use was significantly lower for RALM ($p<0.001$). A meta-analysis of randomised controlled trials to compare laparoscopic and open myomectomy that included six studies and 576 patients[4] found significantly lower postoperative pain intensity in the LM group.

RALM has been shown to be as safe as LM and AM in other studies[8,13,18,19]. The estimated blood loss, operative and postoperative complications of the three routes of myomectomy were similar in our study. Although our study did not show the advantages of RALM over LM, robotic surgery can be performed comfortably while sitting and endowrist of robotic surgery did offer the surgeon freedom of movement and make the extensive dissection and intensive suture of myomectomy easier. The learning curve for suturing for robotic surgery was noted to be less steep than that for laparoscopy, and may allow a less skilled or experienced laparoscopist to perform safe suturing in a shorter time period[8].

This study have several limitations. First, this study was based on a single community hospital with limited cases of RALM and LM to date. There may be a true difference in the re-bleeding complication between the abdominal and the robotic or laparoscopic routes but the sample size may not be big enough to make it statistically significant. We did not specifically analyse the relationship between the surgeon's experience and the surgical outcome. Surgeons performing different types of myomectomy varied in their level of experience and had their own technique for performing myomectomies. Generally we had more experience with laparoscopy than robotic surgery as robotic gynaecological surgery was only introduced at PYNEH in 2010. In addition, this was a retrospective study and long-term outcomes such as resolution of symptoms, recurrence, rates of pregnancy, uterine rupture and adhesion formation could not be determined. Whether the advantage of the meticulous suturing of robotic myomectomy can be transformed to a better outcome such as less uterine rupture in subsequent pregnancy will be a meaningful study question. Prospective and randomised trials can be considered in the future to compare the short-term outcomes as well as to determine the long-term outcomes of these three different approaches of myomectomy.

Conclusion

AM was more efficient for the removal of fibroids of heavier weight in a shorter operating time when compared with LM and RALM. Patients with RALM and LM on the other hand had less postoperative pain compared with AM patients, as reflected by less need for intravenous morphine. The estimated blood loss, operative and postoperative complications of the three routes of myomectomy were similar. Patients who underwent LM had least postoperative pain and shorter postoperative hospital stay. RALM was not shown to be superior to LM but was at least as safe as the other routes of myomectomy. We believe that RALM is feasible and safe and can overcome some of the surgical difficulties of conventional laparoscopy. Future studies when more experience and cases have accumulated are suggested to compare the short-term and long-term outcomes of these three different approaches of myomectomy.

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Emergency Contraception: A Survey of Hong Kong Women's Knowledge and Attitudes

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Objectives: To investigate the knowledge and attitudes towards emergency contraception among women in Hong Kong.
Methods: A questionnaire survey was conducted among women who attended the general gynaecology clinic at a regional hospital from July 2014 to September 2014. Questions regarding the use of emergency contraception, knowledge, and attitudes towards emergency contraception were explored.
Results: Of the analysed cohort of 395 women, 215 (54.4%) had heard of emergency contraception. Among these women, 167 (77.7%) knew the correct timing for its use, and 87 (22%) had previously used emergency contraception. The media and friends represented the most common source of information. Doctors and the Family Planning Association of Hong Kong were rarely the source. Increased advertisement of emergency contraception was supported by 70% of women, while 37.5% supported over-the-counter availability of emergency contraceptive pills. Reasons for and against these responses were explored.
Conclusion: The awareness and knowledge of emergency contraception among local women has significant room for improvement. More women supported increased advertisement of emergency contraception and the sale of emergency contraceptive pills over the counter. The provision of emergency contraceptive pills over the counter may be an important means if its availability is improved in Hong Kong. Improved education of the public is required to promote awareness and local acceptance of emergency contraception.
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Keywords: Attitude; Contraception, postcoital; Knowledge; Nonprescription drugs

Introduction

Emergency contraception (EC) is an effective emergency contraceptive method for women who have unprotected sexual intercourse. In Hong Kong, there are currently three methods of EC: the traditional levonorgestrel-only pill, the newer ulipristal acetate pill, and the intrauterine contraceptive device (IUCD). These are highly effective methods with a low failure rate. The failure rate of the levonorgestrel-only pill is 2% to 3%; the failure rate of the ulipristal acetate pill is 1% to 2%; the failure rate of IUCD at 0.09% is the most effective method[1]. Levonorgestrel-only pills are well known to be safe[2] with only short-term side-effects such as nausea, vomiting, and menstrual disturbance[3]. They are well tolerated, and pose no risk of overdose with no major drug interactions or contra-indications[2].

The effectiveness of emergency contraceptive pills (ECPs) is limited by timing of administration. Hence, expedited accessibility to the pill is of utmost importance. In Hong Kong, the levonorgestrel-only pill is registered as a Part 1 Schedule 3 Poison that must be prescribed by a doctor. To increase availability of the drug, the Family Planning Association of Hong Kong has been advocating advanced provision of ECPs[4]. The next step may be to follow the practice of other countries and provide ECPs over the counter. Nonetheless whether this practice will be well accepted by local women is another issue. This study aimed to investigate the knowledge and attitudes of women in Hong Kong towards EC.

Methods

This was a cross-sectional study consisting of women who attended the general gynaecology clinic for consultation in a regional public hospital in Hong Kong from July 2014 to September 2014. When patients registered at the clinic for consultation, eligible women were invited by the clinic nurses to complete a questionnaire consisting of 30 questions. Eligible women were Hong Kong residents aged between 15 and 50 years. They had to be able to read either English or Chinese.

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The questionnaire was pilot-tested. Written information concerning the objective and details of the study was provided to the participants prior to completion of the questionnaire. The sample size was calculated based on the formula:

$$n_0 = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 p(1-p)}{(p_0 - p)^2}$$

where α is the significance level (α=0.05) and β=1-power, assuming the power to be 80%; p is the proportion of women who support the sale of ECPs over the counter and is set to be 35%; p_0 is the proportion of women who supported provision of ECPs over the counter according to the 2004 study in Hong Kong, which is 25.7%[5]. Hence a sample size (n) calculated to be 259 would be sufficient to identify any difference in the proportion of women who supported the provision of ECPs over the counter compared with the reference figure.

The questionnaire examined demographic data, the woman's use of contraception, knowledge of EC, experience with use of ECPs, and attitude towards EC. It was estimated that women would require 10 to 15 minutes to complete the questionnaire. Significant incomplete questionnaires (those with a missing value for more than half in the questionnaire) were excluded from the analysis. This study was approved by the Institutional Review Board of the Hospital (ref: HKEC-2014-056).

Statistical Analyses

Data analysis was performed using PASW Statistics 18, release version 18.0.0 (SPSS, Inc., 2009, Chicago [IL], US). For categorical data, the Chi-square test and Fisher's exact test were used as appropriate. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used.

Statistically significant variables were adopted as potential predictors and entered into logistic regression to identify significant factors in women who supported the provision of ECPs over the counter. The critical level of statistical significance was set at 0.05. The multiple logistic regression analysis (backward elimination procedure) was performed by including variables found to be significant at a level of p<0.2 by univariate analysis, if considered to be an important demographic variable.

Results

A total of 474 women were approached during the 12-week study period, of whom 35 refused to complete the questionnaire and 10 were excluded because they did not fall into the age range of 15 to 50 years. A total of 429 questionnaires were returned; among these, 34 were incomplete and 395 were available for analysis. The response rate was 92.1%.

Characteristics of Participants

The demographic characteristics are shown in Table 1. The mean age of the participants was 38.4 years. A large proportion (15%) were housewives and 3% were students. Around 20% of women had no previous formal method of contraception.

Awareness and Knowledge of Emergency Contraception

A total of 215 (54.4%) of the women had heard of EC. Their knowledge of EC and the most common sources are shown in Table 2. Awareness was greater among younger women. There was also evidence of an association between awareness and the women's monthly income, with a statistically significant (p<0.01) higher awareness among women with higher monthly income. The awareness of EC was not statistically associated with education level, number of children, number of previous abortions, marital status or whether they had been pregnant after the use of ECP (Table 3). Our data also showed that there was an association between knowledge of the time frame of administration of levonorgestrel-only pills and age, with younger women being better informed. In addition, knowledge about timing was higher in women with previous use of EC (Table 3).

To further analyse local women's knowledge of EC, a score was assigned for the five questions that tested knowledge. In all, 131 (60.9%) women who had heard of EC answered three (of five) questions correctly. There continued to be an association between a high level of knowledge and young age. Among women who had heard of EC, 90% of those aged 15 to 24 years answered at least three questions correctly, and 72% of those aged 25 to 34 years. These associations were statistically significant (p<0.001).

There was also an association between knowledge and education level. Of women with an undergraduate degree, 77% answered at least three (of five) questions correctly. In contrast, among those with a secondary school qualification, the figure was 56%. These associations were statistically significant (p<0.001).

The above data indicate that women who were younger, had a higher education level, and had used

Table 1. Characteristics of participants (n=395)*

Characteristic	Data
Age (years)	38.4 (40 [33-45])
Occupation	
Managers and administrators	8 (2)
Professionals	19 (5)
Associate professionals	30 (8)
Clerks	54 (14)
Service workers and shop sales workers	43 (11)
Elementary occupations	6 (2)
Self-employed	1 (0.3)
Unemployed	5 (1)
Housewife	59 (15)
Student	13 (3)
Missing data	157 (40)
Education level	
No formal education	4 (1)
Primary school	33 (8)
Secondary school	243 (62)
Undergraduate or above	114 (29)
Missing data	1 (0.3)
Women's monthly income (HK$)	
<10,000	184 (47)
10,000-29,999	171 (43)
30,000-50,000	29 (7)
>50,000	11 (3)
Religious belief	
None	265 (67)
Buddhism	53 (13)
Christianity	61 (15)
Catholic	15 (4)
Others	1 (0.3)
Ethnic origin	
Chinese	385 (98)
Caucasian	1 (0.3)
Filipino	5 (1)
Indonesian	4 (1)
Smoker	
Yes	41 (10)
No	354 (90)

* Data are shown as median (interquartile range) or No. (%) of subjects. Because of rounding, not all percentages total 100

Table 1. (con'd)

Characteristic	Data
No. of children	
0	169 (43)
1	100 (25)
2	106 (27)
≥3	20 (5)
No. of induced abortions	
0	296 (75)
1	55 (14)
2	31 (8)
≥3	13 (3)
Marital status	
Married	245 (62)
Single	116 (29)
Divorced / separated / widowed	34 (9)
Sexual status	
Never sexually active	40 (10)
Previously sexually active, but inactive for recent 1 year	93 (24)
Sexually active for recent 1 year	262 (66)
Method(s) of contraception previously used	
None	77 (20)
Other reasons (not mention)	29 (7)
Not sexually active	40 (10)
Trying to conceive	8 (2)
Withdrawal method	91 (23)
Calendar method	33 (8)
Barrier method (including male and female condom, diaphragm)	241 (61)
Spermicide	6 (2)
Hormonal contraceptive pills	79 (20)
Injectables	18 (5)
Intrauterine device	37 (9)
Male / female sterilisation	5 (1)

EC before had the greatest knowledge about timing of administration of the levonorgestrel-only pill.

Use of Emergency Contraceptive Pills

In this cohort, 87 (22%) women had previously used ECPs. In all, 49 (12.4%) women had used it once, 18 (4.6%) had used it twice, five (1.3%) had used it 3 times,

and 15 (3.8%) had used it ≥4 times.

Of these 87 women, 28 (32%) were aged between 25 and 34 years and 40 (46%) were aged 35 and 44 years. The correlation was statistically significant (p<0.001). The number of times a woman became pregnant after taking ECPs, the source and reason for use of ECPs are shown in Table 4.

Attitudes towards Emergency Contraceptive Pills

Attitudes towards EC are shown in Table 5. In particular, 309 (78%) women stated that provision of ECPs over the counter would not reduce the likelihood of using condoms as a regular contraceptive method. Among these women, 289 (93.5%) had never been pregnant after taking ECPs. This association was statically significant (p<0.05).

Table 2. Participants' knowledge of emergency contraception (n=215)*

	No. (%)
Can intrauterine contraceptive device be used as emergency contraception?	
Yes	23 (11)
Within 72 hours after unprotected sex	6 (3)
Within 5 days after unprotected sex	3 (1)
Within 1 week after unprotected sex	1 (0.5)
Anytime after unprotected sex	3 (1)
Do not know	10 (5)
No	112 (52)
Do not know	80 (37)
Do emergency contraceptive pills cause abortion?	
Yes	44 (21)
No	54 (25)
Do not know	117 (54)
Are emergency contraceptive pills 100% effective?	
Yes	15 (7)
No	143 (67)
Do not know	57 (27)
When should emergency contraceptive pills be taken?	
Within 72 hours after unprotected sex	167 (78)
Within 5 days after unprotected sex	1 (0.5)
Within 1 week after unprotected sex	3 (1)
Anytime after unprotected sex	4 (2)
Do not know	40 (19)
Can emergency contraceptive pills replace regular contraceptive methods?	
Yes	12 (6)
No	167 (78)
Do not know	36 (17)
Source(s) of emergency contraception knowledge	
Family Planning Association	38 (18)
Media	80 (37)
Friends	75 (35)
Doctors	31 (14)
School	20 (9)
Parents	4 (2)

* Because of rounding, not all percentages total 100

Table 3. Awareness of existence of EC by age and monthly income, and identifying correct timing of levonorgestrel-only pills by age and experience*

	Heard of EC (n=215/395; 54%)	p Value	Able to identify correct timing of levonorgestrel-only pills (n=167/215; 78%)	p Value
Age (years)		<0.01		<0.05
15-24	20/31 (65%)		20/20 (100%)	
25-34	55/88 (63%)		43/55 (78%)	
35-44	93/163 (57%)		72/93 (77%)	
>44	47/113 (42%)		32/47 (68%)	
Income (HK$)		<0.01	–	
≤10,000	184 (46%)			
$10,001-29,999	171 (60%)			
$30,000-49,999	29 (66%)			
≥$50,000	11 (82%)			
Use of EC before	–			
Used			65/67 (97%)	
Not used			102/148 (69%)	

Abbreviation: EC = emergency contraception

* Because of rounding, not all percentages total 100

Table 4. Previous pregnancies after taking emergency contraceptive pills, as well as reasons for and source of emergency contraceptive pills (n=87)*

	No. (%)
Have you ever been pregnant after taking emergency contraceptive pills?	
Yes	12 (14)
1	7 (2)
2	2 (2)
3	1 (1)
≥4	2 (2)
No	75 (86)
How did you obtain the emergency contraceptive pills (can choose >1 item)?	
Prescribed by doctor at the Family Planning Association	18 (21)
Prescribed by general practitioner	20 (23)
Prescribed by doctor at accident and emergency department	2 (2)
Advanced prescription by doctor	2 (2)
From the pharmacy	37 (43)
From friend	15 (17)
Why did you use emergency contraceptive pills?	
Condom accident	18 (21)
Did not use regular contraceptive method	43 (49)
Omitted contraception that time	26 (30)

* Because of rounding, not all percentages total 100

Table 5. Attitudes towards emergency contraception (n=395)*

Attitude	No. (%)
Would availability of emergency contraceptive pills over the counter reduce your likelihood of using a condom?	
Yes	86 (22)
No	309 (78)
Would availability of emergency contraceptive pills over the counter reduce your likelihood of using other contraceptive methods?	
Yes	76 (19)
No	319 (81)
Would availability of emergency contraceptive pills over the counter increase your likelihood of unprotected sex?	
Yes	68 (17)
No	327 (83)
In case of unprotected sex, would you be more likely to use emergency contraceptive pills if they were available over the counter?	
Yes	153 (39)
No	242 (61)
Should emergency contraception be more widely advertised?	
Yes	278 (70)
May help to reduce unwanted pregnancies and termination of pregnancies	201 (51)
It is not well-known enough to people at risk	173 (44)
It is useful to specific groups (e.g. rape victims)	159 (40)
No	117 (30)
It may promote inappropriate regular contraceptive practice	62 (16)
It may promote casual sex	82 (21)
It is not morally acceptable	27 (7)
There is already enough publicity	16 (4)
Would you prefer emergency contraceptive pills to be made available over the counter?	
Yes	148 (37)
It will be more convenient for users	86 (22)
It will be less embarrassing for users	45 (11)
It will help to reduce unwanted pregnancies or termination of pregnancies	96 (24)
It will encourage women to use it at times of unprotected sex	44 (11)
No	247 (63)
Women may use it inappropriately	210 (53)
It may promote inappropriate regular contraceptive practice	96 (24)
It may promote casual sex	141 (36)
It is not morally acceptable	36 (9)
It may lead to concerns regarding regulation of pharmacists	109 (28)

* Because of rounding, not all percentages total 100

There was an association between the use of ECPs and support for the provision of ECPs over the counter, with a higher degree of support by women who had previously used ECP. Around 29.1% of those who supported the provision of ECPs over the counter had previous use of ECPs; only 17.8% of those who did not support the provision of ECPs over the counter had used ECPs. These associations were statistically significant ($p<0.01$).

There was also an association between history of induced abortion and support for provision of ECPs over the counter with a higher level of support by women who had a history of induced abortion (37.2%). Only 17.8% of those who did not support provision of ECPs over the counter had a history of induced abortion. These associations were statistically significant ($p<0.001$). Attitudes for supporting the provision of ECPs over the counter were not statistically associated with age or marital status.

Variables that were statistically associated with supporting the provision of ECPs over the counter ($p<0.2$) were further analysed using a logistic regression. These variables were "number of induced abortions" ($p<0.001$), "sexual status" ($p=0.11$), and "use of ECPs before" ($p=0.01$). The results showed that participants who had a history of induced abortion (odds ratio [OR]=1.60; 95% confidence interval [CI], 1.24-2.06, $p<0.001$) and those that had used ECPs before (OR=1.82; 95% CI, 1.11-2.97, $p=0.02$) were more likely to support availability of ECPs over the counter.

Discussion

In this study, subjects were recruited from a regional gynaecology clinic. These women had diverse social, economic, and cultural backgrounds. Given the sensitive nature of the topic, we believe that a response rate of 92.1% was satisfactory and the missing data (as shown in Table 1) would not affect statistical analysis as it did not exceed 1% of valid cases used for analysis in most parameters.

Women's Awareness of Emergency Contraception

Local women's awareness of EC has always been low. In our study, 54.4% of local women had heard of EC. This figure is lower than that from previous studies in Hong Kong. In a local study in an abortion clinic, 67% of respondents said they had heard of EC[6]. Another local study conducted in 2003 by the Family Planning Association of Hong Kong showed that 63.7% of respondents had heard of EC[5]. In the territory-wide survey in 1997 and 2002 on local women's knowledge, attitude and practice about family planning, 73.6%[7] and 71.1%[8] of participants had heard of EC, respectively. In contrast, women's awareness of EC in western countries is comparatively higher. In a Swedish abortion clinic, 83% of the respondents had heard of EC[9]. In a study in Aberdeen, UK, 94% of respondents had heard of EC[10]. This shows that there is an urgent need to improve women's awareness of EC in Hong Kong.

Our study showed that there was a higher awareness of EC among younger women, consistent with previous local[5] and overseas[9] studies. In another UK study[10], there was also an association between awareness of EC and home ownership. In our study, a higher awareness of EC was found in those with a higher monthly income.

Women's Knowledge of Emergency Contraception

Among women who had heard of EC, knowledge was acceptable, with 77.7% aware of the correct time frame for administration of levonorgestrel-only pills. This was lower when compared with a local study conducted in 2003[5] showing that 81.3% of women were aware of the correct time frame. This may be because our study population was drawn from the general gynaecology clinic, not the Family Planning Service.

It is nonetheless encouraging that a higher level of knowledge was present among younger women. All women aged 15 to 24 years could identify the time frame correctly. A higher level of knowledge was also found in those with a higher education level and those who had used EC before.

At the time of the study, ulipristal acetate ECP had been licensed in Hong Kong although not widely publicised locally. Thus knowledge about this pill was not tested in our questionnaire. As use and knowledge about the pill becomes more prevalent, it may be an area worth exploring in future studies.

In 2002, an article published in the *Hong Kong Medical Journal* provided an update for doctors about prescription of EC. It stressed that EC cannot replace regular contraception[11]. Among those women who had heard of EC, 23% believed either that EC could replace regular contraception or did not know the correct answer to this question. This deficiency in knowledge deserves our attention, reminding doctors to educate women not only about the correct time frame for EC administration, but also to stress that it cannot replace regular contraceptive practice.

It is worrying that 75% of women who had heard of EC thought that ECPs cause abortion or could not answer the relevant question. This misconception may negatively affect a woman's attitude towards a more liberal provision of ECPs. It is possible that with enhanced education, this misconception may be corrected and women's attitude towards ECPs may improve.

As with a previous local study[5], most women learnt about EC from friends or the mass media. The source of EC information was rarely from the doctor or the Family

Planning Association of Hong Kong. This situation is similar to that in Australia[12] and the UK[10] and is not ideal since knowledge from these sources may be unreliable. Nonetheless it may also be because doctors are not well informed. In a 2007 study, local gynaecologists in the private sector only scored 6.08 out of 12 in the knowledge test[13]. This may be why local doctors hesitate to discuss EC during routine contraceptive counselling.

Use of Emergency Contraception

In our study, 22% of women had previously used EC. This figure was higher than that found in previous local studies. In a local study published in 19996, only 10% of women who attended an abortion clinic had ever used EC. In a later study conducted in 20035, only 15.7% had previously used EC.

Attitude towards Emergency Contraception

One of the concerns about increasing the availability of EC through advanced provision was the promotion of casual sex[5]. Nonetheless a local randomised controlled trial conducted in 2001 showed that when women were given three courses of progestogen-only pills to keep at home, they did not abuse the ECPs, and their contraceptive choice and consistency of use remained unchanged[14]. A systematic review also showed that advance provision did not lead to increased frequency of unprotected intercourse or change in contraceptive methods[15]. In our study, the majority also claimed that provision of ECPs over the counter would not reduce their likelihood of practising regular contraception (78%) or increase their likelihood of engaging in unprotected sex (83%). Hence, our study suggests that even if ECPs are legalised to be sold over the counter, it is likely that local women will continue to display a responsible attitude towards sexual behaviour and will not neglect their regular contraceptive practices.

The majority of respondents in our study (70%) believed that EC should be more widely advertised. The figure in our study was significantly higher when compared with a previous local study in Hong Kong in 2003 where only 46.3% of local women supported advertisement of ECPs[5].

Provision of ECPs over the counter was supported by 37.5% of women. Again, this figure has increased when compared with the local study in 2003[5] wherein only 25.7% supported over-the-counter sale of ECP.

The attitude of the women in our study was less conservative than before. This is an important point to consider for local regulatory authorities. Women supported the provision of ECPs over the counter mostly because they believed it would be more convenient for users to obtain the drug. Women who objected to over-the-counter provision of ECPs were mostly concerned that it would promote casual sex.

In a 2004 US Food and Drug Administration (FDA) hearing, progestogen-only ECP was not deregulated as there were insufficient data to show that it could be safely used by young adolescent women without the professional supervision of a licensed practitioner[16]. In July 2009, the pill was first approved for use without a prescription for women aged ≥17 years and as a prescription-only option for women <17 years[17]. In April 2013, the product was approved for non-prescription use in women as young as 15 years[18]. In June 2013, the US FDA approved the product to be available without a prescription for use by all women of reproductive potential[19]. This suggests that the acceptance of ECPs over the counter is a process that occurs over time among both users and health care providers. Hong Kong authorities may also learn from the US' progressive steps in the approval of ECP provision over the counter.

Conclusion

Our study shows that local women's awareness and knowledge of EC are still low with significant room for improvement. An increased proportion of local women support wider advertisement and more support over-the-counter provision. This may be of value to local law-making authorities. Meanwhile, education of the public to enhance awareness and local acceptance of EC should be further promoted.

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Predictors of Success of Methotrexate in the Treatment of Ectopic Pregnancy: A New Perspective

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Objectives: Methotrexate is commonly used in the treatment of ectopic pregnancy. Outcomes with a suboptimal drop in human chorionic gonadotrophic (hCG) level are unknown. This study aimed to determine the optimal cutoff value for hCG drop in detecting treatment success, to investigate the predictors of success, and to evaluate outcome following a single dose of methotrexate as treatment of ectopic pregnancy.
Methods: A retrospective study was conducted of 182 patients with ectopic pregnancy treated with methotrexate. Outcomes included resolution of hCG or further surgical intervention. The optimal cutoff value for hCG drop in prediction of treatment success was evaluated using receiver operating characteristic curve analysis.
Results: The success rate was 79.1%. The cutoff value for hCG drop between day 4 and day 7 for prediction of success following a single dose of methotrexate was 3.34%, with a positive predictive value of 91.67%. Compared with subjects with initial hCG level of <1000 IU/L, there was a significant reduction in success for those with initial hCG levels ranging from 1000 to 3999 IU/L (odds ratio=0.184; p=0.02), 4000 to 4999 IU/L (odds ratio=0.116; p=0.03), and ≥5000 IU/L (odds ratio=0.057; p=0.01).
Conclusions: Pretreatment hCG level and hCG drop between day 4 and day 7 are good predictors of success following methotrexate treatment. With a high positive predictive value for success, conservative management with serial hCG monitoring may be considered when drop in hCG level between day 4 and day 7 is ≥3.34%.
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Keywords: Chorionic gonadotropin/therapeutic use; Humans; Methotrexate; Pregnancy, ectopic; Treatment outcome

Introduction

Ectopic pregnancy is potentially life-threatening with an estimated incidence of 1% to 2% of all pregnancies[1]. With the wide availability of transvaginal ultrasound and quantitative serum beta–human chorionic gonadotropin (hCG) assay, ectopic pregnancies can be diagnosed early, leading to successful management without resort to surgery.

Medical treatment with methotrexate was established in the late 1980s[2]. It is an alternative to surgery and has been proven to be safe and effective[3]. Methotrexate is a folic acid antagonist that interferes with DNA synthesis and cell proliferation. Tissues with a rapid cellular turnover, such as trophoblasts, are most susceptible to its action.

Methotrexate is commonly given as a single intramuscular injection at a dose of 50 mg/m^2 body surface area according to the single-dose protocol[4]. Successful treatment in this protocol is defined by a ≥15% decrease in hCG level between day 4 and day 7 after methotrexate administration. A prospective study has found that a 15% decrease in hCG level between day 4 and 7 was a good indicator of success with positive predictive value (PPV) up to 93%[5].

Appropriate patient selection is important for methotrexate treatment success. Success rates have been reported to range from 63% to 97.6%[6]. Although associated with the initial hCG level, there is no consensus on the threshold of hCG above which methotrexate is contra-indicated. A systematic review of several observational studies reported a failure rate of ≥14.3% with single-dose methotrexate when pretreatment hCG level was >5000 IU/L, compared with a 3.7% failure rate for hCG level of <5000 IU/L[7].

The single-dose methotrexate protocol stipulated that when there was a <15% decline in hCG level from day

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4 to day 7, a second injection of methotrexate would be given[4]. How this algorithm was developed was not clearly demonstrated in the article. To the best of our knowledge, no study has evaluated the outcome after a single dose of methotrexate when the drop in hCG level between day 4 and day 7 is <15%.

This study aimed: (i) to determine the optimal cutoff value of hCG drop in detecting treatment success and avoiding the need for second methotrexate dose or surgical intervention; (ii) to identify predictors of success after a single dose of methotrexate in the treatment of ectopic pregnancy; and (iii) to evaluate the outcome following a single dose of methotrexate.

Methods

Study Design and Setting

We conducted a retrospective cohort study in a tertiary hospital in Hong Kong. Patients with ectopic pregnancy managed medically with methotrexate from January 2008 to December 2013 were included. Patients with ectopic pregnancy treated with methotrexate were identified from our hospital Gynaecology Audit Database and cross-checked with the Hospital Authority Clinical Data Analysis and Reporting System. Individual clinical records were reviewed. Ethics approval was obtained from the Kowloon West Cluster Research Ethics Committee of the Hospital Authority.

Subjects

Patients with suspected ectopic pregnancy were evaluated by transvaginal ultrasound and serial measurements of serum hCG concentration measured by enzyme immunoassay (UniCel DxI 800 immunoassay system; Beckman Coulter, US). The diagnosis of ectopic pregnancy was made where there was sonographic identification of an adnexal mass or gestational sac outside of the uterus[8]. If there was no evidence of either intrauterine or extrauterine pregnancy on the initial ultrasound scan, hCG level was taken into consideration. When hCG level was above the discriminatory zone (1500-2000 IU/L), ectopic pregnancy was diagnosed even when no adnexal mass was evident on ultrasound. Ectopic pregnancy was also suggested when there were abnormally rising (<53%) or plateauing hCG levels 48 hours apart and below the discriminatory zone[9]. In order to exclude the diagnosis of and administration of methotrexate to a failing pregnancy, even with the presence of an adnexal mass outside the uterus or hCG level above the discriminatory zone, two hCG levels 48 hours apart were required before administration of methotrexate.

Patients were not eligible for methotrexate treatment if they met the following criteria: haemodynamic instability; signs of peritonitis; abnormal baseline haematological, renal or hepatic laboratory values; and ectopic pregnancy with fetal cardiac activity.

Study Protocol

Patients received a single dose of methotrexate 50 mg/m^2, with the surface area calculated from a nomogram of height and body weight. The hCG level was measured on day 4 and day 7. The day of methotrexate administration was considered day 0. Optimal hCG drop was defined as a ≥15% decrease in hCG level between day 4 and day 7, followed by a weekly hCG level measurement until it became negative. When there was a <15% drop in hCG level between day 4 and day 7 following methotrexate administration, options including conservative management, second dose of methotrexate and surgery were offered to patients depending on symptoms, haemodynamic status, ultrasonographic findings, and post-methotrexate hCG levels. Treatment failure was defined as the need for additional methotrexate or surgical intervention.

Data including patients' demographic information, history of ectopic pregnancy, history of pelvic inflammatory disease, presenting signs and symptoms, hCG levels before and after treatment, and ultrasound results were recorded. In patients who were successfully treated with methotrexate the recovery time was also recorded, defined as the period from the day of methotrexate administration until the day of the last follow-up. Regular follow-up was provided until hCG level was <15 IU/L or a negative urine pregnancy test was obtained.

Statistical Analyses

To establish a cutoff value for hCG drop between day 4 and day 7 that would confirm treatment success, receiver operating characteristic (ROC) curve analysis using weighted Youden's Index was performed, defined as[10,11]:

Youden's Index: J = max {Sensitivity + r x Specificity - 1}
where *r* = (1 - prevalence) / (cost x prevalence).

The optimal cutoff was identified using cost as 1 and prevalence as the proportion of successful cases in the subject sample. The area under the curve, sensitivity, specificity, accuracy, as well as PPV and negative predictive value (NPV) at optimal cutoff were calculated.

Student's *t* test, Mann-Whitney *U* test, Pearson's

Chi-square test or Fisher's exact test was used where appropriate to compare the demographic and clinical characteristics of subjects with methotrexate treatment. Success rate of subjects with different hCG level was calculated. Pretreatment hCG level was stratified into four categories for comparison: <1000 IU/L, 1000-3999 IU/L, 4000-4999 IU/L, and ≥5000 IU/L. The failure rate of methotrexate has been reported to increase when initial hCG level is >4000 IU/L[12]. A systematic review reported an increase in failure when pretreatment hCG levels were >5000 IU/L[7]. Therefore, 4000 IU/L and 5000 IU/L were chosen as cutoff points. Variables with p<0.2 on univariate logistic regression were identified and further analysed by backward multivariate logistic regression. Student's *t* test was used to compare the recovery time between patients with an optimal drop in hCG level after methotrexate and those with a suboptimal drop.

All statistical analyses were performed using the Statistical Package for the Social Sciences Windows version 22 (SPSS Inc., Chicago [IL], US) and the R version 2.15.2 (R Foundation for Statistical Computing website: www.r-project.org). Statistical significance was set at p<0.05.

Results

A total of 1034 patients were diagnosed with ectopic pregnancy during the study period, and 182 received methotrexate. Six (3.3%) patients required a second dose of methotrexate and 32 (17.6%) required surgical intervention. The overall success rate was 79.1% (144/182).

Table 1 shows the demographic and clinical characteristics of the success and failure groups. There was no statistical significance between the two groups regarding patients' background including age, parity, history of

Table 1. Demographic and clinical characteristics of subjects with methotrexate treatment*

Characteristic	Success (n=144)	Failure (n=38)	Total (n=182)	p Value†
Age (years)	33 (30-37)	32.5 (28.8-36.3)	33 (29-37)	0.26
Parity				0.56‡
0	72 (50)	23 (61)	95 (52)	
1	57 (40)	14 (37)	71 (39)	
2	11 (8)	1 (3)	12 (7)	
3	4 (3)	0	4 (2)	
Ectopic pregnancy				0.73§
Yes	28 (19)	9 (24)	37 (20)	
No	116 (81)	29 (76)	145 (80)	
PID				0.75‡
Yes	12 (8)	4 (11)	16 (9)	
No	132 (92)	34 (89)	166 (91)	
Presence of adnexal mass in USG				0.78§
Yes	112 (78)	31 (82)	143 (79)	
No	32 (22)	7 (18)	39 (21)	
Maximum diameter of adnexal mass (mm)	19 (14-28)	20 (16-24)	19.0 (14.5-26)	0.99
Presence of free fluid in USG				0.38§
Yes	82 (57)	18 (47)	100 (55)	
No	62 (43)	20 (53)	82 (45)	
hCG level (IU/L)	1521.5 (624-2387.25)	2773 (1538.25-4365.75)	1621 (731.25-2970.75)	<0.001
hCG level drop (%)	32.86 (18.13-48.74)	1.38 (-4.57 to 13.41)	26.24 (10.85-44.07)	<0.001

Abbreviations: hCG = human chorionic gonadotrophin; PID = pelvic inflammatory disease; USG = ultrasonography

* Data are shown as No. (%) or median (interquartile range). Because of rounding, not all percentages total 100

† Mann-Whitney *U* test

‡ Fisher's exact test

§ Pearson's Chi-square test

ectopic pregnancy or history of pelvic inflammatory disease. There was no significant difference between the two groups for presence or absence of adnexal mass or free fluid in the pelvis on ultrasound. No significant difference was found between the two groups for size of adnexal mass. The pretreatment hCG level of the success group was significantly lower than that of the failure group (median: 1521.5 IU/L vs. 2773 IU/L; p<0.001). A statistically significant difference was also found between the two groups for the hCG drop between day 4 and day 7 after administration of methotrexate (median: 32.86% vs. 1.38%, p<0.001).

The ROC curve analysis using weighted Youden's Index was performed to determine the cutoff value to predict the success of a single dose of methotrexate (Figure). A total of 14 women were excluded because day-4 or day-7 hCG level was not available. Among 168 patients, 51 had hCG drop of <15% between day 4 and day 7 after methotrexate. The cutoff value was found to be 3.34% with a sensitivity of 94.29%, specificity of 57.14%, and accuracy of 88.10%. The PPV was 91.67% and the NPV was 66.67%. The positive likelihood ratio was 2.20 and the negative likelihood ratio was 0.10.

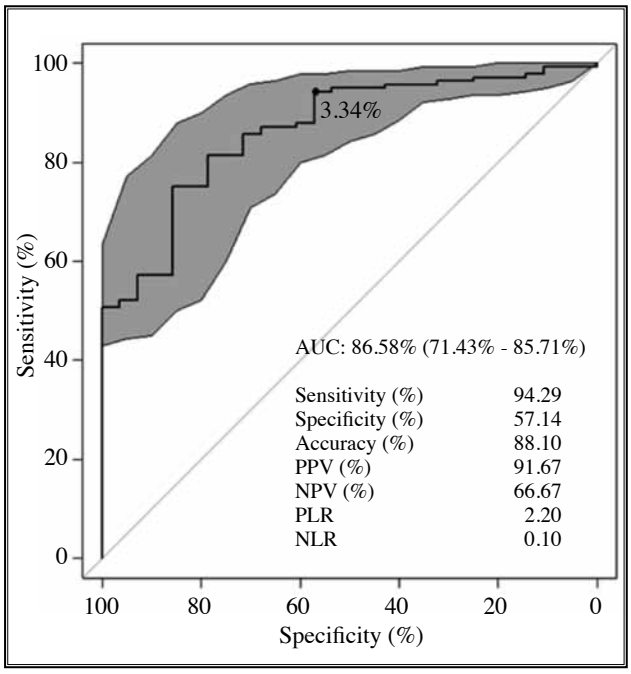

Figure. Receiver operating characteristic plot of the drop in human chorionic gonadotrophic level (%) after one dose of methotrexate

Abbreviations: AUC = area under the curve; NLR = negative likelihood ratio; NPV = negative predictive value; PLR = positive likelihood ratio; PPV = positive predictive value

Pretreatment hCG levels were stratified into different categories for comparison (Table 2). The success rate reduced with an increase in hCG level. Multivariate logistic regression analysis revealed that pretreatment hCG level and drop in hCG level between day 4 and day 7 after methotrexate were factors that remained significant in prediction of success of methotrexate (Table 3). There was a significant reduction in the success rate for subjects with initial hCG value in the range of 1000-3999 IU/L (odds ratio [OR]=0.184, 95% confidence interval [CI], 0.046-0.739; p=0.02), 4000 to 4999 IU/L (OR=0.116, 95% CI, 0.017-0.786; p=0.03), and ≥5000 IU/L (OR=0.057, 95% CI, 0.008-0.417; p=0.01) when compared with those with initial hCG value of <1000 IU/L.

For patients who were successfully treated with one dose of methotrexate, the mean (±standard deviation) recovery time was 29.3 ± 11.8 days. The mean recovery time was 27.4 ± 11.0 days if hCG drop was ≥15% and 33.0 ± 10.9 days if hCG drop was between 3.34% and 15%. The difference between the recovery time of the two groups was significant (p=0.04).

Abdominal pain was the most common side-effect following methotrexate, present in 26 (18.1%) of all successful cases with six requiring hospital admission. Pain was nonetheless self-limiting and all patients were discharged 1 day after admission.

Outcome of the failed cases was also reviewed. There were 38 failed cases in total, of whom six required a second dose of methotrexate. Surgical intervention after methotrexate was required in 32 (17.6%) patients. Among them, 17 (53.1%) patients had a suboptimal drop or rising trend of hCG level and opted for surgery following counselling. Emergency admission was required by 15 (46.9%) patients. Mean day of presentation was 9.2 ± 6.9 days after methotrexate. Typical presentation was abdominal pain with peritoneal signs and ultrasound showed free fluid in the pelvis. No patient suffered haemodynamic instability and laparoscopic surgery was successful in all cases except one where conversion to laparotomy was required due to surgical difficulty associated with haemoperitoneum and dense pelvic adhesions. No failed case required admission to the intensive care unit. Among 22 patients with hCG drop of <3.34% between day 4 and day 7, 14 (63.6%) required surgical treatment or a second dose of methotrexate.

Discussion

The overall success rate of methotrexate in treating ectopic pregnancy in our study was 79.1%. Pretreatment

Table 2. Success rate of subjects with methotrexate treatment

hCG level (IU/L)	Total	Success	Success rate (95% confidence interval) [%]
<1000	62	58	93.55 (83.50-97.91)
1000-3999	96	73	76.04 (66.05-83.91)
4000-4999	11	6	54.55 (24.56-81.86)
≥5000	13	7	53.85 (26.12-79.60)
Overall	**182**	**144**	79.12 (72.35-84.63)

Abbreviation: hCG = human chorionic gonadotrophin

Table 3. Multivariate logistic regression analysis showing association between characteristics of subjects and the success of methotrexate treatment

	Adjusted odds ratio* (95% confidence interval)	p Value
hCG level (IU/L)		
<1000	1	NA
1000-3999	0.184 (0.046-0.739)	0.02
4000-4999	0.116 (0.017-0.786)	0.03
≥5000	0.057 (0.008-0.417)	0.01
hCG level drop (%)	1.070 (1.038-1.104)	<0.001

Abbreviations: hCG = human chorionic gonadotropin; NA = not applicable

* Adjusted odds ratio derived from backward multivariate logistic regression with variables including age, parity, hCG level, and hCG drop

hCG level and drop in hCG between day 4 and day 7 were good predictors of success. When there was a ≥3.34% drop in hCG between day 4 and day 7 after a single dose of methotrexate, the PPV for success was 91.67%. Comparing subjects with pretreatment hCG level of <1000 IU/L, there was a 8.61-fold decrease in the odds of treatment success for those with hCG level in the range of 4000 to 4999 IU/L and a 17.49-fold decrease when hCG level was ≥5000 IU/L.

Methotrexate inhibits DNA synthesis and cell proliferation. The time to achieve maximum concentration of methotrexate following intramuscular administration can vary from 30 to 60 minutes[13]. It combines with glutamate intracellularly to form methotrexate-polyglutamate (MTX-PG) by the process of glutamate polymerisation. The MTX-PGs are less able to be transported out of cells due to their large size, and serve as an intracellular storage pool of methotrexate. They can remain in the cells for a considerable period of time. This explains the efficacy of the single-dose methotrexate regimen for ectopic pregnancy. The disappearance of serum hCG after termination of pregnancy, whether intrauterine or extrauterine, follows a bi-exponential decay characterised by an initial rapid fall in hCG level during the first 48 hours with a half-life of 5 to 13 hours, followed by a slower phase with a half-life of 22 to 52 hours[14,15]. Before methotrexate comes into effect, the viable trophoblastic tissues produce hCG continuously. Therefore, the drop in hCG level following methotrexate can be variable.

Traditionally, a second dose of methotrexate should be administered if the hCG drop is <15% between day 4 and day 7 based on the single-dose methotrexate protocol[4]. No study has evaluated the outcome after a single dose of methotrexate when the drop between day 4 and day 7 is <15%. Our study found that the cutoff value to predict the success of a single dose of methotrexate was 3.34%. When there was a ≥3.34% drop in hCG level between day 4 and day 7 following administration of a single dose of methotrexate, 91.67% of patients had a successful outcome without need for a second dose or surgery. Therefore, if we can provide detailed pretreatment counselling and prompt access to medical care for all patients who receive a single dose of methotrexate, a more conservative approach with serial monitoring of hCG level can be considered when hCG drop is between 3.34% and 15%.

The mean recovery time in various studies has been reported to be 27 to 33 days after methotrexate[16,17]. All our

patients had regular follow-up until hCG level was <15 IU/L or a negative urine pregnancy test was obtained. The mean recovery time in our cohort was 29.3 ± 11.8 days. Women who had a ≥15% drop in hCG level following one dose of methotrexate had a statistically shorter mean recovery time than those who had a hCG drop between 3.34% and 15% (27.4 ± 11.0 days vs. 33.0 ± 10.9 days, p=0.04) . Both groups completed follow-up in a month.

The advantages of our study were that we had a homogeneous population, and all patients followed the same protocol for treatment and monitoring. There are some limitations to this study. It was a retrospective study in a Chinese population only with a small sample size, especially for the failure group. The decision to continue conservative management, proceed to a second dose of methotrexate or surgical intervention was not based on the drop in hCG level alone. The ultrasound findings, clinical condition, willingness to have regular follow-up visits and other factors that might affect patients' choices and these influences could not be assessed objectively. The study results might not be applicable to other ethnicities. We plan to design a prospective study to validate the new cutoff value of 3.34% for hCG drop between day 4 and day 7, and to confirm that it correctly identifies those who will achieve a successful outcome following a single dose of methotrexate.

Conclusions

Pretreatment hCG level and the hCG drop are good predictors of success of methotrexate in the management of ectopic pregnancy. When there was a ≥3.34% drop in hCG level between day 4 and day 7, the PPV for success without the need for a second dose of methotrexate was 91.67%. Therefore, a conservative approach with hCG monitoring can be considered when the hCG drop between day 4 to day 7 is ≥3.34%. A prospective study is required for validation.

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Is Tension-free Vaginal Tape in the Correct Place? An Assessment by Postoperative Transperineal Ultrasonography at Three Months

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Objectives: To determine the position of tension-free vaginal tape (TVT) by transperineal ultrasound following placement by a standard blind insertion technique, and to investigate the relationship between position of TVT and associated clinical outcome.
Methods: Postoperative evaluation was conducted at 3 months with transperineal 2-dimensional ultrasound scan, standardised symptomatology questionnaire, visual analogue scale (VAS), and validated short form Incontinence Impact Questionnaire 7 in 32 women who had undergone TVT placement for genuine stress urinary incontinence.
Results: At 3-month examination, 90.6% of 32 women were subjectively cured. Tension-free vaginal tapes were placed within the target range of 50% to 70% of the urethral length in 65.6% of women. There was no difference in the urinary outcome between women with TVT placed within and outside the target range. Women with tape–longitudinal smooth muscle (tape-LSM) distance of <3 mm or >5 mm had a significant improvement in VAS score (p=0.04) compared with those with tape-LSM distance of 3 to 5 mm. Nonetheless those with tape-LSM distance of <3 mm had voiding dysfunction (15.4% vs. 0%; p=0.08). Tape width reduced from an initially manufactured 11 mm to a mean width of 6.4 mm.
Conclusions: About one-third of TVTs were found by postoperative transperineal ultrasound to have been placed outside the target range using a standard blind insertion technique.
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Keywords: Perineum/ultrasonography; Urethra; Urologic surgical procedures/methods

Introduction

Stress urinary incontinence in women is a common, distressing, and socially disabling condition. It is a major problem that affects more than 20% of the female population in the United States[1]. Stress urinary incontinence is defined by the International Continence Society[2] as the complaint of involuntary loss of urine on effort or physical exertion or during sneezing or coughing. Urodynamic stress incontinence (USI) is confirmed during urodynamic testing in the presence of leakage of urine during filling cystometry associated with increased abdominal pressure, in the absence of a detrusor contraction.

Although non-surgical treatments such as pelvic floor exercises are effective in some women[3], surgical intervention is superior in respect to subjective and objective cure and long-term cure[4]. During the last 10 years, the insertion of tension-free vaginal tape (TVT)[5] has become the gold standard in treatment of stress urinary incontinence because of its minimally invasive nature, high success rate, and similar or even lower complication rate compared with traditional abdominal surgery, i.e. open or laparoscopic Burch colposuspension[6-9].

According to Petros and Ulmsten's integral theory of female incontinence[10], positioning of TVT should be at the middle third of the urethra, which is also known as the high pressure zone, in order to be maximally effective in ensuring continence postoperatively. Westby et al[11] estimated that this zone lies in an area between 53% and

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72% along the urethral length. According to the literature report from Kociszewski et al[12], there is a significantly higher cure rate (93.1% vs. 88.2%) when the TVT is placed within the target zone with 3-to-5-mm tape–longitudinal smooth muscle (LSM) distance ($p<0.001$).

To date, TVT procedures have largely adopted a standard approach described by Ulmsten et al[5] in which the vaginal incision is made 10 mm from the external urethral orifice. This technique does not take into account individual urethral length, and is highly dependent on the surgeon's experience. Because of the natural differences in urethral length, which can vary between 20 and 50 mm, a wide variation in tape position in relation to the mid-urethra has been observed[13]. These possible discrepancies in tape position have not been properly assessed in Hong Kong or many other developed countries.

With the development of high-resolution ultrasound machines, use of ultrasonography in urogynaecology has become a well-established, non-invasive real-time means of assessing the anatomy and function of the lower urinary tract[14,15].

This study aimed to assess the anatomical position of TVT, inserted by a blind technique, with the use of perineal ultrasound postoperatively, and to investigate its relationship with clinical outcome.

Methods

This prospective pilot cohort study recruited 32 women with USI who underwent a TVT procedure in the Department of Obstetrics and Gynaecology of a tertiary urogynaecology referral centre in Hong Kong between 1 December 2013 and 31 December 2014. Women who were aged above 18 years, mentally able to provide written consent, diagnosed with USI, and consented for TVT were recruited. Women who refused or were unable to give written consent, who had undergone previous continence surgery, and those who demanded tape excision for voiding dysfunction less than 3 months postoperatively were excluded.

Baseline demographic data including age, parity, number of vaginal deliveries, number of Caesarean sections, heaviest weight of baby delivered, and a history of genital tract trauma were collected for analysis. Preoperative evaluation included completion of a standardised symptomatology questionnaire, i.e. severity of stress incontinence ranging from 0 to 3, with 0 being no symptoms and 3 being severe symptoms; voiding dysfunction assessment (screening for symptoms of poor stream, straining on voiding, sense of incomplete emptying and retention of urine); visual analogue scale (VAS) for subjective urinary incontinence symptoms ranging from 0 to 10, with 0 being 'no incontinence' and 10 being 'unbearable distress related to incontinence' on a 10-cm scale bar; and a validated short form Incontinence Impact Questionnaire 7 (IIQ7) in Chinese or English format for quality of life assessment. Data collection on demographics, symptoms and quality of life assessment was performed by our specialised continence nurse.

The TVT procedures were performed by a registered urogynaecologist or subspecialty trainees under direct supervision. Procedures were performed by one of four surgeons, each of whom had performed more than 30 TVT procedures prior to the beginning of this study. All TVT procedures were carried out using the GYNECARE TVT obturator device that comprises PROLENE polypropylene mesh 11 mm x 45 mm (Ethicon [J&J] Johnson & Johnson, US), according to the manufacturer's instructions, under general or regional anaesthesia and with preoperative antibiotic cover. A Foley catheter was inserted to empty the bladder before the procedure. The exit points were located by tracing a horizontal line 2 cm above the level of the urethral meatus; 2 cm lateral to the folds of the thigh. Two 0.5-cm transverse skin incisions were made bilaterally at the exit points. A 10-mm midline vaginal incision was made starting 10 mm proximal to the urethral meatus[5]. At the mid-urethral level, dissection was carried out from the vaginal skin incision behind the pubic bone towards the obturator foramen. With the safely winged guide, along the dissected track, the obturator membrane was perforated and the tip of the needle brought up to the skin incision. As soon as the needle tip reached the skin incision, the proximal end of the needle was disconnected and the tape was pulled upward through the skin. The procedure was then repeated on the other side. Check cystoscopy was performed to confirm integrity of the bladder. Caution was taken to avoid positioning the mesh with excessive tension by using Mayo curved scissors. Once the tape had been positioned properly, the plastic sheath was removed carefully. The ends of the tape were cut at skin level and vaginal and skin incisions were closed. All women received the same routine postoperative care that included Foley catheterisation for 1 day and analgesics on demand. Women were discharged on day 1 after surgery.

Postoperative evaluation of incontinence conducted at 3 months included transperineal ultrasound scan, standardised symptomatology questionnaire, VAS, and

IIQ7 questionnaire.

The postoperative transperineal ultrasound examinations were performed in a standard manner by qualified ultrasonographers using the ACCUVIX XG ultrasound system (Samsung Medison, South Korea). With the woman lying in the dorsal lithotomy position and standardised bladder-filling volume of 300 ml[14], a clean probe (3.5 MHz) convex 2D transducer, covered with plastic wrap, was placed in the area of the vaginal introitus at the level of the external urethral orifice, exerting minimal pressure and aligning the axis of the probe with the women's body axis[14]. Sonographically, in the mid-sagittal plane, using the pubic symphysis as a landmark, and bladder, urethra and rectum as standard plane for measurement, the longitudinal position of the TVT in relation to the urethra was measured. The shortest perpendicular distance between the LSM complex and TVT, also called the tape-LSM distance, was measured to determine the approximation of the two structures. The tape width was measured and compared with the manufactured width to determine the effective postoperative tape width (Figure 1). Ultrasound images were captured and saved for offline analysis. Images were magnified for more precise measurement with three measurements made and the average calculated.

Women with no incontinence subjectively were considered cured at the time of postoperative evaluation. Women were classified as improved if they had decreased frequency of stress incontinence.

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS version 22.0). Descriptive statistics of women demographics, mean tape distance from the target zone, and the mean tape-LSM distance were analysed using t test. Results were considered clinically significant at $p \leq 0.05$ for all statistical analysis.

The ethics committee of the Kowloon Central Cluster/Kowloon East Cluster approved the study (Study No. KC/KE-13-0164/ER).

Results

Characteristics of the Study Population

From a total of 57 TVTs performed during the study period, 32 women were recruited. The remaining women were not recruited either due to refusal or manpower limitations. The mean (± standard deviation) age of the study subjects was 61.2 ± 9.7 years and mean number of previous vaginal deliveries was 2.4 ± 1.2. Three of them (9.4%) had a history of Caesarean section. The mean weight of the heaviest baby delivered was 3.4 ± 0.5 kg. No woman had any history of genital trauma or major perineal tear (Table 1). Within this cohort, seven women underwent concomitant vaginal hysterectomy for pelvic organ prolapse, one underwent laparoscopic sacrocolpopexy for vault prolapse, and one underwent total laparoscopic hysterectomy for adenomyosis and menorrhagia.

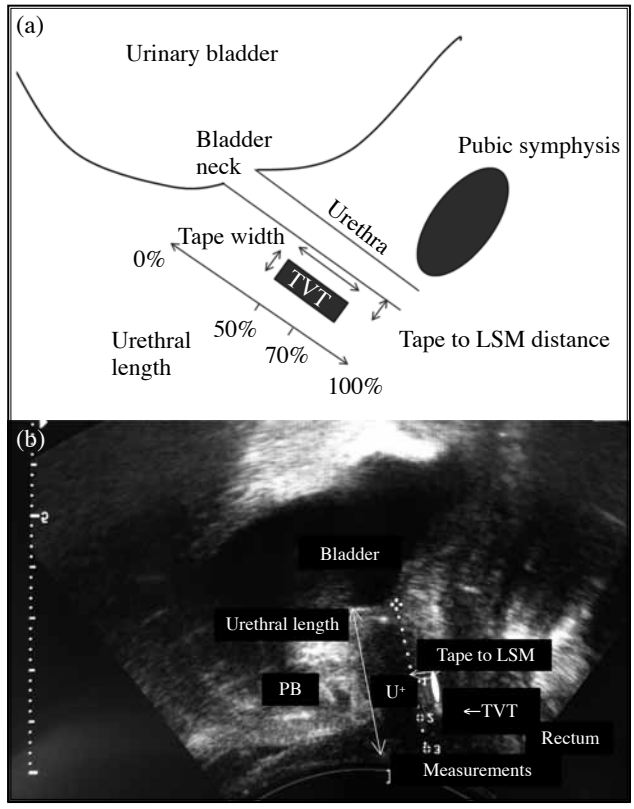

Figure 1. (a) Diagram and (b) transperineal ultrasound image showing standard transperineal ultrasound plane for measurement

Abbreviations: LSM = longitudinal smooth muscle; PB = pubic bone; TVT = tension-free vaginal tape; U+ = urethra

Table 1. Demographics of women who underwent tension-free vaginal tape insertion for stress urinary incontinence (n=32)

Demographics	Mean ± standard deviation
Age (years)	61.2 ± 9.7
Parity	2.6 ± 1.0
No. of vaginal delivery	2.4 ± 1.2
No. of Caesarean section	0.2 ± 0.5
Heaviest baby delivered (kg)	3.4 ± 0.5

All women had symptoms of USI, and 26 (81%) experienced stress urinary incontinence on a daily basis. The mean preoperative IIQ7 and VAS score was 39.2 ± 22.9 and 6.5 ± 2.1, respectively (Table 2).

Postoperative Outcomes

At 3-month follow-up, 29 (90.6%) women were subjectively cured, and the remaining three (9.4%) improved. Severity of stress incontinence was significantly lower in the postoperative group (p<0.001). The mean postoperative IIQ7 score at 3 months was 4.8 ± 13.4 and VAS score being 0.7 ± 1.2; both were significantly lower (p<0.001). Voiding dysfunction was present in two (6.3%) women; one had poor stream and one reported a sense of incomplete emptying. Neither had retention of urine with measured residual urine 0 ml (Table 2).

Ultrasound Findings

Ultrasonography showed that tape positioning between 50% and 70% urethral length was accomplished in 21 (65.6%) women (i.e. >50% of tape positioned 50%-70% along urethral length). The mean urethral length was 33.3 ± 4.8 mm. There was no significant difference in mean urethral length (32.4 mm vs. 35.1 mm) between the groups with tape placed within the target zone and outside the target zone (p=0.12).

The mean preoperative tape width reduced from 11 mm to 6.4 (± 1.2) mm postoperatively. There was no significant difference in the mean tape width between the groups with tape placed within the target zone and outside the target zone (6.2 mm vs. 6.5 mm; p=0.35). The mean tape-LSM distance was 3.6 ± 1.2 mm.

Subgroup Analysis of Clinical Outcomes in Relation to Tape Position

In subgroup analysis, women with tape positioned at the target zone had subjective cure rates comparable with those women with tape positioned proximal or distal to the zone (p=0.97). No significant difference in subjective severity, IIQ7 score or VAS score between these two groups were found (Table 3).

The mean tape width in the cure group was longer than that in the non-cured group, though not statistically significant (6.4 mm vs. 6.0 mm; p=0.62).

In tape-LSM distance subgroup analysis, women with tape-LSM distance of <3 mm or >5 mm showed a significant improvement in VAS (p=0.04) compared with women with tape-LSM distance of 3 to 5 mm. Nonetheless in this group there was an associated 15.4% incidence of voiding dysfunction that approached a level of statistical

Table 2. Overall outcome at 3 months' follow-up for women with tension-free vaginal tape for stress urinary incontinence*

	Mean ± standard deviation		p Value
	Preoperative	Postoperative	
Subjective severity of stress incontinence score	3.7 ± 0.7	1.0 ± 0.2	<0.001
Incontinence Impact Questionnaire 7 score	39.2 ± 22.9	4.8 ± 13.4	<0.001
Visual analogue scale score	6.5 ± 2.1	0.7 ± 1.2	<0.001

* Data are shown as mean ± standard deviation

Table 3. Comparison of outcomes based on tape positioning in relation to target zone

	At target zone (n=21)	Proximal / distal to target zone (n=11)	p Value
SI cure rate (%)	90.5	90.9	0.97
Mean improvement in subjective severity of SI	2.6	2.7	0.54
Mean improvement in IIQ7 score	33.3	36.6	0.70
Mean improvement in VAS	5.8	5.9	0.87
Voiding dysfunction (%)	9.5	0	0.29

Abbreviations: SI = stress incontinence; IIQ7 = Incontinence Impact Questionnaire 7; VAS = visual analogue scale

Table 4. Comparison of outcomes based on tape-LSM distance

	Tape to LSM 3-5 mm (n=19)	Tape to LSM <3 or >5 mm (n=13)	p Value
SI cure rate (%)	89.5	92.3	0.79
Mean improvement in subjective severity of SI	2.6	2.7	0.64
Mean improvement in IIQ7 score	29.8	41.3	0.15
Mean improvement in VAS score	5.2	6.7	0.04
Voiding dysfunction (%)	0	15.4	0.08

Abbreviations: SI = stress incontinence; IIQ7 = Incontinence Impact Questionnaire 7; VAS = visual analogue scale; LSM = longitudinal smooth muscle

significance (p=0.08). All women with voiding dysfunction had a tape-LSM distance of <3 mm. There was no significant difference in the improvement of subjective cure rate, subjective severity, or IIQ7 score between the two groups (Table 4).

Discussion

In our study, using a standard blind insertion technique to place TVT could only accomplish mid-urethral tape placement in 65.6% of women as revealed by ultrasonography at 3 months, with 6.2% (n=2) of TVTs placed closer to the bladder neck and 28.1% (n=9) closer to the urethral opening. This ultrasound success rate is comparable with the rate of 67.7% in an earlier study[16,17], according to the target zone suggested by Petros et al[10] and Westby et al[11].

A sonographic observational study by Kociszewski et al[13] found a wide variation in tape position relative to the percentage of urethral length in women who underwent TVT placement using the standard approach for starting the incision. Hence this group[13] proposed the theoretical assumption that consideration of individual urethral length is required to achieve consistent placement of TVT at the target zone. Later study from the same group demonstrated a higher success rate of 88.2%, achieved by determining the incision position based on the preoperative sonographically measured urethral length[12]. As illustrated in Figure 2, if there was no ultrasound to evaluate the urethral length preoperatively, tape tended to be placed closer to the bladder neck in women with a short urethra; on the contrary closer to the urethral opening in women with a long urethra. In our study, the mean urethral length of Hong Kong women was 33.3 (range, 26.8-42.8) mm. This result is comparable with a French study in which the mean urethral length was 33.1 mm[18]. We found no significant difference in mean urethral length (32.4 mm vs. 35.1 mm) between the groups with tape placed within and outside the target zone.

Another possible explanation that may contribute to the discrepancy in tape position is variable postoperative tape width. Our study observed that all tape width reduced postoperatively, from initially manufactured 11 mm to a mean of 6.4 (range, 3.3-8.9) mm. As demonstrated by Figure 3, a shortened tape width has a higher chance of placement outside of the target zone. Nonetheless this again was not well demonstrated in our study as there was no significant difference in the mean tape width between the two groups

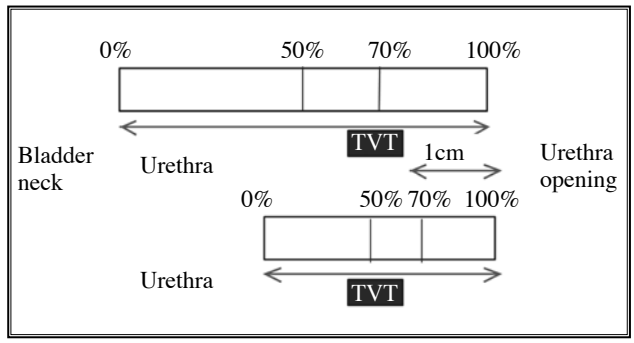

Figure 2. Diagram showing the estimated tape position in relation to urethral length by blind insertion technique
Abbreviation: TVT = tension-free vaginal tape

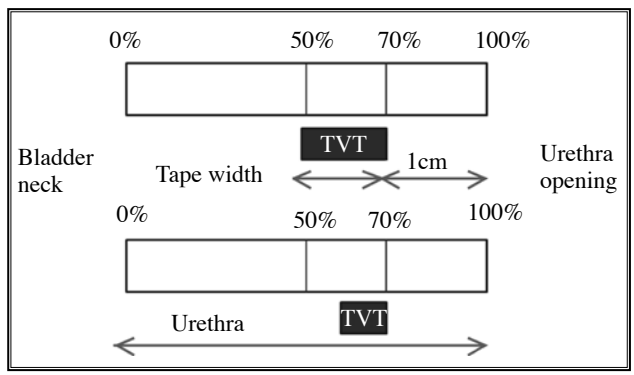

Figure 3. Diagram showing tape position in relation to tape width
Abbreviation: TVT = tension-free vaginal tape

(6.2 mm vs. 6.5 mm). We postulate that shortening of the tape could be due to folding inside the placement pathway that would happen if the dissected pathway was either too narrow, or if the tape became coiled inside the pathway during improper TVT placement. Another possible explanation was inappropriate tension adjustment during the TVT procedure. TVT is a polypropylene mesh with elastic properties due to its knitted composition. Under high tension, the tape may be stretched with consequent reduction in tape width.

In our study, women with ultrasound findings of tape within the target zone did not show significant difference in subjective cure rate, subjective severity, or quality of life assessment score when compared with the group with tape outside the target zone. Currently the relationship between tape position and clinical outcome remains contradictory. Earlier studies have demonstrated favourable clinical outcome when TVT is placed at the target zone[13,19]. Nonetheless other published work has failed to show a significant difference in postoperative outcome in relation to tape position[17]. As the success of TVT is based on reinforcement of the defective pubourethral ligaments, theoretically, a reduced tape width may decrease treatment efficacy because the effective supportive zone is reduced. Mean tape width in the cure group was wider than that in the non-cured group although not to a level of significance. Future study with a larger sample size may provide a more representative conclusion about the relationship between target zone, tape width, and clinical outcome.

In our study, women with tape-LSM out of the optimal 3-to-5-mm zone showed a significantly higher improvement difference in VAS score compared with the other group. This may reflect better control of continence and hence VAS with tape placed closer to the urethra. Nonetheless women with tape-LSM distance of <3 mm had more voiding dysfunction. This observation corresponds to findings in Kociszewski et al's study[12]. Due to the limited sample size in our preliminary study, the difference was not statistically significant. TVT placed too far from the LSM may be associated with a higher risk of not being cured[12]. On the contrary, TVT placed too close to the LSM will apply excessive tension and this close approximation may affect mobility or even obstruct the proximal urethra leading to voiding dysfunction. This demonstrates that tension adjustment is crucial in TVT placement, especially in women with pre-existing voiding dysfunction or a low peak flow rate. Ultrasound may play a role in the objective assessment of tension rather than the traditional technique of using a pair of Mayo scissors that is rather subjective and difficult to teach and learn.

The results of our study are limited by the fact that it was a single-centre pilot study with a small sample size. A prospective longitudinal multicentre study with a longer study period and more patients are needed for better statistical evaluation.

Conclusions

Our study determined by postoperative transperineal ultrasound that approximately one-third of TVTs were not placed at the target zone and most were placed too proximal, despite use of the standard described technique. Tape-LSM distance of <3 mm was associated with voiding dysfunction and hence appropriate tension adjustment is crucial in TVT placement to avoid this postoperative complication. Our current evidence for the relationship between target zone, tape width, and clinical outcome is inconclusive. Future study with a larger sample size is warranted.

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A Prospective Longitudinal Study of Postnatal Quality of Life among Hong Kong Women: Comparison between Normal Vaginal Delivery and Caesarean Section

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Objective: To compare the quality of life (QOL) in Hong Kong women who gave birth by normal vaginal delivery (NVD) and those delivered by Caesarean section (CS). Women were evaluated on discharge from hospital and 4 weeks after delivery.
Methods: This was a prospective longitudinal study conducted in the obstetrics unit of United Christian Hospital in Hong Kong from December 2009 to March 2010. A total of 75 women with NVD and 75 women with CS were recruited. QOL was measured by a generic questionnaire, Short Form 12 version 2 on discharge from hospital and at 4 weeks after delivery. The first questionnaire involved completion of a self-reported form, the second was completed by telephone interview. The data were analysed using Microsoft Excel and the IBM SPSS software.
Results: On discharge from hospital, 86% (129/150) of women returned a completed questionnaire. The mean scores of physical functioning (p=0.01), vitality (p=0.003), social functioning (p=0.003), bodily pain (p=0.02), mental health (p=0.01), as well as physical component summary (p=0.01) and mental component summary (p=0.03) scores were significantly higher in women who delivered by NVD than by CS. At 4 weeks after delivery, 75% (113/150) completed the questionnaire. There was a remarkable difference in general health (p=0.01), physical component summary measure (p=0.003), and social functioning (p=0.05) between NVD and CS groups.
Conclusion: Women who had a NVD enjoyed a generally better QOL than those who delivered by CS, both on discharge from hospital and 4 weeks after delivery. NVD is recommended for women without indications for CS.
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Keywords: Cesarean section; Delivery, obstetric; Postpartum period; Quality of life

Introduction

A study in 2007 stated that 15% of births worldwide occurred by Caesarean section (CS). In developed countries, the proportion of CS has been reported to be 21.1%[1]. In China, the CS rate soared drastically from 3.4% to 39.3% between 1988 and 2008[2]. Some cases had no medical or obstetric indications of need for CS[2,3].

The rising trend remains controversial in developed countries. A higher CS rate has not resulted in additional health gain, on the contrary increased maternal and neonatal risk[1,4]. Risk of ectopic pregnancy and placental problems is increased in future pregnancy[5] and other studies have shown that CS is associated with a significantly increased risk for re-hospitalisation for uterine infection, obstetric surgical wound complications, and cardiopulmonary and thromboembolic conditions[6]. In the 2004-2008 World Health Organization Global Survey on Maternal and Perinatal Health, the incidence of severe maternal outcome associated with CS in the absence of medical indications was about 3 times greater than that associated with spontaneous vaginal delivery[7].

Nonetheless CS is regarded as a modern obstetric practice by many mothers. It is safe in developed countries, it gives mothers a sense of control, and it preserves their dignity. Women also avoid the pain of labour[8]. Some women have also been reported to be afraid of postpartum urinary incontinence that is strongly associated with vaginal delivery[9,10]. Nonetheless a recent local study showed that age, pre-pregnant body mass index, and a history of incontinence during pregnancy all contributed to stress incontinence, even after delivery by CS[11].

The available evidence about CS focused mainly on maternal physical health. More than half a century ago, the World Health Organization defined health as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity"[12]. Over the past two decades, clinical researchers have broadened their

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definition of clinical outcome to include a concern for the patient's psychological and social wellbeing. The clinical significance or effectiveness of an intervention or treatment now often includes an evaluation of quality of life (QOL) that encompasses not only physical health, but mental and social health as well from the patient's perspective[13].

A recent study in Iran concluded that normal vaginal delivery (NVD) may lead to a better QOL, and should be the preferred option for women with no medical indication for CS[14]. On the contrary, a UK study concluded that mode of delivery had no significant effect on QOL or the areas they identified as most important[15]. This current study aimed to examine this issue in the context of QOL to compensate for the paucity of such studies. We aimed to compare the QOL in Hong Kong women with NVD and CS on discharge from hospital and 4 weeks after delivery. A possible difference in QOL related to delivery by NVD or CS, if identified, may become a consideration when health care professionals counsel women on the mode of delivery or make a clinical judgement. This will enable women to make an informed choice.

Methods

This was a prospective longitudinal study of QOL following NVD and CS among Hong Kong women.

Sampling

The study was conducted in the obstetrics unit of United Christian Hospital in Hong Kong from December 2009 to March 2010. Based on the selection criteria, 75 women who underwent NVD and 75 who underwent CS were recruited. The inclusion criteria were age 18 to 40 years, married with a Hong Kong Identity Card, able to read Chinese, and gave birth by NVD or elective or emergency CS.

Women were excluded from analysis for the following reasons: instrumental delivery, child had congenital malformation or required admission to the neonatal intensive care unit, mother had a major psychiatric problem or medical condition that required regular treatment, marital status was divorced or widowed.

Ethical Considerations

Ethics approval was obtained from the Hospital Authority Research Ethics Committee (Kowloon Central / Kowloon East) prior to commencement of the study and women gave their written informed consent for voluntary participation. They had the right to withdraw from the study anytime with no adverse effect on treatment.

No patient identifier was recorded in the questionnaire or the background information sheet, and only a study code was used. All data were accessed by the researcher and used in this research only, and destroyed 1 month after the report was finished.

Data Collection

The researcher approached the women in the postnatal ward, a few days following birth. An information sheet was distributed and consent was sought at the same time. The first questionnaire (acute form) and the background information sheet (including age, number of children, education level, caregivers, and number of days being hospitalised) were distributed to the participants. Participants were expected to complete the questionnaire on a self-reported basis upon discharge from hospital, placing it in a collection box at the nurse's station. All postnatal ward staff were aware of the study objectives and methodology.

The second questionnaire (standard form) was completed by telephone interview 4 weeks after delivery. To prevent loss of contact, the most current telephone number was recorded during distribution of the first questionnaire.

Measurements

The main predictor variable was mode of delivery. The potential confounding variables included parity, obstetric history, economic status, employment status, and birth experience.

The QOL was measured by a generic questionnaire, Short Form 12 version 2 (SF-12v2) on discharge from hospital and 4 weeks after delivery. The SF-12v2 is a shorter version of the Short Form 36 version 2 (SF-36v2) Health Survey and uses 12 questions to measure physical and mental wellbeing from the patient's point of view. It takes only 2 to 3 minutes to complete and covers the same eight health scales as the SF-36v2. The eight scales are physical functioning, physical health, bodily pain, general health, vitality, mental health, emotional health, and social functioning. A shorter version may increase the return rate and minimise the missing data as postnatal mothers usually suffer from fatigue after delivery.

The SF-36 has been regarded as an indicator of QOL in many studies of pregnant or postnatal women[16,17], and has been proven to be highly feasible and reliable[18]. The SF-12 has been used for validation of another tool for measuring postnatal QOL[15,19].

Statistical Analysis

The hypothesis was that there is a difference in postnatal QOL between Hong Kong women delivered by NVD and those delivered by CS. In a similar previous study[14], the differences between the two groups were significant for vitality and mental health at 6 to 8 weeks. For mental health, the standard deviation (SD) was 16.8 and difference in means between the two groups being 8.4. To set α=0.05 and β=(1-0.8)=0.2, by the equation of unpaired t test, the sample size of each group should not be <63.

Data were entered into QualityMetric Health Outcomes Scoring Software 3.0. The score of each scale was calculated according to the author's recommendation, where 0 denotes the worst and 100 the best QOL. All scores above or below 50 were interpreted as above or below the general population norm, respectively. The aggregate scores for physical and mental summaries were computed according to the eight scales and presented as physical component summary (PCS) and mental component summary (MCS) scores[20]. The data were exported to Microsoft Excel and IBM SPSS Statistics version 18 for analysis.

Results

Of the 150 women recruited, 19 women withdrew and two returned questionnaires with missing data. These two questionnaires were excluded from data analysis. Of the 129 women left, 16 could not be contacted 4 weeks after delivery. Characteristics of the women are shown in Table 1.

Generally, the difference in demographics between NVD and CS groups was <10%, except for age-group and length of hospital stay. Of the 65 women with NVD, 23% were aged 18 to 25 years compared with 5% in the CS group. In the NVD group, 97% of women remained in hospital for ≤3 days compared with 59% of women in the CS group who spent 4 to 6 days in hospital and 31% who

Table 1. Characteristics of subjects

Characteristic	Normal vaginal delivery (n=65)	Caesarean section (n=64)	Total (n=129)
Age (years)			
18-25	15 (23%)	3 (5%)	18 (14%)
26-30	18 (28%)	20 (31%)	38 (29%)
31-35	20 (31%)	26 (41%)	46 (36%)
36-40	12 (18%)	15 (23%)	27 (21%)
No. of children			
1	38 (58%)	29 (45%)	67 (52%)
2	23 (35%)	26 (41%)	49 (38%)
3	3 (5%)	7 (11%)	10 (8%)
4	1 (2%)	2 (3%)	3 (2%)
Education level			
Primary	2 (3%)	0	2 (2%)
Secondary	44 (68%)	41 (64%)	85 (66%)
Tertiary	19 (29%)	23 (36%)	42 (33%)
No. of caregivers of the baby			
1	13 (20%)	11 (17%)	24 (19%)
2	45 (69%)	44 (69%)	89 (69%)
3	6 (9%)	9 (14%)	15 (12%)
4	1 (2%)	0	1 (1%)
Hospital stay (days)			
≤3	63 (97%)	6 (9%)	69 (54%)
4 to 6	2 (3%)	38 (59%)	40 (31%)
>6	0	20 (31%)	20 (16%)

stayed >6 days. The scores of the questionnaire completed by the two study groups on discharge from hospital and at 4 weeks after delivery were analysed by t test and are shown in Tables 2 and 3, respectively.

On discharge from hospital, the mean scores for physical functioning (p=0.01), vitality (p=0.003), and social functioning (p=0.003) were significantly higher in the NVD group; their mean scores for bodily pain (p=0.02) and mental health (p=0.01) were also higher, as expected. Both PCS (p=0.01) and MCS (p=0.03) scores were higher in NVD than in CS group (Table 2).

At 4 weeks after delivery, there was a remarkable difference in general health (p=0.01) and PCS score (p=0.003) between NVD and CS groups. The score for social functioning was also higher in NVD group (p=0.05) [Table 3]. Comparison of scores between the groups are illustrated in Figure 1.

Discussion

Clinical Implications

Sherbourne et al[21] emphasised that medical practice should strive to balance different health domains when making treatment decisions and thus improve mental and social health outcomes. The results of this study demonstrate that there is a difference in postnatal QOL in Hong Kong women delivered by NVD and those delivered by CS. On discharge from hospital, there were significant differences in physical functioning, vitality, and social functioning.

Table 2. Quality of life in women with normal vaginal delivery and Caesarean section, measured on discharge from hospital.

Health scale	Normal vaginal delivery (n=65)	Caesarean section (n=64)	Mean difference	p Value
Physical functioning	41.0 ± 10.4	36.0 ± 10.4	5.0	0.01
Physical health	41.5 ± 7.9	38.9 ± 8.3	2.6	0.07
Bodily pain	35.3 ± 9.9	31.1 ± 10.4	4.2	0.02
General health	47.2 ± 8.4	44.8 ± 9.1	2.4	0.12
Vitality	50.3 ± 7.5	45.9 ± 8.9	4.4	0.003
Social functioning	44.7 ± 11.0	38.6 ± 11.5	6.1	0.003
Emotional health	45.0 ± 8.6	43.1 ± 10.0	1.9	0.23
Mental health	52.8 ± 7.2	49.4 ± 7.9	3.4	0.01
Physical component summary	38.2 ± 8.4	34.3 ± 8.9	3.9	0.01
Mental component summary	52.4 ± 7.6	49.2 ± 9.6	3.2	0.03

* Data are shown as mean ± standard deviation, unless otherwise specified

Table 3. Quality of life in women with normal vaginal delivery and Caesarean section 4 weeks after delivery.

Health scale	Normal vaginal delivery (n=58)	Caesarean section (n=55)	Mean difference	p Value
Physical functioning	54.7 ± 4.2	52.7 ± 6.4	2.0	0.06
Physical health	52.5 ± 7.3	50.8 ± 8.0	1.7	0.24
Bodily pain	52.3 ± 7.9	49.8 ± 8.1	2.5	0.10
General health	48.0 ± 9.7	43.0 ± 10.0	5.0	0.01
Vitality	48.6 ± 12.3	50.3 ± 12.0	-1.7	0.46
Social functioning	53.4 ± 8.1	49.8 ± 11.0	3.6	0.05
Emotional health	50.3 ± 9.4	51.6 ± 8.0	-1.3	0.43
Mental health	54.8 ± 8.6	54.1 ± 7.9	0.7	0.68
Physical component summary	51.9 ± 5.3	48.4 ± 6.8	3.5	0.003
Mental component summary	51.5 ± 9.7	52.1 ± 8.2	-0.6	0.70

* Data are shown as mean ± standard deviation, unless otherwise specified

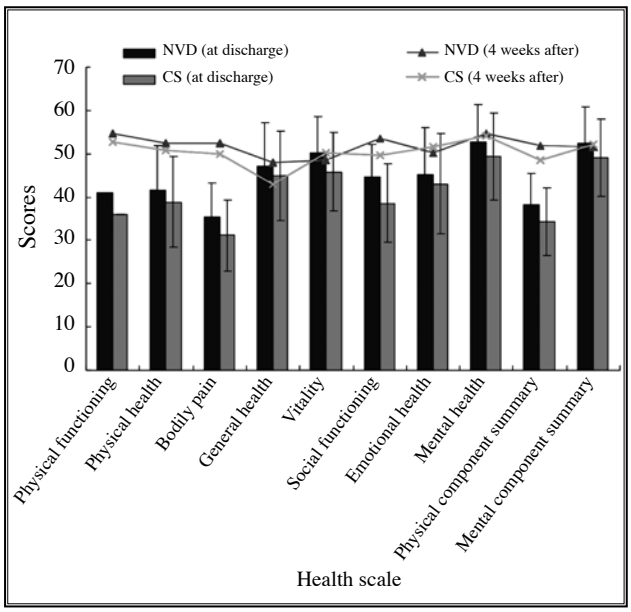

Figure 1. Comparison of mean scores of health scales and summary measures in women with normal vaginal delivery (NVD) and Caesarean section (CS) on discharge from hospital and 4 weeks after delivery

At 4 weeks after delivery, significant differences were also identified in general health and PCS measures. When health care professionals counsel women or make a clinical judgement, QOL should be a consideration.

Overall 97% women with NVD stayed ≤3 days in hospital. On the contrary, 59% women with CS stayed 4 to 6 days in hospital and 31% stayed for >6 days. The association between QOL and length of hospital stay was not investigated. Nonetheless a number of studies report that early discharge combined with home midwifery support benefits not only the mothers' health, but also significantly reduces the financial burden on the hospital without compromising the health and wellbeing of the mothers and babies[22]. In addition, level of maternal satisfaction is reported to be higher among women discharged early[23]. Thus, NVD is suggested in view of the shorter length of stay.

A cross-sectional interview survey found that previous CS and conception by in-vitro fertilisation were determinants of a preference for elective CS in Hong Kong Chinese pregnant women[23]. Nevertheless the recent literature shows a high success rate for vaginal delivery in women with one previous CS[24,25]. The risks and benefits of different modes of delivery, as well as the associated QOL should be illustrated clearly, especially for this group of women.

Apart from a health issue, the decision about mode of delivery is complex and also influenced by many other factors such as the socio-economic environment, personal financial status, cultural beliefs, peer pressure, personal values and attitude towards delivery[2]. Women frequently seek medical advice from obstetricians or midwives when considering mode of delivery. It is surprising that a UK study reported 31% of female obstetricians in London requesting CS for their own pregnancy[26]. A recent survey in 2008 also revealed that pregnant women were willing to accept higher risks of potential complications of vaginal delivery than their attending clinician[27]. For the health and welfare of the women and the babies, clinicians should enable women to make an informed choice by providing them and their family with comprehensive and objective information.

Evaluation of the Study Design

The reliability and validity of this study tool, SF-12v2, were high. Its use has been proven by review in hundreds of published literature and various tests in different subjects[20]. Nonetheless it is not designed for postnatal mothers in Hong Kong.

During the period of "doing the month", a traditional Chinese custom of 1-month confinement after delivery, Chinese postnatal women are encouraged to rest at home and discouraged from performing any physical activities[28]. For example, climbing stairs may be avoided and household chores taken over by relatives. Some may not even care for their baby. Thus the three questions "Does your health now limit you in these activities: Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or doing tai chi?" (question 2); "…such as climbing several flights of stairs?" (question 3); and "How much of the time have you had any of the following problems with your work or other regular daily activities?" (question 4) may not reflect the real physical fitness of the mothers in our study who may have been completely inactive for 4 weeks.

In addition, the questionnaires did not include issues that some women may consider important, such as the relationship with their husband and family members, sexual health, or feelings towards their baby. A pilot study[19] that assessed postnatal QOL by Mother-Generated Index revealed that sense of fulfilment, self-esteem, family relationship, happiness with the baby, and personal time were all regarded as important factors in postnatal QOL.

Recruitment of the Sample and Data Collection

As expected, an increasing trend for cross-border marriage, and an increasing number of new immigrants from mainland China[29] results in the return of many women to China for "doing the month", even if they hold a Hong Kong Identity Card. Within this cohort, around 10% women were uncontactable after 4 weeks. This problem may have been overcome by excluding women during the recruitment stage if they planned to return to China, or allowing the questionnaire to be returned in a prepaid addressed envelope.

Potential Confounding Variables

Interaction between the length of hospital stay and QOL was unclear. Daily activities and family visits may have been interrupted by hospital policy and ward routine during hospitalisation. For instance, resting time might be interrupted by meal times, doctor's rounds or nursing duties. Family support and meeting may have been limited by standard visiting hours. A study that compared women with early and traditional discharge following a minimum of 48 hours' hospital stay showed that the level of maternal satisfaction with early discharge was higher than 90%[30]. Thus, the length of stay could be a confounder to the scores.

Of the 65 women with NVD, 23% were aged 18 to 25 years, compared with 5% in the CS group. Figure 2 shows that the mean PCS and MCS scores on discharge from hospital, as well as the PCS score at 4 weeks after delivery were highest in the youngest age-group. The result was consistent with a younger age and presumed better physical fitness.

Improvement and Extension of the Research

Söderquist et al[31] assessed the risk factors for post-traumatic stress and depression in 1224 women at 12 to 20 weeks and 32 weeks of gestation and 1 month after delivery, and revealed that specific risk factors could be identified in early pregnancy. In this research, only postnatal health scales were assessed. In future studies, questionnaires completed before delivery as a baseline would allow evaluation of a pre- and post-delivery difference for individuals. Whether postnatal QOL is affected by some pre-existing risk factors and not just mode of delivery warrants further exploration.

In this study, the difference in QOL score between women who underwent an elective or emergency CS was not evaluated. A previous study in 2005[32] showed that emergency CS did not increase the risk of postnatal depression compared with elective CS, whereas another study in 2006[33] indicated that emergency CS was associated with post-traumatic stress disorder. Further study on this aspect is worthwhile.

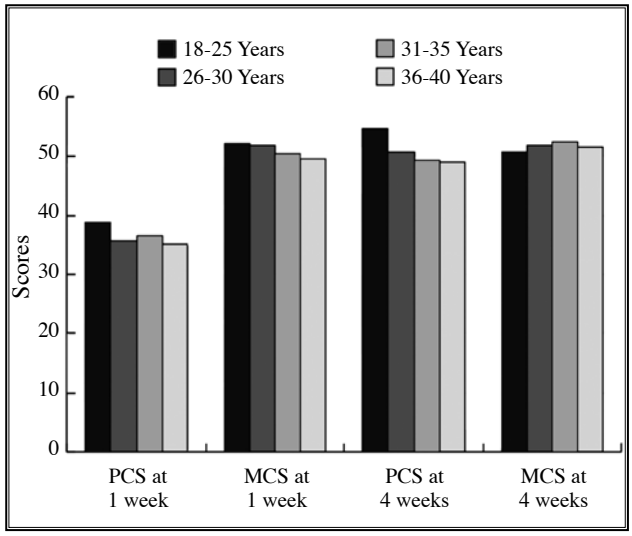

Figure 2. Comparison of mean physical component summary (PCS) and mental component summary (MCS) scores among different age-groups

Success with breastfeeding has also been found to be significantly related to the QOL of postnatal mothers in a previous study in Brazil[34]. Thus mode of feeding may be included in future studies.

Conclusion

This study shows that women who underwent a NVD had a better QOL than those who required delivery by CS, both on discharge from hospital and at 4 weeks after delivery. Thus, NVD is recommended for women in whom CS is not medically indicated.

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