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Transvaginal Sonographic Measurements of Crown-Rump Length as a Predictor of Gestational Age

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Abstract : *The relation between fetal crown-rump length (CRL) and gestational age was determined by crossed sectional analysis of 251 normal fetuses (6-14 weeks) using transvaginal sonography. Mathematical modelling of the data demonstrated that the CRL growth curve is nonlinear. Predicted menstrual age values in days for specific CRL measurements in millimeters were calculated and are reported in tabular forms. The variability (± 2 SD) associated with predicting menstrual age from CRL is ± 5.8 days between 6-14 weeks. CRL can be used as an adjunct in estimating menstrual age, and may be useful in predicting fetal outcome of threatened abortion in the first trimester. Predicted CRL values at various points in gestation were comparable to the results of other investigators. (Thai J Obstet Gynaecol 1993;5:1-5.)*

Key words : crown-rump length (CRL), gestational age, ultrasound

After the sonographic appearance of the fetal pole, one can establish fetal age to within 3-5 days by measurement of the fetal crown-rump length (CRL)[1-4]. This is the earliest and most accurate way to assess gestational age during pregnancy. The measurement is most accurate between 8 and 12 weeks when the long axis of the fetus is clearly visualized[4]. Results of CRL measurements in a western population have been published by several workers. Unfortunately, no report of the growth of fetal CRL in pregnant Thai women has been conducted, and some evidence has demonstrated that the size of Thai babies is somewhat lower than that of western ones[5,6], and some sonographic parameters are shorter than ones of western population, e.g. fetal femur length[7]. The CRL normogram of previous studies, therefore, may not be appropriate for evaluating Thai pregnancy and we need our own data to have the standard values for the Thai population. Moreover, CRL measurements in previous studies were achieved by using transabdominal sonography of which

the imaging is poorer than transvaginal sonography[8]. We, therefore, decided to measure the fetal CRL using transvaginal sonography in pregnant northern Thai women to create a normogram of fetal CRL for our population.

Patients and Methods

The studied patients consisted of 251 normal pregnant women attending the antenatal clinic at Maharaj Nakorn Chiang Mai Hospital from March 1,1991 to September 30, 1992. The subjects had to meet the following criteria : firstly, gestational age between 6-14 weeks; secondly, history of regular menstruation and knowledge of the exact dates of the last menstrual period; thirdly, singleton pregnancy without medical or obstetrical complications or fetal congenital anomalies; fourthly, the gestational age calculated from date consistent with clinical estimation and Dubowitz scores, subsequently assessed. The measurement was performed only once for each patient.

The fetal CRL, and the long axis of the fetal pole were measured by means of electronic calipers from the top of the crown (head) to the bottom of the rump and the average length from three seperate best images were used as recommended by Robinson and Fleming[4]. All examinations were performed by the author who did not know the menstrual age of the patients, using the real-time transvaginal sector scan with 5.0 MHz (Aloka, Model SSD 650). The collected data were stored in a microcomputer and subsequently analyzed.

Results

A total of 251 measurements of CRL were obtained from 251 normal Thai pregnant women from the 40th to the 100th day calculated from the last menstrual period, at least 20 measurments for each week of gestation. The distribution of CRL for each day of gestation between 6-14 weeks is presented in Fig. 1. There is progressive increase of CRL throughout the first trimester. The linear quaudratic function was the best model for describing the relation between CRL(mm) and gestational age (days) (r^2 = 0.92.71, SE=4.39157, p=0.0000). The correlation was formulated, gestational age (days) =25.66177+

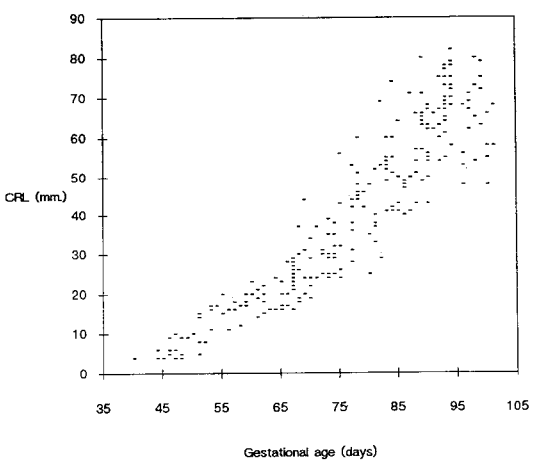

Fig. 1 The distribution of CRL for each gestational day.

Table 1 Predicted gestational age (days) from crown-rump length with upper and lower limit (95% confidence interval)

CRL mm.	GA days	Lower limit	Upper limit	CRL mm.	GA days	Lower limit	Upper limit
4	43	39.22	46.78	44	81	79.00	83.00
5	45	41.30	48.70	45	82	80.00	84.00
6	47	43.36	50.64	46	82	79.98	84.02
8	50	46.51	53.49	47	83	80.96	85.04
9	51	47.58	54.42	48	83	80.94	85.06
10	53	49.65	56.35	49	84	81.91	86.09
11	54	50.72	57.28	50	84	81.87	86.13
12	55	51.79	58.21	51	85	82.85	87.15
14	58	54.93	61.07	52	85	82.81	87.19
15	59	55.99	62.01	53	86	83.76	88.24
16	60	57.07	62.93	54	86	83.72	88.28
17	61	58.13	63.87	55	87	84.68	89.32
18	62	59.19	64.81	56	87	84.62	89.38
19	63	60.24	65.76	57	88	85.58	90.42
20	64	61.31	66.69	58	88	85.53	90.47
21	65	62.36	67.64	60	89	86.42	91.58
22	66	63.42	68.58	61	90	87.36	92.64
23	67	64.47	69.53	62	90	87.31	92.69
24	67	64.53	69.47	63	91	88.24	93.76
25	68	65.58	70.42	64	91	88.18	93.82
26	69	66.64	71.36	65	91	88.13	93.87
27	70	67.68	72.32	66	92	89.07	94.93
28	71	68.72	73.28	67	92	88.99	95.01
29	71	68.76	73.24	68	93	89.93	96.07
30	72	69.81	74.19	69	93	89.86	96.14
31	73	70.85	75.15	70	93	89.79	96.21
32	74	71.87	76.13	71	94	90.72	97.28
33	74	71.91	76.09	72	94	90.65	97.35
34	75	72.94	77.06	73	95	91.58	98.42
35	76	73.96	78.04	75	95	91.44	98.56
36	76	73.98	78.02	77	96	92.28	99.72
37	77	75.00	79.00	78	96	92.21	99.79
38	78	76.00	80.00	79	97	93.14	100.9
39	78	76.03	79.97	80	97	93.007	100.9
40	79	77.03	80.97	82	98	93.91	102.1
41	79	77.03	80.97	83	98	93.84	102.2
42	80	78.03	81.97	85	99	94.68	103.3
43	81	79.03	82.97	86	99	94.61	103.4

8.61475 $\sqrt{CRL}$ - 0.00086015 (CRL)[2]. Predicted gestational age values, calculated from the equation, for specific CRL measurements are indicated in Table 1 and Fig. 2.

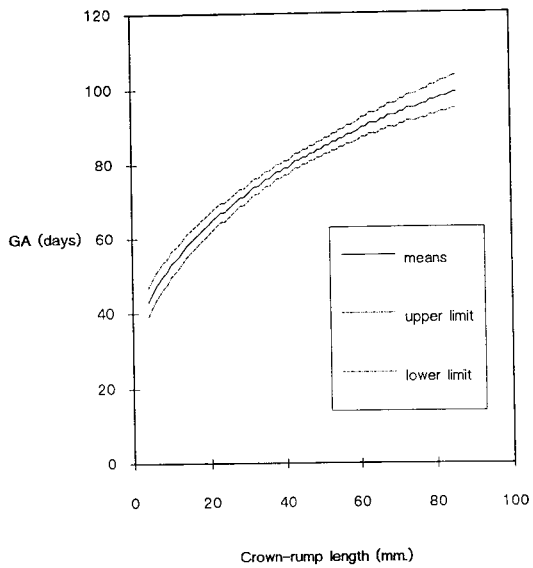

Fig. 2 Predicted gestational age from CRL and 95% confidence interval.

The variability (± 2 SD) associated with predicting gestational age from CRL is ± 5.8 days between 6-14 weeks.

In comparison with other studies, the CRL growth pattern was consistent with sonographic studies of the western investigators[1-4].

Discussion

The initial accuracy of the CRL was felt to be extremely high, approaching ± 2.7 days, and was therefore recommended as the best measurement to establish the gestational age[4]. Since then, other observers have evaluated the CRL and found it to be somewhat less accurate. Although still one of the best estimates, with an accuracy of ± 5-7 days, the CRL is comparable with a second trimester biparietal diameter measurement[3,9]. Robinson and Fleming[4] noted that variations in CRL can be attributed to 1) biologic variations in fetal size, 2) variation in the timing of ovulation and fertilization, and 3) errors in the measurement techniques. The variations of CRL due to errors in measurement technique in this study may be reduced by transvaginal sonography and being performed by only one sonographer. This study indicates that the biological variation of the fetal CRL growth is progressive with gestational age, the 95% confidence interval is wider at the end of the first and early second trimesters.

When measuring the CRL, it is very important to avoid including the yolk sac in the measurement, this will artificially lengthen the measurement and lead to an overestimation of gestational age. This error could be corrected with transvaginally examination due to the better imaging. The CRL should be used only until the fetal head is identified. As the fetus continues to grow beyond 12 weeks, it is more likely to flex and extend, making the CRL measurement less accurate.

In comparison with other studies, the CRL growth pattern was consistent with sonographic studies of

western investigators[1-4]. However, the values of this study are somewhat lower than the western ones, this may be due to the racial factor.

Due to the fact that this normogram was created from the various unselected socio-economic population and adequate sample size for each gestational week, calculated from the variability of a previous study[4], so we believe that this series can be effectively used as a standard one for application with northern Thai women. This CRL normogram is more appropriate for application with pregnant northern Thai women than western ones.

In addition to the prediction of gestational age, CRL can be used as prognostic factor in threatened abortion. It was previously demonstrated that the CRL growth delay in first trimester abortion with the presence of fetal heart beat would predict poor pregnancy outcome[10].

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Predictive Values of Sonographic Parameters for Antenatal Diagnosis of Small for Gestational Age Fetus

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Abstract : *This prospective study examined the reliability of various sonographic parameters in detecting SGA fetus in utero. Sonographic BPD, AC, HC/AC ratio, FL/AC ratio, EFW and AFV were obtained within ten days of delivery of SGA (N=221) and non-SGA (N=276) newborns. The effectiveness of each ultrasound variable for antenatal diagnosis of the SGA fetus was assessed. Predictive values were computed using Bayes theorem and based upon a 10% prevalence rate of SGA. An HC/AC ratio was the best predictor, which could detect 87% of SGA with 76% of positive predictive value. Other variables (AC, FL/AC, EFW, AFV, BPD) were less accurate for predicting SGA. Negative predictive value was greater than 92% for all variables. However, with the exception for HC/AC and FL/AC ratios, the positive predictive values were disappointing. This report establishes the limitations of each ultrasound parameter in the antenatal diagnosis of the SGA fetus. (Thai J Obstet Gynaecol 1993;5:7-14.)*

Key words : abdominal circumference, head circumference, femur length, fetal weight, amniotic fluid volume

Accurate antenatal diagnosis of the small for gestational age (SGA) fetus could greatly decrease the high perinatal morbidity and mortality associated with this condition. The challenge remains primarily with the obstetrician to identify the fetus who is inappropriately growing in utero. This difficulty is understood by the fact that such identification is not always possible even after birth. Numeruous studies indicate that when selective clinical techniques are used to diagnose SGA, most cases continue to be missed. The diagnostic accuracy of SGA may be improved by sonographic parameter measurements[1,2]. Various sonographic techniques for diagnosis of SGA have been proposed. For a criterion to be clinically useful,

a positive finding must allow one to be confident that SGA is presented and a negative finding must allow one to exclude SGA confidently, therefore, positive and negative predictive values of each criterion should be evaluated. Mostly, only single sonographic variable was evaluated for its accuracy in each previous report, therefore, this study was carried out to compare various commonly used parameters in the same population. We conducted a large prospective study to evaluate the accuracy of each ultrasound parameter, i.e. biparietal diameter (BPD), abdominal circumference (AC), head to abdominal circumference ratio (HC/AC ratio), femur length to abdominal circumference ratio (FL/AC ratio), estimated fetal weight (EFW), and amniotic fluid volume (AFV) for diagnosing SGA.

Materials and Methods

The study population consisted of 497 patients with complete inclusion criteria referred for ultrasound examination during 32-40 gestational weeks due to clinically suspected SGA. Sonographic examinations were done several times in most patients but only the last one, within 10 days of the delivery, was evaluated. An SGA infant was typically defined as a birth weight below the 10th percentile for gestational age, and a non-SGA infant was defined as birth weight at or above the 10th percentile. Intrauterine growth curve for evaluation of newborns used in this study was the growth curve derived from our population[3]. All of the ultrasound measurements were performed by one experienced perinatal sonographer at the Maternal-Fetal Medicince Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University, Thailand, from June 1, 1988 to September 31,1992.

This study included only singleton pregnancies who were delivered between 32-40 complete weeks of gestation, patients with history of regular menstruation, exact dates of last menstrual period was also noted, attending antenatal clinic in the first trimester and clinical estimation of gestational age agreed with menstraul age calculated from dates, and Dubowitz scores, assessed by the pediatrician, had to confirm this age.

Sonographic measurements of BPD, HC, AC, and FL were performed on 497 liveborn fetuses within 10 days before delivery, using commercially available curvilinear real-time systems with 3.5 MHz tranducers (Aloka Model 650). FL was measured from the greater trochanter to the distal metaphysis and BPD from the outer margin of the proximal skull table to the inner margin of the distal skull table, using internal electronic calipers and a speed of sound of 1540 m/sec in tissue. HC was measured along the outer margin of the calvaria at the level of the BPD, and AC was measured along the outer bounderies of the abdomen at the level of the porto-umbilical vein complex. Circumferences were measured by mod-

ern electronic clipse caliper, that could be adjusted in all directions. The HC/AC ratio and FL/AC ratio were calculated from HC, AC, FL measurements; estimated fetal weight (EFW) in grams was derived using Hadlock' s equations[4].

EFW, BPD, and AC below 10th percentile, HC/AC ratio and FL/AC of +2SD, or greater, and decreased amniotic fluid volume (AFV) were considered to be sonographic diagnosis of SGA. Decreased amniotic fluid volume or oligohydramnios has been defined using the vertical diameter method as no pocket of fluid of > 1 cm[5]. The standard values of BPD[6], AC[7] HC/AC ratio[8] for each gestational week and FL/AC ratio, which were constant throughout the second half of pregnancy (+2SD =0.234)[9],used in this study were derived from northern Thai pregnant women.

All of the data were prospectively collected and stored in a microcomputer and subsequently analyzed with statistic program SPSS/PC+.

The means of various ultrasound variables of SGA infants were compared with those of the non-SGA group. A *t-test* was used to analyze differences. Statistical significance was accepted at the 0.05 level. To avoid biasing the results, we corrected them for a population in which 10 % of infants would be SGA, which is the prevalence of SGA in our population corresponding to the commonly accepted definition of SGA : fetal weight at or below the 10th percentile for gestational age.

For each ultrasound variable, the percentages of true/false positive and true/false negative based on the actual percentage of positive tests in our SGA and non-SGA groups would be determined. The accuracy of each test in predicting an SGA fetus in a population with an expected 10% prevalence of SGA was assessed by calculating the sensitivity, specificity, positive predictive value, and negative predictive value. The positive and negative predictive values were determined using Bayes theorem[10].

Results

The study population consisted of 221 and 276 patients, each of whom delivered an SGA and non-SGA infants respectively within 10 days after ultrasound examination.

Table 1 shows the mean values and standard deviation for the various ultrasound growth variables in the SGA and non-SGA fetuses. The menstrual age of both groups at delivery ranged from 224-280 days. The interval between the time of ultrasound study to delivery averaged 4.4 days. All ultrasound variables among both groups were significantly different.

Table 2 shows the results of each test in detecting abnormal ultrasound variables as previously defined in the known SGA and non-SGA groups (true-positive/false-negative and false-positive/true-negative rates). The expected results for screening a popu-

Table 1 Comparative values for SGA and non-SGA population

Variables	SGA	Non-SGA (n=221)	p (n=276)
Menstrual age at delivery (days)	259±10	278±11	<0.05
Menstrual age at study (days)	254±9	274±10	<0.05
Birth weight (g)	2001.6±402	2781.5±422	<0.05
BPD	8.4±0.5	8.8±0.4	<0.05
AC	27.0±1.9	32.5±2.1	<0.05
HC/AC ratio	1.129±0.011	0.982±0.013	<0.05
FL/AC ratio	0.237±0.006	0.203±0.004	<0.05
EFW	2086±368	2890±452	<0.05

SGA = small-for-gestational age, BPD = biparietal diameter, FL/AC = femur length/abdominal circumference ratio, HC/AC = head/abdominal circumference ratio, EFW = estimated fetal weight.

Table 2 Accuracy of prediction for ultrasound variables (The results shown are actual numbers of incidence)

Population	BPD	AC	HC/AC	FL/AC	EFW	AFW
SGA (n=221)						
True-positive	151	203	192	68	156	60
False-negative	70	18	29	153	65	161
Non-SGA (n=276)						
False-positive	77	80	8	5	25	9
True-negative	199	196	268	271	251	267

SGA = small-for-gestational age, BPD = biparietal diameter, FL = femur length, AC = abdominal circumference, FL/AC femur length/abdominal circumference ratio, EFW = estimated fetal weight.

lation of 497 women (Table 3), based on a 10 % prevalence of SGA, were calculated from the percentage of abnormal measurements in the SGA and non-SGA groups (Table 2). As found in the true-positive rate, the highest sensitivity was obtained for abdominal circumference alone, followed by HC/AC ratio at 86% sensitivity. Estimated fetal weight had a sensitivity of 60%, compared with only 30% and 27.15% for FL/AC ratio and decreased AFV respectively. With exception for BPD and AC, the specificity was high for

Table 3 Sensitivity, specificity, and predictive values in detecting SGA for each ultrasound variable

Parameters	Ultrasound variables					
	BPD	AC	HC/AC	FL/AC	EFW	AFV
Sensitivity(%)	68.33	91.86	86.87	30.76	70.59	27.15
Specificity(%)	72.10	71.02	97.10	98.19	90.94	96.70
Predictive value						
Positive(%)	21.25	26.06	76.32	63.27	46.71	50.00
Negative(%)	95.29	98.76	98.53	92.74	96.58	92.28

Data are calculated from percentages for abnormal measurements shown in Table 2, based on 10% prevalence of SGA in the population.
SGA = small-for-gestational age, BPD = biparietal diameter, FL = femur length, AC = abdominal circumference, FL/AC femur length/abdominal circumference ratio, EFW = estimated fetal weight.

all tests. Positive predictive value of an abnormal variable was above 50 % for only HC/AC ratio and FL/AC ratio. The negative predictive value was greater than 92% for all ultrasound variables.

Discussion

Small for gestational age is strongly associated with perinatal mortality and morbidity, and long term handicap[11]. Accurate antenatal diagnosis offers the best opportunity to prevent the problems. As the SGA is, by definition, smaller in size than a normal fetus of the same gestational age, a variety of prenatal ultrasonographic dimensions have been proposed as predictors of SGA.

The sonographic BPD measurements for diagnosing SGA would be expected to be less accurate than measurement of the AC, because the fetal weight and growth appear to be better correlated with AC[12]. This observation corresponds with the fact that most cases of impaired fetal growth are asymmetric or brain-sparing, therefore, abnormal BPD measurements would not be expected when the ultrasound study is done. Our results indicate that BPD is a bad predictor for SGA due to low sensitivity, specificity and positive predictive value.

Of the ultrasonic variables we evaluated for the detection of the SGA fetus, an abnormal AC was the best sensitive parameter for antenatal detection of SGA (a sensitivity of 91.86%), as opposed to FL/AC ratio or AFV, which had 30.8% and 27.15% sensitivity respectively. However, AC measurement did not allow a confident antenatal diagnosis of SGA to be

made because the positive predictive value was very low.

Hadlock et al[13] suggested that the FL/AC ratio was the best parameter in detecting fetal growth impairment in the patient with inaccurate dates because this ratio may become abnormal before individual variables of BPD, abdominal circumference, femur length, or fetal weight. From our results, a FL/AC ratio of greater than +2SD (0.234)[9] correctly identified only 30.8% of our SGA, which is less than the findings in other study[13]. However, elevated FL/AC ratio has a 63% chance of being SGA, which is much higher than other studies[13,14], and may be useful in case of uncertain dates because it is date-independent predictor of SGA[9,13]. The low sensitivity of FL/AC ratio in this study may by due to the fact that the cut off level for diagnosis at +SD, suggested by Hadlock et al[13], is too high.

The most direct technique to predict fetal weight is to use EFW. The criterion of an EFW below the 10th percentile can be expected to help detect 70% of SGA fetuses. EFW, as determined by the formula using the BPD, femur length, and abdominal circumference, was moderately sensitive and predictive in confirming the SGA fetus in our series, however, it could not be used as a single reliable parameter.

The original report of the relationship of AFV and SGA suggested that the presence of normal AFV conveyed a low risk of SGA[5]. However, we found that the presence of normal AFV could not be used as a reliable method to exclude the diagnosis of SGA, the finding is consistent with some previous reports[15,16]. AFV may be well correlated with only abnormal growth but not all SGA fetuses. SGA infants are a heterogeneous mix and include a preponderance of normal small fetuses, such poor negative predictive value of normal AFV estimate is not surprising.

The best positive predictive value was obtained using the ratio of head to abdominal circumference. Use of the HC/AC ratio is based on the knowledge that chronic utero-placental insufficiency results in asymmetrical growth retardation. Since the liver is the most severely affected body organ, the AC measured at the level is significantly smaller than normal. On the other hand, the head circumference is less affected because the brain tend to be spared. As a result, the HC/AC ratio is unusually high in the asymmetrically growth-retarded fetus.

The only two techniques with a positive predictive value above 50% were estimation of HC/AC and FL/AC ratios. However, FL/AC ratio measurments have little practical use, since the technique has very low sensitivity. The 76% predictive value of the HC/AC ratio with a sensitivity of 98% appears to be the best clinical tool. Moreover, this ratio is particularly valuable in patients referred for initial scanning after 30 weeks gestation when it is difficult to distinguish accurately between true intrauterine

growth retardation and an error in dates on the basis of BPD measurements alone.

Each of the commonly used ultrasound variables had strong negative predictive value, whereas, predictive values of a positive finding were rather disappointing. This study also points out the weaknesses of each test as individual screening tools for SGA, as seen by the fairly high false-positive rate found for BPD, abdominal circumference in our non-SGA population.

Despite these low predictive values, it may be claimed that a negative predictive value of 92% to 98% proves the value of these tests because the obstetrician can safely conclude that the risk of SGA is small. However, the high negative predictive values may be less a reflection of the excellence of the tests than of the low prevalence of SGA. Ninety per cent of fetuses are not SGA, so the negative predictive value of any reasonable test will, of necessity, be at least that high. None of the proposed sonographic measurements allow a confident antenatal diagnosis of SGA to be made. Practically, however, we believe that the combinations of these sonographic parameters will be highly predictive for this condition.

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The Influence of Beta-Endorphins on Gestational Diabetes Development

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Abstract: *The relationship between beta-endorphin and insulin secretion in pregnant women was studied by means of radioimmunoassay technique. The study was carried out by determination of beta-endorphins in peripheral blood samples of 28 pregnant women with gestational diabetes. They consisted of two subgroups:14 women with insulin-independent and 14 with insulin-dependent disease. Beta-endorphin increase was found in both groups, according to the progression of gestation, significantly higher in the insulin-dependent group. Also, in the mentioned group, insulin administration caused a marked rise of beta-endorphins. Beta-endorphins, inhibiting insulin secretion, can influence gestational diabetes development. (Thai J Obstet Gynaecol 1993;5:15-18.)*

Key words: beta-endorphins, gestational diabetes

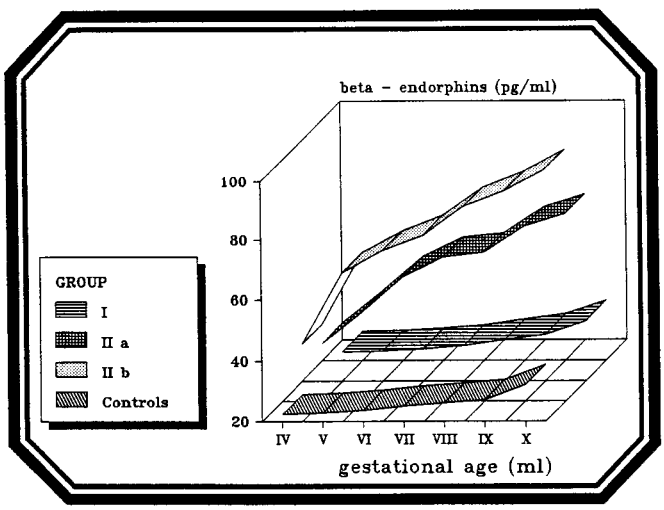
It has been shown that infusion of beta-endorphin (beta-EP) caused a significant rise of plasma glucose concentrations preceded by a significant release in peripheral glucagon levels. Beta-EP also inhibited glucose suppression of glucagon levels while the inhibition of insulin secretion was of biological relevance[1]. In normal volunteers infusion of beta-EP caused a clear-cut inhibition of insulin responses to a glucose pulse[2]. These data confirmed that beta-EP stimulates glucagon and inhibits basal and glucose-stimulated insulin secretion. In experimental conditions, it has been found that intravenous administration of small doses of beta-EP caused an immediate suppression of basal and glucose-stimulated insulin secretion[3]. However, up to now, the link between beta-EP concentrations in pregnant women's peripheral blood and gestational diabetes development still remains unresolved.

Materials and Methods

This study was performed in

the Department of Clinical Pathology, Clinic of Gynaecology and Obstetrics and Institute of Anatomy, University Clinical Center in Belgrade.

The investigations comprised 28 pregnant women, 14 with insulin-dependent and 14 with insulin-independent gestational diabetes. Fourteen women with physiologically normal pregnancy were used as controls. For each of them, beta-EP concentrations in peripheral blood samples were



Beta - Endorphins (pg/ml, mean)		Month of Gestation						
Group		IV	V	VI	VII	VIII	IX	X
I Insulin independent gestational diabetes		22.9	23.1	23.8	24.9	26.8	28.5	32.8
II Insulin dependent gestational diabetes	a) before insulin application	32.4	42.8	56.2	62.7	72.2	78.6	84.2
	b) after insulin application	38.8	62.2	69.6	74.8	84.5	89.9	97.2
III Controls		22.3	22.8	23.7	25.1	26.1	27.2	32.2

Fig. 1 Concentrations of beta-endorphin in peripheral blood samples of pregnant women.

determined early in the morning, under fasting, from the 4th until the 10th gestational month. The insulin-dependent group was tested before and 1 hour after subcutaneus insulin administration (10 IU of crystal insulin and 10 IU of insulin with medium protracted action).

Beta-EP determination in peripheral blood samples was based on radioimmunoassay techniques (RIA-Nichols Institute kits).

The obtained data underwent Student's t test statistical analyses.

Results

Immunoreactive beta-EP in peripheral blood of pregnant women was found to increase with the progression of gestation. This finding was particularly noted in insulin-dependent pregnant women. It has also been found that insulin caused a significant rise of beta-EP concentrations 1 hour after subcutaneus administration ($p < 0.01$) (Fig. 1). The maximal beta-EP concentration of 97.2 pg/ml was detected at the end of gestation in women with insulin-dependent diabetes, after insulin administration.

Discussion

Pancreas is found to be a very important source of many hormones and opioid peptides during fetal and neonatal lives[4].

In pregnancy maternal and fetal production of beta-EP gives an increase of its blood concentrations[5]. There is a putative bidirectional network carrying information between the endocrine and reproductive systems[6,7]. Pancreas is incorporated in the endocrine axis of hypothalamus, pituitary and gonadal glands. The production (secretion) of opioid peptides in human fetal pancreas is increased according to the progression of gestation[8].

This study indicates that serum concentrations of beta-EP rise during gestation, reaching the peak at the end of the 10th lunar month. Peripheral blood beta-EP levels did not significantly differ in insulin-independent patients in comparison with the controls, while the insulin-dependent ones presented significantly higher levels.

The obtained data also confirm that insulin, 1 hour after administration, causes a significant increase of beta-EP levels. So, by inhibiting insulin secretion, beta-EPs might be incorporated in the complex mechanism of gestational diabetes development.

Further research of the link between beta-EP and insulin secretion during gestation is necessary for reaching an exact view of gestational diabetes pathogenesis.

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Beta - Endorphin Level Elevation in Human Fetal and Neonatal Pancreas: A Consequence of Intrapartal Stress or the Possible Existence of Pancreatic Islet Cells Autocrine Control?

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Abstract: *The presence of neurohormones in the human fetal and neonatal pancreas has not been systematically investigated until now. It has been found that hypoglycemia induced by insulin stimulates beta-endorphin (beta-EP) production, which is also confirmed in stressful situations. Therefore, we investigated beta-EP production and concentrations in human fetal pancreas during gestation and in the immediate neonatal period. Methodology of beta-EP determination was based on its concentrations evaluation in the membranes and cytosol of the pancreas cell substrate using radioimmunoassay. Results indicate that beta-EP production in pancreas exists, with concentrations rising concomitantly with gestational progression and in the stressful intrapartal period. According to our opinion, beta-EPs are incorporated in the endocrine regulation of pregnancy and delivery. (Thai J Obstet Gynaecol 1993;5:19-24.)*

Key words: beta-endorphin, pancreas, ectopic hormone secretion, intrapartal stress, antireproductive factor

Beta-endorphin (beta-EP) is a neurohormone (neuropeptide) cleaved from precursor pro-opiomelanocortin (POMC) under the control of corticotropin releasing hormone (CRH). Beta-EP is generated in the central nervous system, hypothalamus and anterior pituitary[1] but it is detected in the ovarian, testicular, thymic and placental tissues as well[2,3].

Developmental patterns of pancreatic opioid peptides, especially beta-EPs and islet hormones studied in experimental conditions indicate their

surge during the first postnatal week[4]. Beta-EP containing cells are in close proximity to insulin containing cells in the endocrine pancreas. It has been confirmed that beta-EP stimulates glucagon release and inhibits somatostatin secretion, effects that can be reversed by naloxone[5,6]. Recent studies indicated that beta-EP infusion caused a significant rise in plasma glucose concentrations preceded by a significant increase in peripheral glucagon levels but no changes occurred in the plasma concentrations of insulin and C peptide[7]. Beta-EPs have morphine-like analgesic properties, behavioral effects and neurotransmitter (neuromodulator) functions, but their role in the perinatal period stays, as yet, unresolved.

The aim of this study was to estimate the production and concentration variations of beta-EPs in the human fetal and neonatal pancreas during the gestation (third trimester) and in the early neonatal period in order to explain their possible function in pregnancy, especially the influence on delivery initiation and on insulin secretion.

Materials and Methods

This study was performed in the Department of Clinical Pathology, Clinic of Gynaecology and Obstetrics, in collaboration with Institute of Anatomy and Institute for Biomedical Scientific Information, Belgrade the School of Medicine.

We determined the concentrations of beta-EP in human fetal (FPG) and neonatal (NPG) pancreas glands tissue. Samples were obtained at autopsy immediately after spontaneous preterm labour in the eight and a half (n=4), nine (n=4) and nine and a half (n=4) months of gestation as well as at term delivery (n=4). Estimations of beta-EP levels were also performed in placental tissues of the same feto-placental units (n=16).

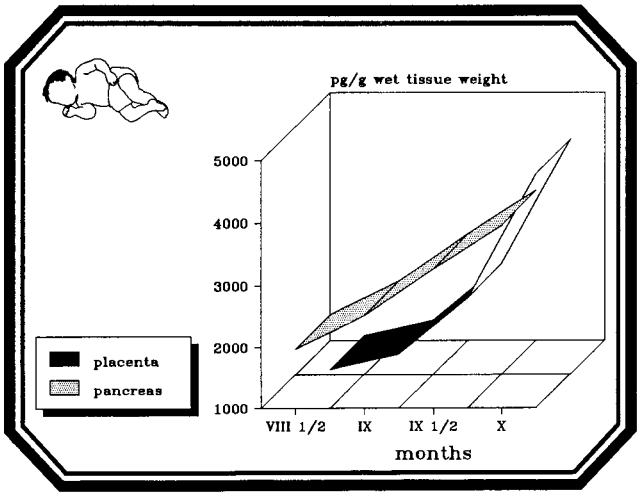
Peripheral blood samples of non-gravid healthy persons (n=10) were taken as controls.

After they were obtained, pancreatic and placental tissue specimens were placed directly into liquid nitrogen and transported to the laboratory. One gram of tissue was cut and, after the microdismembranation process[8], put in 5 ml of homogenization buffer. Beta-EP determination was based on the evaluation of concentrations in both membrane and cytosol of the pancreatic and placental cell substrate by using radioimmunoassay techniques (RIA-Nichols Institute). So results were expressed in picograms of beta-EP in 1 g of wet tissue weight, mean ± SD. Beta-EP concentrations in peripheral blood were determined using RIA Nichols kits.

The obtained data were analyzed by Student t and x^2 tests.

Results

Immunoreactive beta-EP in the human pancreas was found to increase



Beta - Endorphins	Month of Gestation			
Wet tissue weight (pg/g, mean +/- SD)	VIII 1/2	IX	IX 1/2	X
Pancreas	1980 +/- 186	2520 +/- 223	3276 +/- 648	3960 +/- 637
Placenta	1086 +/- 212	1336 +/- 288	2243 +/- 548	4234 +/- 848

Fig. 1 Concentrations of beta-EP in human fetal and neonatal pancreas and placenta.

Immunoreactive beta-EP levels in peripheral blood of non-pregnant women were 45 ± 8 pg/ml.

in pancreatic and placental cellular substrates with the progression of gestation. The highest beta-EP levels were observed in term pancreatic and placental tissue specimens (3960 ± 637 pg/g and 4234 ± 840 pg/g, respectively) (Fig. 1).

Discussion

The pancreas develops from two buds growing from the fetal endoderm, the dorsal evagination budding first followed by the ventral one. The system of budding and evagination forms interlobular ducts and ductules and the intralobular ductules from which the acini develop[9]. It is also confirmed that ductules form the islets of Langerhans[10]. According to the opinion of most authors, islet cells are derived

from the neural crest as a part of the dispersed endocrine system or amino precursor uptake and decarboxylation (APUD) system[11,12]. Nevertheless, some studies indicate that islets develop in embryos even after removal of the neural crest[13]. Immunoreactive insulin and glucagon are demonstrable in pancreatic tissue from the 90th day of gestation onwards. At the beginning of the 6th month of gestation, lymphocytes are stated to be numerous in the interlobular connective tissue, but decrease during the 10th month[14]. It has been proved that lymphocytes have hormone receptors and that they can produce large amounts of beta-EP[15,16]. The pancreas is found to be a very important source of many hormones and opioid peptides during fetal and neonatal life[4].

In pregnancy, and particularly during labour, which represents an extremely stressful situation, maternal and fetal production of blood beta-EP is increased[17], which our study confirmed. There is a putative bidirectional network carrying information between the endocrine and reproductive systems[18]. The pancreas is incorporated in the hypothalamic-pituitary-gonadal axis and production (secretion) of opioid peptides during the gestational period is likely to be increased[19]. Results of this investigation indicate that opioid peptides beta-EPs are components of the intrapancreatic regulatory system, that means beta-EP of pancreatic origin may function as ultrashort loop or autocrine regulator of pancreatic islet cells, because their concentration rises during gestation, throughout the intrapartal period and in early neonatal life.

While hypophyseal and gonadal hormones feedback information to the pancreatic islet cells exists, providing a modulatory system for regulation of pancreatic cell maturation and peptides production, the pancreas and its peptides secretion can exert a modulation of gonadotropin secretion via a direct action at the hypothalamic LHRH level[18].

Neurohormone beta-EP appears to have a significant physiological role as a regulator of pain perception, by increasing the threshold of this perception and as an endocrine factor in human reproduction. Beta-EP stimulates secretion of prolactin (PRL), growth hormone (GH) and vasopressin (AVP), and inhibits production of oxytocin (OT), dopamine, follicular stimulating (FSH) and luteinizing (LH) hormones, resulting in depression of copulative effects, that is, it exerts anti-reproductive influence both in female and male reproductive tract[6]. It is worth noting that pancreatic islet cells were found to produce several neurohormones, including beta-EP[4], which show antagonistic effects. This interaction has already drawn attention of investigators in the field of neuroendocrinology. It has been found that beta-EP protects the reproductive system from both the excessive secretion and effects of pituitary trophic hormones. The mechanism of opioid

peptide action is via opioid receptors and can be antagonized by competitive binding antagonist naloxone. Naloxone and its possible relationship to fetal endorphin levels and fetal distress have been studied by Goodlin[5].

The results obtained in this study could suggest that the identified increased beta-EP production in both membrane and cell substrate cytosol from fetal and neonatal pancreas are most probably caused by intrapartal stress. As an alternative hypothesis we propose that beta-EP of the pancreatic origin represents an anti-reproductive factor, throughout intrauterine fetal and early neonatal lives. There is no doubt that beta-EP of pancreatic origin influences intrapancreatic hormones and other opioid peptides synthesis, that means beta-EP may function as ultrashort loop or autocrine regulator of pancreatic islet cells.

Endocrinology of pancreatic cells requires further research in order to obtain a definitive exact insight in human reproduction.

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Therapy of Hypothyroidism in Pregnancy

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Abstract : *This report presents the prospective analysis of 46 pregnant women with hypothyroidism who were treated before and during pregnancy with thyroid hormone substitutional therapy. Novothyral in a constant dose was administered to 23.9% of pregnant women compared to the non-pregnant patients. The greatest number of pregnant women (76.1%) received Vobenol in a dose ranging from 75-200 μg. Depending on the clinical and laboratory analysis, Vobenol dose was increased in 40.0% of women with idiopathic and in 22.6% with postoperative hypothyroidism. The dose of the drug was not lowered during the whole pregnancy course in any of the patients. The delivery occurred in 82.6% of patients. In 13.2% of women delivered prior to term, while spontaneous abortion was present in 17.4% of the treated patients. There were 5.3% stillbirths which corresponds to the rate of perinatal mortality.One infant was born with hydrocephalus while the others were healthy. The authors are of the opinion that it is necessary to achieve normal metabolic status before pregnancy which should be maintained with substitutional therapy during the whole pregnancy. (Thai J Obstet Gynaecol 1993;5:25-31.)*

Key words : hypothyroidism, pregnancy, substitutional therapy

It is clear today that in patients with hypothyroidism the pregnancy outcome is significantly better in adequately treated pregnant women, but the question of substitutional therapy mechanism effect on the fetus remains still open.

The placental transfer of thyroid hormones (TH) is not completely clear and there is a general statement that in physiological conditions it is limited in the direction mother-fetus and vice versa[1]. Thyroid hormones in early pregnancy do not pass the placental barrier[1]. However, by the end of pregnancy, and especially during delivery, a certain quantity may be transfered into fetal circulation, indicating more the exchange of hormones than real transport. It has been reported that the placenta contains an enzyme that deiodinates thyroxine (T4) into inactive metabolite reverse triiodothyronine (rT3) and also inactivates triiodothyronine (T3) by conversion to diiodothyronine, substrates

that are not transfered into the fetus[2]. It is possible that this enzyme plays a major role in preventing the maternal TH transport into the fetal circulation. Considering that thyroid-stimulating hormone (TSH) does not enter into the fetus either, the question of thyrotropin-releasing hormone (TRH) placental transport arises, which might have the role of mediator in fetal thyroid function. Special interest has been aroused by the hypothesis that fetal TH, especially near term, may pass the placenta and compensate the thyroid status of a hypothyroidal pregnant woman[3,4]. It seems that TH transfer into fetal circulation in a large amount depends on the mutual effect of TH and plasma proteins. Since the binding capapcity of the maternal hormones, especially of thyroxine surpasses their fetal capacity, the TH transfer from the fetus may be expected.

The majority of investigators are of the opinion that the TH placental transfer is not necessary when the fetal pituitary-thyroid axis remains intact. There are investigators who determined the development of athyreosis in children of euthyroid mothers and, in contrast to this, a normal development of children born to hypothyroid mothers, indicating the relative autonomous maternal and fetal thyroid functions[1].

The aim of this study was to investigate the course and outcome of pregnancies in women with hypothyroidism on thyroid hormone substitution therapy, especially the dose requirements of thyroxine.

Patients and Methods

The study involved 46 pregnant women with hypothyroidism which had developed as a consequence of vairous etiopathogenetic factors which were treated before and during pregnancy with thyroid hormone substitutional therapy. All patients were regularly follow-up and delivered at the Clinic of Gynaecology and Obstetrics, University Clinical Center in Belgrade. The analysis was completely prospective, performed in the ten-year period, from 1981-1990.

The follow-up of the basic disease was performed in collaboration with the internist, endocrinologist with the evaluation of clinical parameters and routine laboratory analyses and radioimmunologic assessment of thyroxine (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) (INEP kits) in pregnancy trimesters, and of free hormones (FT4 and FT3 with Amersham kits) in the first and last trimesters, while the pregnancy course was monitored with available means for evaluation of fetal status and the feto-placental unit. The range of normal TSH values were from 0.6-6mU/l,from 64-164 nmol/l for T4, from 1.4-3nmol/l for T3, from 9.5-25.0 pmol/l for FT4 and from 2.9-8.9 pmol/l for FT3.

The control group included 20 healthy pregnant women with normal gravidity course, term delivery with normal endocrinology status deter-

mined before pregnancy.

The majority of pregnant women received Vobenol (since commercially available), a synthetic L-thyroxine preparation (one tablet contains 100 μg of levothyroxine sodium). In the initial phase of this study a smaller number of patients received Novothyral, also a synthetic preparation, which is a combination of T3 and T4 (one tablet of Novothyral contains 20 μg of T3 and 100 μg of T4).

Statistical data analysis was done with Student t-test of proportions, χ^2 and Fisher's tests of real probability, while the variance analysis was done for tendency evaluation of examined parameters according to pregnancy trimesters.

Results

In order to obtain the most precise interpretation of the results all pregnant women were divided into two groups according to the disease causes:

I-Postoperative hypothyroidism (31) of very heterogeneous structure, developed as a consequence of subtotal thyroid gland resection (26), due to Graves disease (8), non-toxic goiter (6), follicular adenoma (5), carcinoma (7), or total thyroidectomy due to carcinoma (5).

II-Idiopathic hypothyrodism (15) involved patients (4) with mettabolic impairment during pregnancy which in spite of increased daily doses of Vobenol (200 μg) persisted throughout the pregnancy (IIa).

The analysis of Table 1 indicates that in all patients with hypothyroidism the TSH concentrations increased above normal values, significantly higher comparing to the control group.

The concentration of T4 was significantly lower in relation to the corresponding trimester in the control group. T3 values did not indicate greater deviations compared to the healthy pregnant women.

Patients with idiopathic hypothyrodism with impaired metabolic status during gravidity (IIa) were separately analyzed.

Graphicon 1 shows that in pregnant women with hypothyroidism the FT4 concentration was significantly lower value while concentration of FT3 had unsignificant lower value compared to the healthy pregnant women.

Table 2 shows that Novothyral in a constant dose was administered to 11 pregnant women (23.9%) compared to non-pregnant patients. The

Graph 1 FT4 and FT3 in pregnancy

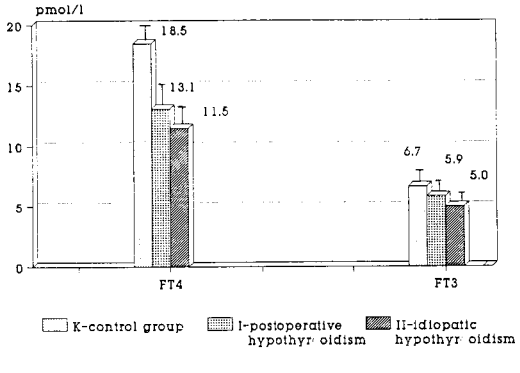

Table 1 The value of thyroxin (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) in pregnancy trimesters

Groups	Trimesters	T4 (nmol/l)		T3 (nmol/l)		TSH mU/l	
		$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
K n=20	I	123.4	12.8	2.21	0.27	5.92	0.85
	II	136.9	12.9	2.37	0.15	5.74	0.83
	III	144.3	11.7	2.52	0.18	5.52	0.79
	test	F = 13.542 p < 0.001		F = 7.951 p < 0.001		F = 0.988 p > 0.05	
I n=31	I	109.2	14.3	2.37	0.31	9.37	1.13
	II	112.9	11.3	2.49	0.23	9.17	1.03
	III	113.2	15.9	2.47	0.27	8.91	1.09
	test	F = 1.057 p > 0.05		F = 1.315 p > 0.05		F = 1.586 p > 0.05	
II n=11	I	108.5	18.5	2.20	0.36	11.5	2.8
	II	117.8	22.6	2.29	0.41	10.4	2.3
	III	122.1	16.4	2.34	0.33	10.0	3.0
	test	F = 1.822 p > 0.05		F = 0.875 p > 0.05		F - 1.071 p > 0.05	
IIa n=4	I	74.5	27.5	1.55	0.47	35.2	8.1
	II	88.0	8.6	1.877	0.13	37.3	10.1
	III	53.0	2.9	1.48	0.06	56.0	7.1
	test	F = 1.102 p > 0.05		F = 3.836 p > 0.05		F = 2.736 p > 0.05	

K - control group
I - postoperative hypothroidism
II - idiopathic hypothyroidism

greatest number of pregnant women (76.1%) received Vobenol (since commercially available) in a dose from 75 μg to 200 μg. Depending on the clinical and laboratory analysis, Vobenol dose was increased in 14 (30.4%) of pregnant women with the progression of gestation. The dose of the drug was not lowered during the pregnancy in any of the patients.

Table 2 Therapy before and during pregnancy

Characteristics	N	Novothyral			Vobenol				
		n	2* 1/2	2* 1	n	75 μg	100 μg	150 μg	200 μg
Without changing the dose	32 69.6	11 23.9	7 15.2	4 8.7	21 45.7	8 17.4	8 17.4	5 10.9	- -
Increase the dose	14 31.4	14 -	1 -	13 -	30.4	-	-	2.1	28.3
Total	11 46	7 23.9	4 15.2	35 8.7	8 76.1	8 17.4	6 17.4	13 13.0	28.3
I	8 31	7 25.8	1 22.6	23 3.2	6 74.2	6 19.3	4 19.3	7 12.9	22.6
II	3 15	1 20.0	2 6.7	12 13.3	2 80.0	2 13.3	2 13.3	6 13.3	40.0

I - postoperative hypothyroidism
II - idiopathic hypothyrodisim

Table 3 Pregnancy outcome

Groups	N	Pregnancy outcome		
		Delivery		Abortion
		Total	Preterm	
I	31	26 (83.9%)	3 (11.5)	5 (16.1%)
II	15	12 (80.0%)	2 (16.7)	3 (20.0%)
Total	46	38 (82.6%)	5 (13.2)	8 (17.4%)

I - postoperative hypothyroidism
II - idiopathic hypothyroidism

Table 3 shows that 82.6% of our patients were delivered, 13.2% had preterm deliveries, while 17.4% had spontaneous abortions of which 6.5% were in the first trimester of pregnancy. There were two stillbirths so perinatal mortality was 5.3%.

Discussion

Since Howitz, in 1892, first reported that dried lamb thyroid gland given orally to the patients with hypothyroidism has an active effect, preparations with various biological activity were used. Novothyral, administered to a small number of subjects in the initial phase of this study, caused serum peaks immediately after the absorption, followed by a sudden fall. Pure thyroxine is nowadays generally accepted as the drug of choice and the only preparation which is ca-

pable to achieve adequate physiological control. There is disagreement on the optimal daily thyroxine doses in pregnancy; some authors suggest unchanged, constant doses compared to non-pregnant conditions while others suggest higher or lower doses depending on hormonal parameters[5-7]. The discrepancy in data on daily thyroxine doses is probably a consequence of a different clinical status, especially of the etiologic factors of hypothyroidism. In 30.4% of our subjects, the dose of Vobenol was increased with the progression of gestation based on clinical and laboratory findings. It is reported that pregnant women who underwent thyroidectomy are most suitable for evaluation of L-thyroxine appropriate doses[7]. However, there is disagreement here as well. While some authors describe unchanged doses, and even insignificant decrease of doses compared to non-pregnant conditions[6], others assume that it is necessary to increase thyroxine doses due to the metabolic and hormonal changes which normally occur in pregnancy[7].

Although the data on the effects of hypothyroidism on the course and outcome of pregnancy and the status of the newborns are contradictory, the majority of authors observed differences which occurred depending on the treatment before and during gravidity. According to the referential data since 1897, Potter[8] reported the improvement of pregnancy outcome in patients with hypothyroidism treated with subsitutional therapy.

Spontaneous abortions occurred in 17.4% of our pregnant women with hypothyroidism, in the first trimester in 26.7%, and preterm delivery occurred in 13.2%, which is concordant to the results of the other investigators. The reported incidence of spontaneous abortion is 14.3% as much as 50% of them in the first trimester, and preterm deliveries from 8.9% to 20.8%[6, 9, 10]. In our subjects there were 5.3% of stillbirths which corresponds to the rate of perinatal mortality. The data on stillbirths reported by other authors have a wide range, from 1.8% to 12.5% with perinatal mortality from 3.6% to 12.5%[6, 9,10], and even to 20% in older publications. High prevalence of congenital malformations is of remarkable importance, from 10% to 20% as well as impaired mental and somatic development is 50% to 60% of surviving newborns[11]. By applying intelligence test Man[11] found that it was much lower in children of untreated pregnant women with hypothyroidsm compared to the children born to adequately treated hypothyrotic mothers. The incidence of congenital anomalies in recent reports ranges from 7% to 9%[6, 10], but it can not be explained only by thyroid function disorders. We reported that one newborn was born with hydrocephalus in the group of pregnant women with autoimmune hypothyroidism so the incidence of anomalies was 2.6%. The development of hypothyroidism was not observed in the newborns.

In conclusion one can say that

pregnancies in women suffering from hypothyroidism must be followed up from the very beginning, as a high risk pregnancy, since the pregnancy and puerperium itself influence the course and outcome of the pregnancy. It is necessary to achieve eumetabolic status in these patients before pregnancy which should be maintained during the whole gestational period in order to lower the incidence of complications of the mother and her fetus. During the pregnancy the control of the feto-placental unit by all available means is recommended. Special care must be put on the control of the basic disease, particularly the dosage of TSH, total and free TH, in order to determine the optimal daily doses of thyroxine according to the clinical and laboratory parameters.

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Antibiotherapy Choice in the Treatment of the Severe Forms of Urinary Tract Infections During Pregnancy

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Abstract : *Bacteriuria and urinary tract infection (UTI) are relatively common in pregnant women. It has been proven that bacteriuric patients have an increased incidence of acute pyelonephritis, premature labour and fetal loss. These complications can be avoided by proper eradication of UTI in early pregnancy, especially in gravidas suffering from diabetes mellitus and in those with previous UTI. The aim of this study was to investigate the antibiotherapy choice in the treatment of the severe forms of urinary infections in pregnancy. A retrospective study was made on 46 prospectively followed-up high risk pregnancy patients. The presence of bacteriuria was analyzed in relation to previous UTI (Group 1) and in relation to diabetes mellitus (Group 2). Urinary tract infections were found to be more frequent than microbial contamination (27:19), and microbes appeared more often in diabetic patients ($p<0.01$). The incidence of positive urine cultures were the highest in the third trimester gravidas, almost equally in both groups. Analyzing the microbial aspect of UTI causes it was found that E.coli predominates. This microbe was discovered in 70.37% of urine cultures, while Enterococcus, Klebsiella, P. mirabilis and Saprophytes were diagnosed less often. Pregnant women with confirmed infection received antibiotics according to antibiograms. Ten-day cephtriaxon therapy (2 g daily) resulted in sterile urine cultures in all the probands with no side effects for mother and fetus, while other antibiotics were less efficient. Therefore, we recommend this antibiotic for the treatment of UTI in high risk pregnancies. (Thai J Obstet Gynaecol 1993; 5:33-37.)*

Key words: antibiotics, urinary tract infection, pregnancy

The most common urogynaecologic disorders are lower urinary tract infection (UTI) and urinary incontinence. Only a few risk factors have been identified with either disorders, and they are the sources of much physical and emotional distress as well as a major health care cost[1].

The finding of asymptomatic bacteriuria, which is not necessarily associated with clinical inflammation of the urinary tract, is not a rare finding in pregnant women[2]. It has been reported that 4.6-7% of gravidas show evidence of asymptomatic bacteriuria at the time of their first antenatal

visit[3,4]. Kass[5] has published that there is an incidence of 40% clinical UTI among these bacteriuric patients and showed an increase in the incidence of acute pyelonephritis, premature labour and fetal loss. It is taught that these complications can be avoided by proper eradication of UTI in early pregnancy[6]. Ledger[7] reported that infection can cause premature labour. Most clinicians practice universal screening for gestational diabetes. It is well known that intensive fetal surveillance, elective delivery and high caesarean rates are common in pregnancies complicated by insulin-dependent diabetes mellitus[8,9]. Martinell et al[10] showed that the incidence of bacteriuria during first pregnancies was significantly greater in women with (9.47%) and without (6.27%) renal scarring after childhood urinary infection than in controls (1.2%). It is also proven that women with a history of previous UTI had a high incidence of bacteriuria during pregnancy, and those with renal scarring and persistent reflux were prone to develop acute pyelonephritis[10,11].

The aim of this study was to investigate the antibiotherapy choice in the treatment of severe forms of urinary tract infections during pregnancy.

Materials and Methods

The retrospective study was carried out during a period of two years on 46 prospectively follow-up gravidas hospitalized for the reason of developed urinary tract infection diagnosed throughout the laboratory screening of high risk pregnancies, at the Division of High Risk Pregnancy, University Clinical Center in Belgrade. The analyzed patients were divided into two groups: the first group comprised of the patients with previous urinary tract infections and the second one consisted of diabetic gravidas. Clean, voided mid-stream urine specimens were cultured quantitatively and isolated agents were identified by standard microbiological methods. In cases of significant bacteriuria (>100000 / ml) the antibiotic treatment in accordance with the result of the sensitivity tests was ordinated. After the treatment was finished, control urine cultures were performed. The success of the applied therapy as well as other obtained results, were cultivated by x^2 *test.*

Results

A retrospective study was made on prospectively follow-up patients with high risk pregnancy. The presence of bacteriuria was analyzed in relation to previous UTI (Group 1) and in relation to diabetes mellitus (Group 2). The results showed that infections appeared more frequently than bacterial contamination (27:19), and that microbes appeared more often in diabetic gravidas ($p<0.01$) (Table 1).

Analyzing the presence of bacteria in relation to gestational age, it was found that the incidence of positive urine cultures were highest in the third trimester gravidas, almost

Table 1 The presence of microbes in urine of studied high risk gravidas

Risk groups	Number of patients		
	Contamination	Infection	Total
I	7	9	16
II	12	18	30
Total	19	27	46

Table 2 Gestational age of patients with positive urine cultures

Groups	Trimesters			
	First	Second	Third	Total
I	4	2	10	16
II	6	12	12	30
Total	10	14	22	46

equally in both groups (Table 2).

Particular attention was paid to the causes of UTI. E.coli was found to predominate. This microbe was discovered in 70.37% of urine cultures, while Enterococcus, Klebsiella, P. mirabilis and Saprophytes were diagnosed less often. Statistical analyses have proven that the incidence of urinary E.coli was higher in diabetic patients ($p<0.05$) (Table 3).

Pregnant women with confirmed infection received antibiotics according to their antibiograms. The results are presented in Table 4. Cephtriaxon (2 g daily) was administered in 21, Benzilpenicilin and Ampicillin in two and Cephalexin and Gentamicin in one patient. Ten-day Cephtriaxon therapy resulted in sterile urine cultures in all the probands. Gravidas treated with Benzilpenicillin demonstrated high levels of Pseu-

Table 4 Antibiotics treatment of severe forms of urinary infections in pregnancy

Antibiotics	Number of patients
Cephtriaxon	21
Benxilpenicillin	2
Ampicillin	2
Cephalexin	1
Gentamicin	1
Total	27

Table 3 Urinary tract infections in studied patients

Groups	Microorganisms					
	E.coli	Enterococci	P. mirabilis	Klebsiella	Saprophytes	Total
I	5	2	1	/	1	9
II	14	/	/	1	3	18
Total	19	2	1	1	4	27

domonas aeruginosa in the control urine cultures, while Cephalexin showed to be inefficient, as the concentration of microbes was only slightly decreased, despite the therapy.

Discussion

It seems likely that the prevalence of bacteriuria among women increases during pregnancy. Symptomatic or clinical urinary tract infection (cystitis or pyelonephritis) occurs more frequently during pregnancy which suggests that factors exist which allow, more readily, proliferation of bacteria in urine[5,12]. This could be partially due to urinary stasis and also to pregnancy-induced changes in the composition of the urine which favors an increase in the rate of bacterial multiplication. Risk pregnancies are more inclined to this infection[6,10]. Our results also confirm that the incidence of urinary tract microorganisms increases with the progression of gestation. Lawson and Miller[3,4] reported an incidence of urinary tract infection of 3.1% among pregnant women with negative urine cultures and 27.7% among asymptomatic patients. Little[6] reported 25% incidence of acute pyelonephritis during pregnancy among asymptomatic group of gravidas. Golan et al[2] found asymptomatic bacteriuria in 5.9% of normal pregnancies, 12.5% among the diabetics and in 18.5% of the previous urinary tract infection patients. In our study, 9 patients (33.33%) were asymptomatic UTI, while bacterial contamination and infection was two times higher in diabetic gravidas than those with previous urinary tract inflammation. According to literature data the main cause is E.coli[7,13]. In our study, this microbe was found to be present in more than two-third of the examined specimens of urine (70.37%). The other microbes were considerably less often isolated. Matorras and co-workers[14] were especially interested in correlation between maternal diabetes and urinary infection produced by group B streptococcus. They revealed that urinary tract colonization with this microbe in diabetics was twice as high as in non-diabetics (20% versus 10.9%). In spite of this, none of the urine cultures showed the presence of this cause in concentrations over 100000/ml. Detrimental drug effects in pregnancy were described long ago. It is known that Polymixin has neurotoxic and nalicidic acid haemolytic effects. Sulphonamide therapy often results in nuclear icterus. More recent investigations point out beta-lactamase benefits, since their untoward effects to the fetus have not been described as yet[13]. Contemporary treatment of urinary infections also involves the treatment of asymptomatic bacteriuria, because it is known that 30-40% of untreated cases may develop acute pyelonephritis[9,12]. Some authors suggest single Amoxicillin doses of 3 g with eventual repetition four days later[13]. Some regimens of UTI management involves also a chronic suppressive therapy with 100 mg nitro-

furantoin in the evening[15]. In our study, Cephtriaxon has proved to be very efficient and reliable for the microbe eradication, with no side effects to mother and fetus. Even the first control urine cultures 10 days from the onset of the therapy have shown to be sterile. Therefore, we recommend this antibiotic for the treatment of UTI in high risk pregnancies.

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The Comparative Study of the Human Sperm Hypoosmotic Swelling Test and Routine Semen Analysis

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Abstract: *To ascertain the value of the hypoosmotic swelling (HOS) test in predicting male fertility, semen samples from 213 males of infertile couples were assessed by the HOS test and the results correlated with routine semen analysis. The HOS test for the 138 normal semen samples was significantly higher than for the 75 abnormal semen samples ($p<0.001$). A strong positive correlation was observed between sperm swelling and sperm motility ($r=0.83$, $p<0.0001$), and sperm viability ($r=0.82$, $p<0.0001$). Lower correlation was obtained between sperm swelling and sperm concentration ($r=0.63$, $p<0.0001$), and total count ($r=0.52$, $p<0.0001$). The cut off value of the HOS test that showed the best sensitivity, specificity, and predictive values was 37%. The results indicate that the simple and inexpensive HOS test may be a useful addition to the standard semen analysis. (Thai J Obstet Gynaecol 1993;5:39-44.)*

Key words: human sperm, hypoosmotic swelling test, routine semen analysis

A routine semen analysis has long been the standard laboratory test for the assessment of male infertility. The parameters widely measured include the volume of the ejaculate, pH, sperm concentration, motility, morphology, viability, white blood cells, and sperm antibodies. However, it has become increasingly clear that these parameters may be inadequate for diagnostic purposes[1,2]. Although the in vitro human sperm zona-free hamster ovum penetration assay (SPA), first described by Yanagimachi et al[3], can assess the functional capacity of human spermatozoa, the assay is time - consuming and complex.

The hypoosmotic swelling (HOS) test for investigating the functional integrity of the human sperm membrane has been proposed as a useful assay in the diagnosis of the infertile male[4]. Membrane integrity is not only important for sperm metabolism, it is also imperative for normal fertilization, i.e. for sperm capacitation, the acrosome reaction, and the binding of the spermatozoon to the egg surface. Jeyendran et at[4] found that there was good correlation

between the HOS test and SPA (r= 0.90). Lower correlation was observed between the HOS test and sperm morphology (r=0.30), motility (r= 0.61), and viability (r=0.52).

To ascertain the value of the HOS test in male fertility predictions, the objectives of this study were to correlate the HOS test with standard semen analysis, to compare the HOS test between normal and abnormal semen samples, and to determine the cut off value of the HOS test.

Materials and Methods

A total of 213 semen samples were collected from male partners of couples first attending the Infertility Unit, Department of Obstetrics and Gynaecology at Siriraj Hospital, from March 1989 to June 1990. Semen samples were collected by masturbation after 3 to 5 days abstinence and allowed to liquefy at room temperature. Semen analyses were performed within 2 hours after collection according to standardized methods defined by the World Health Organization[5].

The HOS test on the sperm was performed as described by Jeyendran et al[4] by one of the authors without knowing the results of the semen analyses. The hypoosmotic swelling technique consisted of mixing 0.1 ml of the undiluted ejaculate with 1.0 ml of hypoosmotic solution prepared by mixing 7.35g sodium citrate . $2H_2O$ and 13.51g fructose in 1 litre of distilled water. After incubation at 37°C for 30 minutes, the sample was examined under phase contrast microscope (x 400 magnification). At least 100 spermatozoa were evaluated for swollen tails, and the percentage of swollen tails was calculated for each sample.

Statistical significances were analyzed by Student's unpaired t-test. Correlations between the percentage of swollen sperm and the results of routine semen analysis were analyzed by correlation coefficient.

Results

The results of the HOS test in normal and abnormal semen samples are shown in Fig. 1. The percentage of swollen sperm for the 75 abnormal semen samples varied from 5 to 40 %, and for the 138 normal samples varied from 20 to 90%. Only 10 samples (7.2%) in the normal semen group gave sperm swelling percentages of less than 60.

Table 1 shows the HOS test for normal semen samples and samples with low concentration, poor motility, and both abnormal parameters. The mean values of percentage of swollen sperm were 71.3, 26.1, 23.0, and 19.1 respectively. The HOS test for the normal semen group was significantly higher than for the abnormal semen group ($p<0.001$).

The correlation between the HOS test and various semen parameters was calculated. A good correlation was observed between the percentage of swollen sperm and sperm

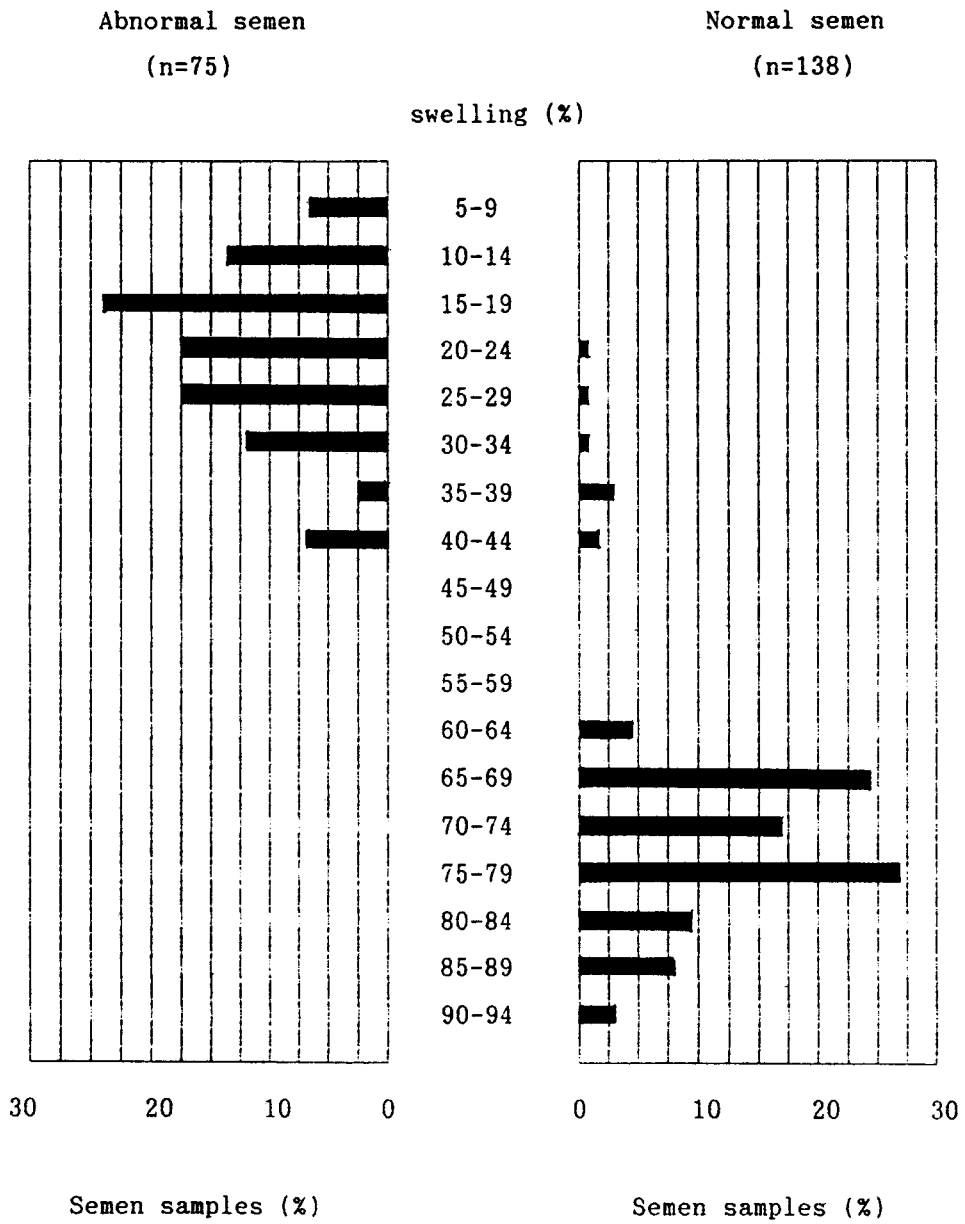

Fig. 1 The hypoosmotic swelling test in normal and abnormal semen samples.

concentration (r=0.63, p<0.0001), total count (r=0.52, p<0.0001), viability (r=0.82, p<0.0001), and sperm motility (r=0.83, p<0.0001).

Considering Fig. 1, the cut off value of the HOS test should be located in the percentage of sperm swelling between 30 and 44. Table 2

Table 1 The hypoosmotic swelling test for semen samples with normal and abnormal parameters*

Semen parameters	N	Sperm count ($x10^6$/ml)	Total count ($x10^6$)	Viability (%)	Motility (%)	Sperm swelling (%)
Normal	138	69.1±26.6	149.4±88.6	82.5±11.9	80.5±12.0	71.3±12.5
Abnormal :						
Low count	14	10.4±6.8	21.5±16.6	66.4±13.7	65.2±15.9	26.1±8.7
Poor motility	25	51.8±24.5	107.9±72.8	32.4±13.9	25.8±12.3	23.0±9.1
Both	36	8.1±6.4	15.5±19.8	28.0±12.0	22.7±11.7	19.1±7.8

* mean ± SD

Table 2 Sensitivity, specificity, positive predictive value, and negative predictive value of the hypoosmotic swelling test

Percentage of sperm swelling	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
30	78.7	98.5	96.7	89.5
31	88.0	98.5	97.0	93.8
32	88.0	98.5	97.0	93.8
33	90.7	98.5	97.1	95.1
34	90.7	97.8	95.8	95.1
35	90.7	97.8	95.8	95.1
36	92.0	97.8	95.8	95.7
37	93.3	97.8	95.9	96.4
38	93.3	95.6	92.1	96.3
39	93.3	95.6	92.1	96.3
40	93.3	94.9	90.8	96.3
41	100.0	93.5	89.3	100.0

shows sensitivity, specificity, and predictive value of the HOS test when the cut off value is set at various percentages of sperm swelling. It was clear that at 37% of sperm swelling, the HOS test showed the best sensitivity and specificity, 93.3 and 97.8% respectively. The positive and negative predictive values at this cut off point were 95.9 and 96.4 % respectively.

Discussion

The development of assays that can assess the functional activity of

human sperm should be of importance in the diagnosis of infertile men. The HOS test, developed for human sperm by Jeyendran et al[4], was found to be highly correlated with the percentage of hamster eggs penetration (SPA) and, thus,fertilizing potential. However, most results obtained on investigating the usefulness of the HOS test only demonstrated low to moderate positive correlations with the different semen parameters; count, motility, viability, and morphology[4,6-9]. In the present study, we found that the HOS test for normal semen samples was significantly higher than for abnormal ones. A strong correlation was obtained between sperm swelling, sperm motility and viability. A lesser degree of correlation was observed between sperm swelling and sperm count. It should be noted that this test is used as an indicator of normal membrane integrity and function. Good motile and live spermatozoa probably require a biochemically intact plasma membrane, thus, showing higher correlation. The sperm morphology was not included in this study because of imperfect data.

A strong relationship between the results of the HOS test and the performance of spermatozoa in an in vitro fertilization (IVF) program has been reported[10,11]. Van der Ven et al[10] found that none of the semen samples that showed less than 60 % swelling in the HOS test fertilized oocytes, and proposed that ejaculates are classified as "normal" when more than 60 % of the spermatozoa respond in the HOS test, less than 50 % is "abnormal", and 50-60 % is a "gray area". Further evidence was shown by Check et al[12] that pregnancies only occurred with ejaculates that possessed more than 50 % of sperm swelling in the HOS test.

Our present study showed that the cut off value for the HOS test was 37 %. None of the abnormal semen samples showed more than 40 % reaction in the HOS test, whereas only 7.2 % of the normal semen samples showed less than 60 % swelling. We agree with the figures proposed by Van de Ven et al[10] that differentiate the HOS test as normal (>60 %), doubtful (50-60 %), and abnormal (<50 %).

Although the standard semen analysis is simple and economical, but it lacks the reliability to predict the fertilizing potential of the ejaculated spermatozoa. The HOS test which evaluates the functional integrity of the sperm membrane, appears to be useful by a number of studies including ours. The test is economical and easy and can be readily performed in any clinical setting. We propose that the HOS test may be a useful addition to the standard semen analysis in the evaluation of male fertility.

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Cis-platin and 5-Fluorouracil for Recurrent, Persistent, and Metastatic Cervical Cancer

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Abstract : *From January 1986 to December 1989, 20 patients were treated with cis-platin and 5-fluorouracil for persistent, recurrent and distant metastatic cervical cancer. Eight patients (40%) responded, 2 complete and 6 partial. Median duration of response was 7 months. Median survival for the responders and for the non-responders were 17 and 9 months respectively. Toxicities were all transient in nature. (Thai J Obstet Gynaecol 1993; 5:45-49.)*

Key words : cervical cancer, chemotherapy

One of the choices for recurrent, persistent and distant metastasis of cervical cancer is salvage chemotherapy. Among the active single agents, cis-platin is the most active agent with response rate of 20-50%[1-5]. Another agent is 5-fluorouracil, and combination with cis-platin has been found effective in squamous cell carcinoma of the head and neck[6,7]. We evaluated this combination in patients with recurrent, persistent and distant metastatic cervical cancer.

Materials and Methods

Between January 1, 1986, and December 31, 1989, we treated 20 patients whose characteristics are shown in Table 1 with cis-platin and 5-fluorouracil. Fifteen had recurrent disease, ten of whom had undergone pelvic radiotherapy. Three patients had had prior surgery and 2 patients had received prior mitomycin-c as an induction chemotherapy followed by, in one case, radiotherapy and, in the other, radical hysterectomy with pelvic irradiation. Three patients had undergone simple hysterectomy because of benign disease without a diagnosis of cervical cancer preoperatively.

Ten of the fifteen patients with recurrent disease had distant recurrence. The sites of distant recurrence were supraclavicular lymph nodes, chest, jejunum and spleen, liver, and spines. Recurrence occurred in the pelvis alone in 4 patients. One had

Table 1 Characteristics of patients

Total number	20
Median age(years)	51(30-63)
Initial stage:	
Ib/IIa	3
IIb	7
III/IV	8
Unstaging	2
Histology:	
Squamous	17
Adenocarcinoma	2
Adeno-squamous	1
Status of disease:	
Persistent	3
Recurrence	
Local	4
Local+distant	1
Distant	10
Distant metastasis	2
Previous therapy:	
Radiotherapy	14
Surgery	3
Radiotherapy+surgery	1
Chemotherapy+radiotherapy	1
Chemotherapy+surgery+radiotherapy	1
Median time since primary therapy (months)*	8.5(0-38)

* Median values are followed by ranges in parentheses.

both pelvic and distant recurrence. The site of distant recurrence in this patient was the supraclavicular lymph nodes. All recurrences and distant metastases except that in the lung were histologically confirmed and tumour assessment was based on clinical and/or radiographic or ultrasonographic evaluations.

The eligibility requirements included a performance status of greater than 30% Karnofsky scale, white blood cell count >3000/mm^3, granulocytes >1500/mm^3, platelets count >100,000/mm^3, and normal renal and hepatic functions.

Treatment consisted of cis-platin 50 mg/m^2 by intravenous infusion on day 1 and 750 mg/m^2 of 5-fluorouracil by continuous intravenous infusion on day 1 through day 4 for a total of 3 g/m^2. Prehydration was given before cis-platin infusion with one-half normal saline intravenously at a rate of 300-500 ml per hour for 2-4 hours, and 100 ml of 20% mannitol infused in 20 minutes. Another 1000 ml of one-half normal saline was also infused intravenously in 6 hours immediately after cis-platin infusion. The antiemetic protocol consisted of a combination of metoclopromide, dexamethasone and diazepam.

Complete response was defined as no clinical or radiological evidence of disease lasting greater than 1 month. Partial response was defined as 50% reduction of measurable disease in a single largest diameter for at least 1 month. Non-responders had stable or progressive disease. Stable disease was defined as less than 50% reduction of measurable disease or no change. Time to progression was defined as the length of time from start of the chemotherapy to the date of reappearance or progression of disease. Survival was defined as the time from the start of chemotherapy. Patients without progression or who were still alive after completion of this study were considered as censored. Survival curve was calculated by the method of

Kaplan and Meier, and survival compared with log-rank test.

Results

The median number of chemotherapy courses was 5 (range 3-9). Table 2 shows the results of treatment. Of the 20 patients, 2 (10%) achieved complete response and 6 (30%), partial response, yielding a total response rate of 40%. The sites of complete response in 2 patients were supraclavicular lymph nodes. One of these 2 patients is still alive without disease 36 months after treatment. Although none of the patients with local recurrence had a response, one patient with persistent disease had partial response for 10 months. The sites of partial response in the other 5 patients were chest, supraclavicular lymph nodes, and spines. The median duration of response was 7 months (range 2-40). The median time to progression for the whole group was 4.5 months (range 0-40). Survival curves are shown in Fig. 1. Median survival was 11 months (95% confidence interval: 9-15 months) for all patients, 17 months (95% confidence interval: 12-21) for responders, and 9 months (95% confidence interval: 9-10) for non-responders (stable and progressive disease).

Table 2 Results of treatment

Median number of courses	5(3-9)
No. of responding	8
Complete response	2
Partial response	6
No. of non-responding	12
Stable disease	9
Progression	3
Median duration of response (months)*	7(2-40)
Median survival (months)*	11(3-36)
Median time to progress (months)*	4.5(0-40)

*Median values are followed by ranges in parentheses.

The most common toxicity was nausea and vomiting. Ten patients required continuation of antiemetic drugs. Eight patients developed anemia which required blood transfusion before starting the next course of chemotherapy. Nephrotoxicity, which was defined as an increase in serum creatinine above 2 mg% developed in 3 patients. Alopecia and peripheral neuropathy developed in 3 and 2 patients respectively. None of the patients had neutropenia or thrombocytopenia.

Discussion

In this study, the combination

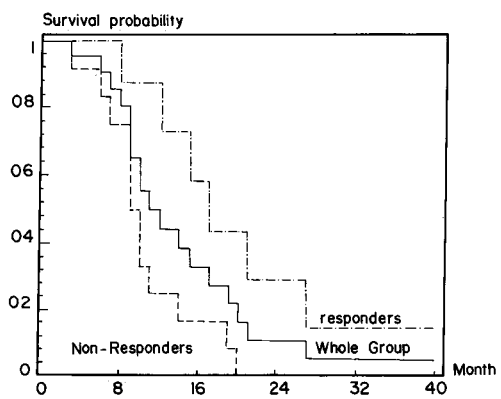

Fig. 1 Survival curve of patients with recurrent, persistent and metastatic cervical cancer treated with cis-platin and 5-fluorouracil.

Table 3 Toxic effects in cis-platin plus 5-FU-treated patients

Hematological toxicity:	
Anemia (hemoglobin<10 g/dl)	8
Leukopenia	0
Thrombocytopenia	0
Stomatitis	1
Nausea/vomiting	10
Nephrotoxicity	3
Peripheral neuropathy	2
Alopecia	3

of cis-platin and 5-fluorouracil in the treatment of recurrent, persistent and metastatic cervical cancer did not yield a high response rates as in the treatment of squamous cell carcinoma of the head and neck. Indeed, the overall response rate, 40%, is slightly lower than that of Kaern et al[8] or Rotmensch et al[9] which achieved 44% and 50% response rates respectively, using a similar regimen or of Kumar and Bhagava[10], who achieved a 66% response rate using a combination of bleomycin, ifosfamide and cis-platin. However, 10% of the patients in the current study had cervical adenocarcinoma and the dose of 5-fluorouracil was slightly low. From the study by the Gynaecology Oncology Group, there were no differences in median response or survival durations of patients treated with either low- or any intermediate-dose cis-platin regimens[11].

Neither median duration of response nor median duration of survival differed greatly from other combination chemotherapies[9,12,13] indicating that combination chemotherapy is unlikely to offer a significant survival advantage over single agent cis-platin[14]. However, responders in this study had a statistically singificant survival advantage over non-responders ($p = 0.013$, log-rank).

The toxicities of this regimen were not severe. The most common was nausea and vomiting and could be controlled by antiemetic drugs. Stomatitis, which is frequent in continuous infusion of 5-fluorouracil occurred in only one case and none of the patients developed neutropenia or thrombocytopenia. This low toxicity may be a result of the low dose of 5-fluorouracil continuous infusion. The major toxic effect of cis-platin, nephrotoxicity, was reversible.

Because this study is unable to compare the survival of the entire treated group with that of untreated patients, which is the best way to demonstrate chemotherapy effectiveness[15], it cannot conclude that the combination of these two familiar drugs, cis-platin and 5-fluorouracil, improve the therapeutic outcome. They can be used to produce 40% response rate but the survival duration is still disappointing.

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Special Article

The Role of Prostaglandins in Labour Induction

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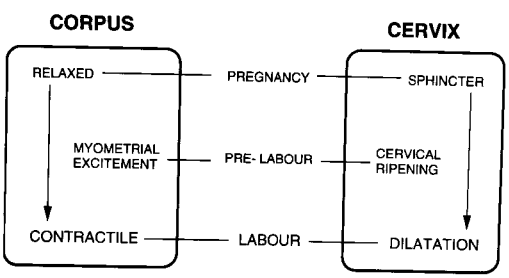
The search for safe and reliable methods of labour induction has led to the exploration of many different techniques and the application of a variety of pharmacological agents. Many of these have had little in common with normal physiology but those proving to be the most successful and most acceptable to patients have been those with a sound basis in normal physiology. The reason the prostaglandins have made such an impact on labour induction is that they represent the method which has hitherto most closely replicated the physiological control of spontaneous labour.

The factors which are responsible for the initiation of human labour, although steadily becoming clearer, are not yet fully understood[1].

The transition from pregnancy to labour entails fundamental physiological changes in the two principal components of the uterus namely the uterine corpus and the uterine cervix. The smooth muscle of the corpus (myometrium) must escape from the inhibitory influences which have maintained it in a state of quiescence while the fetus has grown and developed to the point of maturity required for its birth. Similarly the cervix must abandon its duties as the sentry at the gate of the uterus. It has required to remain rigidly closed to keep the developing fetus within the cavity of the quiescent uterus. Thus both components of the uterus require to undergo a *volte-face.* In the case of the cervix the change is from one of rigid resistance to compliance and dilatation. These changes, however, do not occur suddenly but rather as a gradual phenomenon evolving during the phase of pregnancy which is best described as *prelabour.* The normal onset of labour requires that these two changes occur in synchrony (Fig. 1).



While the precise controlling mechanisms governing these changes have not yet been fully elucidated, the

prostaglandins, especially PGE_2 and $PGF_{2\alpha}$ are indisputably and intimately concerned in the processes of myometrial excitement and cervical ripening[2,3]. The surge of prostaglandin release which accompanies the progression of normal labour is seen most dramatically in amniotic fluid, but changes in the activity of these substances within uterine tissues such as amnion, decidua, myometrium and cervix, together with the well recognised clinical effects of prostaglandins on the myometrium and cervix, point quite clearly to an essential biological role for these agents in the process of parturition. Furthermore, inhibitors of prostaglandin synthesis such as indomethacin represent the most potent tocolytic agents so far described[4]. It is therefore no exaggeration to say that in the absence of prostaglandins labour is not possible and when they are present in abundance, labour is irresistable.

Clinical use of Prostaglandins

When it comes to labour induction, prostaglandin $F_{2\alpha}$ is the poor relation of prostaglandin E_2. It is inferior in terms of potency, specificity and toxicity and its use in clinical practice can only be justified in countries where PGE_2 is available. While it does represent a potent stimulator of myometrial contractility, it appears to have little or no role in the process of cervical ripening and therefore might be considered to be very similar in its actions to oxytocin. Since it causes many more side effects than does oxytocin, it has no clinical advantages as a labour inducing agent over the time honoured use of oxytocin and it will not be further considered here. Prostaglandin E_2 is superior in every regard and will be the main subject of the remainder of this discourse.

It has become abundantly clear in recent years that local routes of prostaglandins hold the key to success. The obstetrician's ability to access the genital tract for the local delivery of prostaglandins has greatly enhanced their value. The local routes which are applicable for cervical ripening and induction of labour are vaginal, endocervical and extraamniotic. The last of these is the most effective and since it requires only a very small dose (0.5 mg PGE_2 in gel), side effects can be minimised. On the other hand it is the most invasive and perhaps the most potentially hazardous. In theory, infection may be introduced although in practice this has not proved to be a serious problem. In addition, haemorrhage may be provoked within the choriodecidual space and if so, the prostaglandins may be absorbed too rapidly with the potential for provoking uterine spasm. The possibility of inadvertent rupture of the membranes during the insertion of an extraamniotic catheter must also be borne in mind although this is also extremely rare in practice.

The vaginal route has the major attraction of simplicity although a significantly larger dose of prostaglandin may be required in order to ach-

ieve cervical ripening (usually 5 to 10 times as much). It may also be necessary to repeat vaginal applications to achieve this purpose and if so, an interval of no less than 6 hours should be allowed between doses and the dose in a gel formulation should not exceed 2 mg PGE_2. A half-way house between these two routes is represented by endocervical administration which may be an appropriate compromise. It is clearly less invasive and less hazardous than extraamniotic therapy and it may allow a more precise delivery of the prostaglandins to the target tissue. The appropriate dose is similar to the extraamniotic dose (around 0.5mg) provided such a dose can be made to stay in the endocervical canal. This technique suffers from disadvantages which arise from the anatomy of the cervix. If the cervix is already effaced and partially dilated it is difficult to identify an endocervical canal in which to place the therapy. On the other hand where the cervix is very unripe the canal may be quite narrow and the space available in which to deposit the prostaglandin gel may be quite small. Prostaglandins administered by this route may quite commonly either pass into the extraamniotic space or run back into the vagina thereby being less effective.

Much interest has concerned the search for appropriate vehicles for delivering prostaglandins and a variety of pessaries and gels have been developed for their differing release and absorption properties. The objectives should be to maximise efficiency and safety margins while minimising the dose rate and side effects. Local administration of prostaglandin E_2 can accomplish this while bringing the additional benefit of representing a form of intervention which has proved popular with mothers. They find it an agreeable approach resembling as it does more closely than any other method, the spontaneous onset of labour.

The intriguing aspect of the mechanism whereby vaginal PGE_2 induces labour lies in the observation that the onset of contractility is delayed for several hours after PGE_2 has been absorbed from the vagina and metabolised[5]. The establishment of uterine contractions is accompanied by a rise in circulating metabolite of $PGF_{2\alpha}$ suggesting that labour is the result of endogenous $PGF_{2\alpha}$ activated by exogenous PGE_2. This would go some way to explaining why the labour we see resembles spontaneous labour so closely.

A Rational Approach to Labour Induction

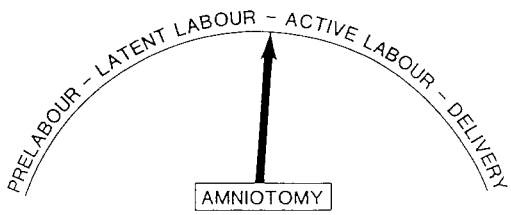
Three principal weapons are available for induction of labour in modern obstetric practice. These are :

1. Local administration of prostaglandin E_2
2. Amniotomy
3. Intravenous administration of oxytocin.

These three weapons should be applied either separately or in combi-

nation and the success of labour induction will depend on tailoring these techniques to the particular circumstances of the individual clinical case. The essence of success lies in an accurate assessment of the degree to which the events of prelabour have occurred. Two expectant mothers, both at their expected date of confinement, might represent two very different propositions and indeed be the opposite ends of a spectrum. The first may be on the threshold of spontaneous labour (i.e. at the end of prelabour) while the second may still be a long way from beginning labour and indeed prelabour may hardly have begun. In outward appearance, they may be indistinguishable, but the best way of distinguishing between them will be to carry out a pelvic assessment and calculate the Bishop score[6]. This particularly applies to primigravidae. A high Bishop score presages the imminent onset of spontaneous labour, while a low score suggests that this remains a distant prospect. More importantly, the response to labour induction is influenced very profoundly by the state of the cervix and again this is particularly in primigravidae. The mother whose labour is a distant prospect will almost certainly have a very low Bishop score, and if her labour is induced by inappropriate techniques such as amniotomy and intravenous oxytocin titration, the response will be disappointing with a high probability of prolonged labour, fetal distress, caesarean section and birth asphyxia[7]. In contrast, the mother on the threshold of spontaneous labour may require nothing more than amniotomy to achieve a successful and satisfactory outcome.

A simple way of viewing this is to focus on the most appropriate timing of amniotomy. Figure 2 shows a developing arc of the processes which make up the components of human parturition, namely prelabour, latent labour, active labour and delivery. This has been deliberately drawn to resemble the speedometer on a motor car. Rather than kilometres per hour, the units of measurement would in this instance be strength and frequency of uterine contractions.



Amniotomy should never be performed before the cervix is ripe. To do so is to increase dramatically the risk of fetal and maternal complications[8]. The optimal time for amniotomy is when uterine contractions are established and the cervix has attained full effacement and is already 3 or 4cm dilated. In spontaneous labour, adherence to this principle maximises the efficiency of labour and the ability of the attendants to supervise the welfare of the fetus. In addition, the amount of analgesia required may be

minimised[9].

If labour induction is required and the above conditions do not prevail, local administration of prostaglandin E_2 should be employed to bring them about. Where the cervix is already ripe, it is still appropriate to initiate the labour with a single applicantion of vaginal PGE_2 and then to add the influence of amniotomy once contractions are established. Such a policy was shown to be highly effective by Kennedy et al[10]. Their study compared the obstetric outcome of two groups, each of 50 mothers with a ripe cervix, requiring induction of labour. They were randomly allocated to a group receiving a single vaginal tablet of PGE_2, 3mg whose membranes were then ruptured 3-6 hours later, or to a group in whom amniotomy was performed at the outset and followed by immediate intravenous infusion of oxytocin. The two groups showed very similar obstetric results in the sense of lengths of labour and mode of delivery, but the prostaglandin approach was found to be markedly superior in respect of a lower incidence of postpartum haemorrhage and of neonatal jaundice. Moreover, the mothers who participated in this study showed a very clear preference for the prostaglandin technique rather than amniotomy and oxytocin (Table 1).

The overwhelming matermal preference for the prostaglandin technique is one of the most compelling arguments in favour of this approach.

Oxytocin remains a very potent pharmacological weapon but its used should now perhaps be restricted to mothers whose labours are not progressing effectively after the membranes have been ruptured.

Conclusions

Prostaglandin E_2 is currently the most effective agent available for the purpose of cervical ripening. If the cervix is already ripe, a small dose of PGE_2 may be all that is required to initiate a labour which very closely resembles spontaneous labour.

Amniotomy is the central event in the labour induction process. Al-

Table 1 Mother's response

Mother's response	Amniotomy +oxytocin	Vaginal PGE_2 tablet
Favourable	8	43
Non-committal	16	7
Unfavourable	26	0
TOTAL	50	50

though labour may progress to delivery with the membranes remaining intact, they would generally rupture at an earlier stage and such rupture is usually associated with a heightened activity of endogenous prostaglandins. The timing of amniotomy is crucial. Peformed too early before the cervix is ripe, it will lead to an increased rate of complications. If delayed beyond the optimal point for its introduction (a fully effaced cervix 3-4cm dilated) we may lose the advantage of its uterine sensitising influence.

Oxytocin remains a powerful myometrial stimulant if the uterus is already primed to respond to it by prostaglandins, either endogenous or exogenous. It must be given intravenously and many mothers find this disagreeable. In most instances of labour induction, a proper combination of prostaglandin therapy followed by amniotomy, may allow the use of oxytocin to be avoided but it remains an important therapy of final resort to carry labour through to its completion.

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