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Ratios of Biochemical Markers in Peritoneal Fluid to Those of Venous Blood for Early Diagnosis of Ectopic Pregnancy: A Prospective Study

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Abstract: Background: Extra-uterine pregnancy (including ectopic pregnancy and pregnancy of unknown location) is a first -trimester disorder that appears in 1.3%–2.4% of all pregnancies, and accounts for up to 6% of pregnancy - associated mortality. Ectopic pregnancy is associated with rupture, hemodynamic instability, hemorrhagic shock / hemodynamic instability, syncope, and death **Aim:** The aim of this study is to determine the value of the peritoneal fluid to venous blood ratio of hCG, Progesterone, CA125, and Creatine kinase for the diagnosis of an ectopic pregnancy and the likelihood of active bleeding. **Methods:** The present randomized clinical trial has been carried out at EL Sahel Teaching Hospital at the department of obstetrics and gynaecology. Peritoneal fluid (5 mol) had been collected by culdocentesis, and venous blood (5 mol) had been collected from the antecubital vein and transferred into Vacutainer. Blood levels of markers had been expressed as CA 125 v, b-chg., Pv, and CKv, and those of the peritoneal fluid as CA125p, b-chip, Pp, and CKp. The ratios of biochemical markers of blood to those of the corresponding peritoneal fluid (Rp /v) will be calculated and expressed as Rp/v-CA125, Rp/v-b-hCG, Rp/v-P, and Rp/v-CK. **Results:** The results pointed out that $R_{p/v}$-CA125, $R_{p/v}$-b-hCG**,** Rp/v-CK, and Rp/v-P are >1**.** CA125p, β-Chip, and CKv levels were significantly lower in the ruptured ectopic group than in the enraptured group, and β-Chg., CKp, Pv, and Pp levels were all significantly higher in the ruptured ectopic group than in the enraptured group **Conclusion:** the peritoneal fluid to venous blood ratio of hCG, CA125, progesterone and Creatine kinase can accurately predict a ruptured ectopic pregnancy. These findings may allow diagnosis of a ruptured ectopic pregnancy in the case of non - diagnostic ultrasound or culdocentesis results, thus allowing prompt intervention and potentially reducing morbidity and mortality.

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1. Introduction

Extra-uterine pregnancy (including ectopic pregnancy and pregnancy of unknown location) is a first-trimester disorder that appears in 1.3%–2.4% of all pregnancies, and accounts for up to 6% of pregnancy-associated mortality. Ectopic pregnancy is associated with rupture, hemodynamic instability, hemorrhagic shock/hemodynamic instability, syncope, and death **(Taran FA et al., 2014).**

The incidence of tubal ectopic pregnancy is increasing worldwide most likely due to a rising incidence of pelvic inflammatory disease caused by Chlamydia trachomatis infection and the increased use of assisted reproductive techniques **(Walker 2007).**

The most common site of ectopic pregnancy is fallopian tube. As tubal ectopic pregnancy (EP) is associated with high morbidity and mortality, early and accurate diagnosis of this condition is warranted. Present protocols for diagnosis of ectopic pregnancy utilize serial serum human chorionic gonadotropin (β-hCG) levels and pelvic ultrasound **(Barnhart KT 2009).**

In general, the majority of patients presenting with pain or bleeding in early pregnancy have an ultrasound scan to ascertain the viability of the pregnancy and if possible the location of the gestational sac **(Joanna C et al., 2009).**

If the ultrasound proves inconclusive, a serum b-human chorionic gonadotrophin (b-hCG) level is ascertained. The diagnosis of an ectopic pregnancy is then based on the combined sonographic findings and serum b-hCG measurements. However, it is difficult to distinguish between an ectopic pregnancy, spontaneous abortion and early ongoing intrauterine pregnancy using a single b-hCG measurement therefore repeated b-hCG measurements are taken **(Joanna C et al., 2009).**

Early diagnosis enables physicians to intervene before rupture of the ectopic pregnancy, which can both reduce mortality and enable nonsurgical interventions. During a normal intrauterine pregnancy, serum human chorionic gonadotropin (hCG) is detectable 8–10 days after ovulation (about 23 days into the menstrual cycle), and its concentration increases with gestational age. The doubling time of hCG is 1.2–1.4 days during the first 3 weeks after fertilization, and3.3–3.5 days during weeks 4–6 after fertilization. In contrast, with an ectopic pregnancy the doubling time of serum hCG is 3– 8 days longer than in a normal pregnancy. These differential rates of hCG increase can be used to distinguish between intrauterine and ectopic pregnancies **(Qi Y et al., 2012).**

As a result, multiple visits for serial β-hCG and ultrasound monitoring are required before a diagnosis can be established and management initiated. This interim period of uncertainty may lead to potential life threatening complications like intra- abdominal bleed and future infertility because of compromised tubal integrity. Therefore, early diagnosis of tubal ectopic not only prevents the added mortality in patients, but also plays an important role in preventing future infertility **(Soundravally R and Pooja D 2015).**

In an ectopic pregnancy, the zygote implants in the oviduct, ovary, or other sites in the peritoneal cavity. The metabolism of hCG in the peritoneal cavity is slower than that in the blood, and with an ectopic pregnancy the hCG content in peritoneal fluid may be higher than that in venous blood. In the case of an intrauterine pregnancy, fluid in the abdomen may be due to luteal rupture, pelvic inflammation, or blood after a miscarriage **(Wang Y et al., 2010).**

Under these conditions, relatively small amounts of HCG are released into the peritoneal cavity, and thus the hCG content of peritoneal fluid is similar to or lower than that of venous blood. Thus, the ratio of hCG in peritoneal fluid to that in venous blood may be useful for the diagnosis of ectopic pregnancy. A previous retrospective study showed that a ratio of >1 had a sensitivity and a specificity of 100% and 100%, respectively, for the diagnosis of ectopic pregnancy **(Wang Y et al., 2010).**

Researchers have also examined other serum markers, including progesterone (P), cancer antigen 125 (CA125), and creatine kinase (CK) to diagnose ectopic pregnancy. For example, one study measured total serum hCG, hyperglycosylated hCG, the free b subunit of hCG, P, and CA125 for early diagnosis of ectopic pregnancies, and found that sequential use of total serum hCG and CA125 were promising, but establishing reliable cutoff values among the different measurements required further work **(Butler SA et al.,2013).**

Creatine Kinase is the enzyme released from damaged muscles, which is currently used in the diagnosis of myocardial infarction. It has been studied extensively, and is often statistically elevated in ectopic pregnancies, especially if ruptured **(Rausch ME et al., 2011)**

CA-125 tumour marker is a cell-surface antigen derived from the surface coelomic epithelium, including the mucosa of the entire female genital tract and maternal decidua. The fetal chorion, amniotic fluid and maternal deciduas contain significant amounts of CA-125 and represent practical sources of the elevated serum levels of the protein in pregnancy. In normal intrauterine pregnancy, ruptured and enraptured tubal ectopic pregnancies, there are contradictory reports investigating the dynamics and comparison of maternal serum CA-125 level **(Schmidt T et al., 2001).**

Maternal progesterone is initially produced by corpus luteum followed by placenta, and ensures appropriate development of the endometrium, uterine growth, adequate uterine blood supply, and preparation of the uterus for labor. Progesterone levels are found to be low in both ectopic pregnancy and other abnormal IUP, when compared to viable IUP **(Lazar L et al., 2006).**

The aim of this study is to determine the value of the peritoneal fluid to venous blood ratio of hCG, Progesterone, CA125, and Creatine kinase for the diagnosis of an ectopic pregnancy and the likelihood of active bleeding.

2. Materials and methods

The present randomized clinical trial has been carried out at EL Sahel Teaching Hospital at the Department of obstetrics and gynaecology.

Inclusion criteria:

1) Normal menstrual cycle and duration of amenorrhea <90 days;

2) Positive urine or blood b-hCG;

3) Ultrasound showed pelvic fluid or culdocentesis results were positive;

4) Laparotomy or laparoscopy and postoperative pathology indicated a tubal pregnancy.

Exclusion criteria:

1) Patients diagnosed with heterotopic pregnancy.

2) Patient with serious gynaecological disorders as ovarian malignancy

Operational design:

Explanation of the procedure to all women participating in the study. A written consent was taken from all patients before starting the study with counseling about risk and benefit of treatment.

Study design: It was a prospective study.

Patients were subjected to:

Complete history taking:

1. Personal history including

2. Name, Age, marital state, address

3. Obstetric history including parity and mode of delivery. 4. Present history: of duration of vaginal bleeding

5. Past history of HTN, DM.

6. Family history of similar condition or diabetes. Secondary

7. History of allergy to any medication

8. Surgical history of operation

Examination:

A. General examination:

1) Evaluation of vital signs

2) Measurement weight, height (BMI)

B. Abdominal and local clinical examination: scar of previous operation, mass, tenderness or rigidity, any abdominal or pelvic clinically detectable pathology.

Investigations:

Pathological and intraoperative findings, as well as patient clinical characteristics. Peritoneal fluid (5 mol) had been collected by culdocentesis, and venous blood (5 mol) had been collected from the antecubital vein and transferred into Vacutainer.

Administrative considerations:

An Official permission was obtained from Faculty of Medicine, Al Azhar University.

Approval from ethical committee in the faculty of Medicine, Al Azhar University.

Ethical consideration:

• Informed consent was obtained from written informed consent was taken from parents for participation in the study. After being informed about the aims and process of the study as well as applicable objectives.

• The study procedures were free from any harmful effects on the participants as well as the service provided.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0).

3. Results

[Table 1] mean age of the studied cases was 26.9±3.9 years with range of (19-33) years.5.6% of cases had ages ≤20, 72.2% had ages (21-30) years and 22.2% of cases had ages >30. Median gravidity was 2 with range of (1-7). Median parity was 1 with a range of (0-4). [Table 2] This Table shows that ruptured tubal pregnancy represented 19% of cases and enraptured tubal pregnancy represented 81% of cases. [Table 3] This table shows zero induced abortion in 25% of cases, 1 time induced abortion in 30% of cases, >1 time in 45%of cases, abdominal surgery history in 66% of cases. [Table 4]. This table shows that mean days since las menstrual period (48.06±6.25) days, vaginal bleeding was i 48% of cases, abdominal pain was in 70% of cases. [Table 5]. This table shows that active intraperitoneal bleeding was in 80% of cases, Intraperitoneal blood volume < 500ml in 65% of cases and Intraperitoneal blood volume ≥ 500ml in 35% of cases. [Table 6]. This table shows that there is no significant difference between ruptured and enraptured pregnancy as regard gravidity, parity or abortion. {table 10] this table shows the CA125p, β-Chip, and CKv levels were significantly lower in the ruptured ectopic group than in the enraptured group, and β-Chg., CKp, Pv, and Pp levels were all significantly higher in the ruptured ectopic group than in the enraptured group. Rp/vCA125 and Rp/v-β-hCG ratios were significantly lower in the ruptured ectopic group than in the enraptured. Rp/v-CK, and Rp/v-P ratios were significant higher in the ruptured ectopic group than in the enraptured group.

Table (1): Studying of demographic data in between the studied groups:

Variable		
Age: (Years):		
Mean ± SD	26.9±3.9	
Range	(19-33)	
Age groups	**N**	**%**
≤20	6	6.0
21-30	72	72.0
>30	22	22.0
Gravidity:		
Median	2	
Range	(1-7)	
Parity:		
Median	1	
Range	(0-4)	
Abortion:		
Median	0	
Range	(0-4)	

Table (2): Distribution of tubal pregnancy cases according to rupture or enraptured pregnancy:

	No.	**%**
Tubal pregnancy:		
Ruptured	81	81.0
Enraptured	19	19.0

Table (3): Operative history of the studied group:

	No.	**%**
Abortion:		
0	25	25.0
1	30	30.0
>1	45	45.0
Abdominal surgery history:		
No	66	66.0
Yes	34	34.0

Table (4): Gynecological assessment of the studied group:

Variable		
Days since last menstrual period Mean ± SD	48.06±6.25	
	No.	**%**
Vaginal bleeding:		
No Yes	52 48	52.0 48.0
Abdominal pain:		
No Yes	30 70	30.0 70.0

Table (5): Intraoperative assessment of the studied group:

	No.	**%**
Active intraperitoneal bleeding:		
No Yes	20 80	20.0 80.0
Intraperitoneal blood volume:		
<500 ≥500	65 45	65.0 45.0

Table (6): Comparison between ruptured and enraptured tubal pregnancy as regard demographic data:

Variable	**Enrapture ectopic N =19**		**Ruptured ectopic N=81**		**T test**	**P value**
Age: (Years):						
Mean ± SD Range	27.1±3.1 (19-33)		26.9±2.8 (19-33)		0.274	0.784
Age groups	**N**	**%**	**N**	**%**	**χ^2**	**P value**
≤20 21-30 >30	1 11 7	5.2 57.9 36.9	5 61 15	6.2 75.3 18.5	3.01	0.221
	Enrapture ectopic N =19		**Ruptured ectopic N=81**		**U**	**P value**
Gravidity:						
Median Range	2 (1-7)		2 (1-7)		0.0	1
Parity:						
Median Range	1 (0-4)		2 (0-4)		13.0	0.843
Abortion:						
Median Range	0 (0-4)		0 (0-4)		0.0	1

Table (10): Comparison between ruptured and enraptured tubal pregnancy as regard Biomarker and biomarker ratios:

Variable	Enrapture ectopic N =19	Ruptured ectopic N=81	T test	P value
CA125v (U/mol):				
Mean ± SD	23.67 ±4.2	22.4 ±6.2	0.846	0.399
CA125p (U/mol):				
Mean ± SD	1334.01±300.2	180.58±25.6	34.61	<0.001 (HS)
Rp/v-CA125				
Mean ± SD	59.51±15.7	7.33±2.1	29.28	<0.001 (HS)
β-chg. (IU/L)				
Mean ± SD	1090.47±201.1	4778±623.4	25.38	<0.001 (HS)
β-chip (IU/L)				
Mean ± SD	20719.24±1112.3	16596±1232	13.35	<0.001 (HS)
Rp/v-β-hCG				
Mean ± SD	11.77±3.1	3.69±1.1	19.10	<0.001 (HS)
CKv (U/L)				
Mean ± SD	57.1±13.2	47.2±0.31	6.85	<0.001 (HS)
CKp (U/L)				
Mean ± SD	151±42.1	182±49.7	2.51	0.013 (S)
Rp/Vck				
Mean ± SD	2.56±0.9	4.68±1.1	7.80	<0.001 (HS)
Pv (nmol/L)				
Mean ± SD	14.3±3.2	19.37±5.1	4.13	<0.001 (HS)
Pp (nmol/L)				
Mean ± SD	38.37±10.2	74.57±19.4	7.86	<0.001 (HS)
Rp/v-P				
Mean ± SD	2.46±0.8	3.28±1.01	3.299	0.0013 (S)

4. Discussion:

Extra-uterine pregnancy (including ectopic pregnancy and pregnancy of unknown location) is a first-trimester disorder that appears in 1.3%–2.4% of all pregnancies, and accounts for up to 6% of pregnancy- associated mortality **(Taran et al.,2015).**

Extra-uterine pregnancy (EUP) is the main cause of first trimester maternal mortality **(Randriambololona et al., 2012).** Besides being life-threatening, due to ruptures with massive hemoperioneum, late diagnosis is also a common factor in resource-challenged settings. Moreover, EUP is correlated to infertility. Indeed, one third of EUP cases occur in nulliparous women, half of whom will remain sterile **(Balde et al., 2014).**

The incidence of tubal ectopic pregnancy is increasing worldwide most likely due to a rising incidence of pelvic inflammatory disease caused by Chlamydia trachomatis infection and the increased use of assisted reproductive techniques **(Walker,2007).**

In the general female population, the widely accepted risk factors for EP include tubal damage resulting from pelvic infection (e.g. chlamydia trachomatis, CT) or previous adnexal surgery, smoking, and in vitro fertilization (IVF) **(Marion, 2012).**

These risk factors are not necessarily independent of one another, and the risk of EP varies among different populations. Fertility intention might have an impact on pregnancy outcome. Women not planning to become pregnant often resort to a variety of contraceptive methods, most of which could prevent unwanted pregnancy (intrauterine or ectopic), but if contraception fails, some contraceptive methods, like intrauterine device (IUD) and oral contraceptive pills (OCPs), could potentially increase the EP risk according to the results of a meta-analysis **(Li et al., 2015).**

Ectopic pregnancy is associated with rupture, hemodynamic instability, hemorrhagic shock/hemodynamic instability, syncope, and death. Early diagnosis enables physicians to intervene before rupture of the ectopic pregnancy, which can both reduce mortality and enable nonsurgical interventions **(Taran et al.,2015).**

During a normal intrauterine pregnancy, serum human chorionic gonadotropin (hCG) is detectable 8–10 days after ovulation (about 23 days into the menstrual cycle), and its concentration increases with

gestational age. The doubling time of hCG is 1.2–1.4 days during the first 3 weeks after fertilization, and 3.3–3.5 days during weeks 4–6 after fertilization.

In contrast, with an ectopic pregnancy the doubling time of serum hCG is 3– 8 days longer than in a normal pregnancy. These differential rates of hCG increase can be used to distinguish between intrauterine and ectopic pregnancies. Guvendag et al. suggested that determining the level of serum hCG should be the first step in diagnosing suspected ectopic pregnancy **(Qi et al.,2012).**

Measurement of hCG can be problematic, however: **Desai et al., (2014)** used 7 different test kits used to measure hCG in 80 standardized samples and reported significantly different measured concentrations (reported values between 74 and 6660 IU/L, $p < 0.0001$).

The results of the current study showed that a ratio of peritoneal fluid to venous blood hCG of >1 is diagnostic for an ectopic pregnancy. In addition, the peritoneal fluid to blood ratios of P, CA125, and CK can also be used to predict an ectopic pregnancy, and more importantly predict a ruptured ectopic pregnancy. The current study is one of little study for diagnosis of a ruptured ectopic pregnancy has been reliably predicted by using the ratio of peritoneal to venous blood biomarker levels.

In an ectopic pregnancy, the zygote implants in the oviduct, ovary, or other sites in the peritoneal cavity. The metabolism of hCG in the peritoneal cavity is slower than that in the blood, and with an ectopic pregnancy the hCG content in peritoneal fluid may be higher than that in venous blood. In the case of an intrauterine pregnancy, fluid in the abdomen may be due to luteal rupture, pelvic inflammation, or blood after a miscarriage. Under these conditions, relatively small amounts of HCG are released into the peritoneal cavity, and thus the hCG content of peritone fluid is similar to or lower than that of venous blood. Thus, the ratio of hCG in peritoneal fluid to that in venous blood may be useful for the diagnosis of ectopic pregnancy. A previous retrospective study showed that a ratio of >1 had a sensitivity and a specificity of 100% and 100%, respectively, for the diagnosis of ectopic pregnancy **(Wang et al.,2010).**

Other study also showed an hCG ratio >1 in peritoneal fluid relative to venous serum (Rp/v) was useful for diagnosis of an ectopic pregnancy, and a ratio 1 consistent with an intrauterine pregnancy **(Qi et al., 2012).**

Researchers have also examined other serum markers, including progesterone (P), vascular endothelial growth factor (VEGF), cancer antigen 125 (CA125), and creatine kinase (CK) to diagnose ectopic pregnancy. For example, **(Butler et al.,2013)** measured total serum hCG, hyperglycosylated hCG, the free b subunit of h CG, P, and CA125 for early diagnosis of ectopic pregnancies, and found that sequential use of total serum hCG and CA125 were promising, but establishing reliable cutoff values among the different measurements required further work.

This is why the study was selected to determine the value of the peritoneal fluid to venous blood ratio of hCG, Progesterone, CA125, and Creatine kinase for the diagnosis of an ectopic pregnancy and the likelihood of active bleeding.

Conclusions

The peritoneal fluid to venous blood ratio of hCG, CA125, progesterone and Creatine kinase can accurately predict a ruptured ectopic pregnancy. These findings may allow diagnosis of a ruptured ectopic pregnancy in the case of non - diagnostic ultrasound or culdocentesis results, thus allowing prompt intervention and potentially reducing morbidity and mortality.

Recommendations

• Further studies on larger populations for more accurate diagnosis.

• Further studies with inclusion of patients with intrauterine pregnancies for comparison and patients who underwent salpingectomy or salpingectomy.

• The multiple markers tests taken advantage of different biologic mechanisms can be more efficient. The clinical applicability of the diagnostic algorithm is yet to be further evaluated in larger samples of retrospective and prospective studies.

• In addition, combining multi-biomarkers, such as vascular endothelial growth factor and markers of abnormal trophoblast, would be a promising trial for predicting the outcome of EP and differentiating EP from hIUP or abnormal IUP.

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