Which one affect the other, Recurrent Pregnancy Loss or Serum Level of E-cadherin and c-MycBP

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Abstract

Recurrent pregnancy loss (RPL) is a foremost life event and a common pregnancy complication, which defined as losses of two or more pregnancies before 20 weeks of gestation. It affects approximately 1% - 2% of couples trying to have children. To evaluate the potential role of cellular myelocytomatosis binding protein (c-MycBP) and epithelial cadherin (E-cad) serum level as biomarkers in maternal blood and focus on the similarity between tumour invasion and embryogenesis as phenomena by c-MycBP and E-cadherin. This case control study included 50 women with RPL (25 primary RPL and 25 secondary RPL) from three infertility clinics in Iraq. In addition to 50 control women with no history of RPL and at least one child birth. Both groups are matched in age and BMI. Blood sampling was done for all and protein level of c-Myc BP and E-cadherin were measured by ELISA Kit and analysis done according to the manufacturer recommendations. The result presented in this study showed a significant difference in c-MycBP level ($p<0.001$) and E-cadherin ($p<0.001$) between patients and control. A significant positive correlation has been found between these two biochemical markers ($p <0.001$, $r=-0.39$). The present study showed that decreasing both c-MycBP and E-cad serum level signpost possible hypothesis that these proteins participate in one way or another in RPL pathogenesis which affect cell proliferation and invasion. However, this binding protein transcription factor is a part of a coordinated network of various set of partners which need further studies in future. Taken together, additional studies are required to understand and clarify the importance of these biomarkers on this multifactorial condition.

Keywords: *Recurrent pregnancy loss (RPL), E-cad, c-MycBP*

Introduction

Recurrent pregnancy loss (RPL) recognised as two or more failed pregnancies according to the American Society for Reproductive Medicine (ASRM), not necessarily consecutive [1]. The two pregnancy losses or more with in less than 20 weeks of gestation. RPL occurs in 1–3% of women trying to conceive [2]. According to the evidence available, women should undergo comprehensive evaluations only after the loss of two or more pregnancies [3-5]. Even after extensive investigations, less than 50% of couples identify a cause for RPL [6]. Subsequently, most cases remain free from a modifiable risk factor [7]. Also associated with RPL are maternal lifestyle factors like smoking, consumption of alcohol and caffeine, and obesity [8]. Maternal age is a significant risk factor for loss of pregnancy, primarily based on the increased incidence with increasing age of foetal aneuploid abnormality [9]. There for, RPL is a great multifactorial condition; acquired and inherited thrombophilia, structural uterine defects, endocrine disorders, and parental balanced chromosomal translocations are among the multifaceted risk factors of RPL [10, 11]. Cellular myelocytomatosis is a family member of the myelocytomatosis (Myc) proteins (c-Myc, MYCN, and MYCL). These proteins are basic helix-loop-helix leucine zipper transcription factors with a vital role in proliferation, differentiation,

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cell cycle progression, metabolism, and cell survival/ apoptosis [12]. This protein regarded as an important cell cycle modulation cytokine. Cell proliferation and transition of resting phase to mitosis phase in cell cycle could be an expected outcome to c-Myc over-expression [13, 14]. Furthermore, phosphorylation of the mitogen-activated protein kinase (MAPK) is important pathway in c-Myc activation[15,16]. The expression and functional regulation of the Myc gene includes a range of mechanisms. One of these mechanisms is based on the Myc binding protein (MycBP) signaling pathway [17]. The MycBP gene encodes a ~11 kDa protein that can bind the Myc N-terminal region via its C-terminal structure, causing Myc to induce tumorigenesis [18]. Earlier studies were conducted to inhibit the expression of MycBP, and thereby Myc pathway, and observe the outcome suppression of the migration and invasion of cancer cells [19, 20].The functional mechanism of c-Myc, mainly, depends on the induction of mitosis and cell cycle growth response. Activation of c-Myc can regulate cell cycle, induce endometrium hyperplasia, upraise endometrium oestrogen receptor level, as well as the c-Myc transcription, eventually leading to gene amplification and over-proliferation of endometrial cell leading to carcinoma of endometrium [21].

Epithelial cadherin (E-cadherin or cadherin1 or E-cad) is transcribed from CDH1 gene into a precursor polypeptide of 135 kDa which is transmembrane glycoprotein that function as cell adhesion molecule (CAM) which bind to various cell types, and are vital in normal tissue morphogenesis and development [22, 23]. This transmembrane protein is regarded as a member of the classical cadherins including the neural cadherin (N-Cad), placental cadherin (P-Cad), and the vascular endothelial cadherin (VE-Cad). E-Cad is an evolutionarily preserved large single-pass transmembrane glycoprotein involved in Ca^{+2}-dependent cell–cell adhesion [24]. The complex of E-cad and β-catenin is closely associated with alteration in cell size, shape, and relative movements that are the foundation of the comprehensive morphogenetic processes producing stereotypical tissues and organs fulfilling their functions during embryonic development and adaptive processes of adult tissues [25-27]. Embryo implantation is a highly controlled event that is necessary for pregnancy establishment. Three successive stages are what implantation goes through which are implantation, adhesion and invasion [28]. The synchronous development of both the embryo and endometrium relies on positive embryo implantation. Often known as essential in implantation are numerous regulatory proteins recognized to play a key role in cancer cell invasion[29].E-cad is found in humans in trophoblasts, and homophilic interaction between cytotrophoblast and endometrium are thought to be mediated through it. This may mean that E-cad involves in the embryo implantation initial stage [30], and it is down-regulated in placental villi during early pregnancy in patients with spontaneous miscarriage may be regarded as one of risk factors of this condition [31].However, no evidence exists to indicate whether or not the down-regulation of E-cad expression in villi or the up-regulation of E-cad expression in extravillous trophoblasts marks the beginning or the terminal stages of trophoblast differentiation in patients with missed and threatened miscarriage[32]. In our study, we evaluated the serum level of MycBP and E-cad and explored the correlation between these two biomarkers with this clinical condition.

Material and Methods

Subjects

in this case–control study a total of 50 RPL subjects (25 primary RPL and 25 secondary RPL) with at least two or more recurrent miscarriage before 20 weeks of gestation were recruited from three different infertility clinics: the Obstetrics and Gynaecology department at Imam Al-Hujjah Hospital, Karbala province, Iraq; Infertility Centre, Babylon Teaching Hospital, Babylon province, Iraq; and Teba Centre for infertility, Babylon province, Iraq. As well as 50 women apparently healthy control group with no history of pregnancy loss and at least one child birth. Furthermore, we excluded individuals with history of smoking, alcohol abuse, infections, endocrine or metabolic disorders, anatomic abnormalities and autoimmune diseases based on history and medical and biochemical examination. All patients with RPL groups experienced recurrent abortions with same partner. The sample has been collected for the period from October 2018 to August 2019. All subjects matched in age, 19-35 years, and body mass index (BMI). PRL patients vs Control Mean ±SD for age (30 ± 4.2 vs 30 ± 4.1), BMI (25.72 ± 2.05 vs 25.25 ± 1.75), gravidity (3.5 ± 1.27 vs 2.42 ± 0.91), parity (1.00 ± 1.23 vs 2.42 ± 0.91) and abortion (2.5 ± 0.81 vs NA)

Ethical Issues

All participants gave written informed consent to participate in this study with objectives and methodology explained to all of them individually. The official approval for this study obtained by The Scientific Committee of Babylon Medical College, University of Babylon, and Research and Development Department of Babylon Health Directorate, Babylon province, Iraq.

Materials

Commercial ELISA sandwich kit for human c-Myc binding protein and E-cad were used as per manufacturer, Bioassay Technology Laboratory, instructions with Cat.No E2901Hu (sensitivity: 0.04ng/ml) and Cat.No E0209Hu (sensitivity: 0.52ng/ml) respectively.

Methods

Blood sample collection, venous blood sample drawn from all subject by using disposable syringe (5 mL) in the sitting position. The needle was disconnected and the blood is evacuated slowly into plain disposable test tubes without anticoagulant. The blood was allowed to clot at 37˚C for 10-15 minutes, and then centrifuged at 3500xg for five minutes. Separated serum was used for protein level measurement (Human c-MycBP, human E-cadherin).

Statistical Analysis

The collected data were tabulated and analyzed by using the Statistical Package for Social Sciences (SPSS) for Windows version 20th version. Data were expressed as (mean ± SD). Independent sample T-test was used to compare means between two groups. ANOVA test was used to compare means of more than 2 groups. Correlation coefficient (r) was used to find the relationship between two continuous variables. P values < 0.05 were considered statistically significant.

Results

Based on our results of the present study, multiple comparisons of c-MycBP serum concentrations (ng/ml) were shown among control and RPL groups, and the significant differences were expressed as ($p < 0.05$) (Table 1, 2). The c-Myc is a transcription factor which play as an essential regulator for cell proliferation, differentiation and embryogenesis [33]. This result indicates that c-MycBP protein may be involved in the pathogenesis of RPL agreeing with Wu *et al* findings that c-Myc regulation of peroxiredoxin2 might have an important role in trophoblast proliferation and apoptosis [34], these results support out this study work outcome.

Table 1. Descriptive of c-MycBP in Control and RPL Groups

Groups	Mean ± SD	95% Confidence Interval for Mean	
		Lower Bound	Upper Bound
Primary RPL	2.18 ± 0.35	2.01	2.30
Secondary RPL	2.00 ± 0.42	1.84	2.18
Control	2.64 ± 0.45	2.51	2.77

Table 2. Multiple comparison dependent variable of c-MycBP

Groups	Comparative Group	95% Confidence Interval		p. value	Mean Difference
		Lower Bound	Upper Bound		
Primary RPL (n=25)	Control	-0.68	-0.27	<0.001	-0.48*
	Secondary RPL	-0.09	0.39	0.21	0.15
Secondary RPL (n=25)	Control	-0.83	-0.42	<0.001	-0.63*
	Primary RPL	-0.39	0.09	0.21	-0.15
Control (n=50)	Primary RPL	0.27	0.68	<0.001	0.48*
	Secondary RPL	0.42	0.83	<0.001	0.63*
*The mean difference is significant at the 0.05 level.					

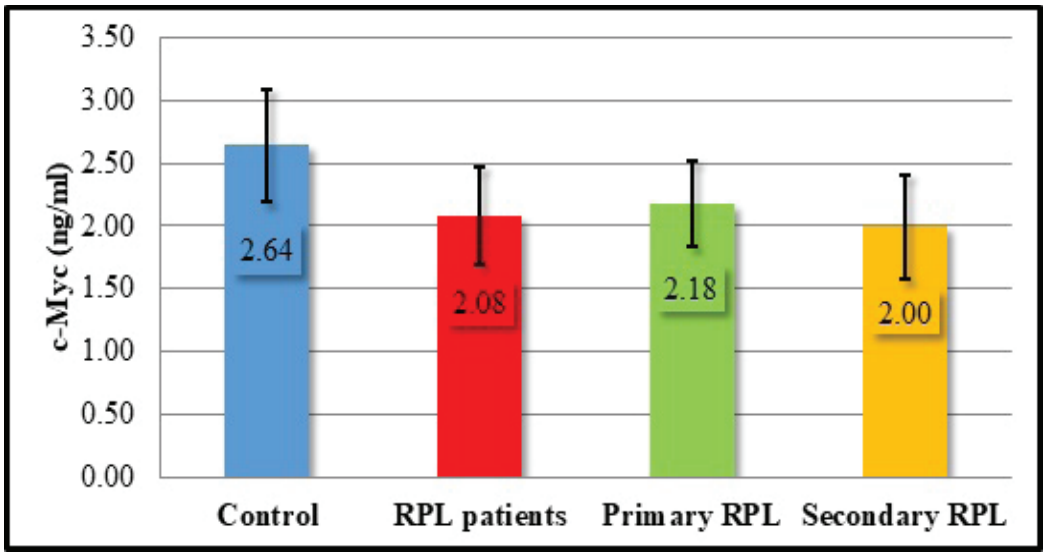

Figure 1. c-MycBP mean ± SD (ng/ml) in control and RPL groups

RPL may be due to infection or attributed to physiological aspects or heavy physical activity during pregnancy [35-37]. The result of the present study showed a very high significant difference in E-cad between RPL groups and control as shown in (Figure 1 and 2). This is consistent with results from Yang *et al*, which indicated a possible role of E-cad in implantation processes and altered expression in women with reproductive failure and E-cad low level linked to RPL [37]. Furthermore, Wu *et al* suggested that placental syncytiotrophoblast is accountable for the transport of oxygen, nutrients and wastes; it also produces hormones for foetal development and maintains immune tolerance. E-cad dynamically changes during the process of cytotrophoblast fusion and that its downregulation is coincident with cell fusion [34]. Likewise, Verma *et al* have shown that the expression of E-cadherin is essential for embryonic development. Mice with E-cad knockout are unable to form functional trophectoderm and therefore could not survive during implantation. Moreover, a decrease in the expression of E-cad has been reported in trophoblast cells during EMT when extravillous trophoblasts (EVTs) migrate or invade into the cell column [38].

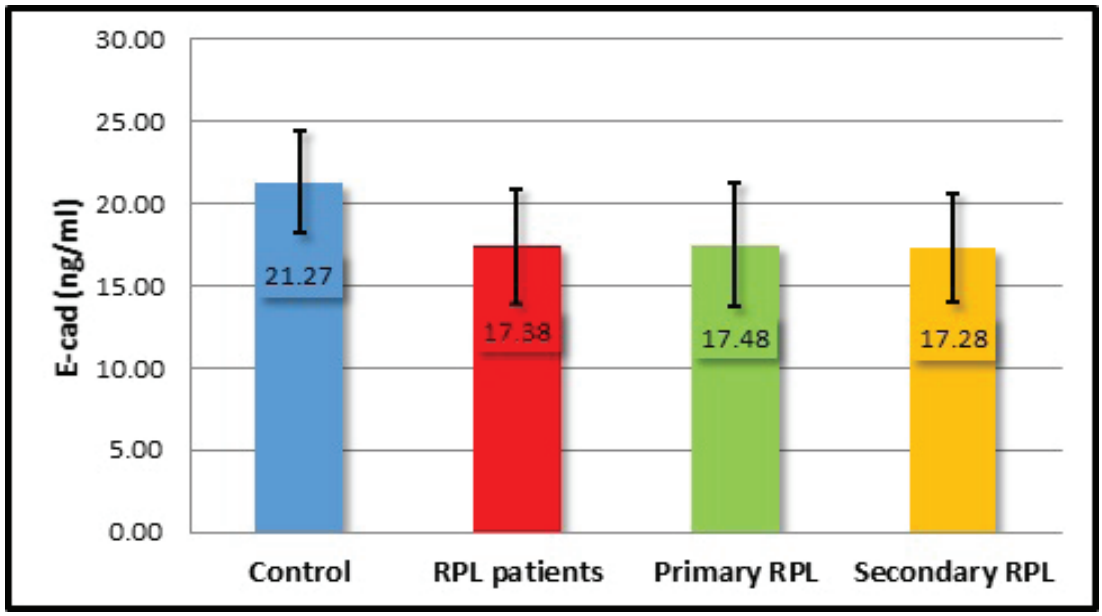

Figure 2. E-cad mean ± SD (ng/ml) in control and RPL groups

ANOVA COMPARISON OF E-CAD BETWEEN CONTROL AND RPL GROUPS

Current study results shown multiple comparisons of E-cad serum concentrations (ng/ml) among control and RPL groups (Mean±SD=17.48 ± 3.72 for Primary PRL, 17.28 ± 3.32 for secondary PRL and 21.27 ± 3.10 for control), and the significant differences were expressed as ($p<0.05$)

Table 3. Multiple comparison dependent variable of E-cad

Groups	Comparative Group	95% Confidence Interval		p. value	Mean Difference
		Lower Bound	Upper Bound		
Primary RPL (n=25)	Control	-5.41	-2.18	<0.001	-3.79*
	Secondary RPL	-1.66	2.07	0.82	0.21
Secondary RPL (n=25)	Control	-5.66	-2.39	<0.001	-4.00*
	Primary RPL	-2.07	1.66	0.82	-0.21
Control (n=50)	Primary RPL	2.18	5.41	<0.001	3.79*
	Secondary RPL	2.39	5.62	<0.001	4.00*
*The mean difference is significant at the 0.05 level.					

CORRELATION OF C-MYC AND E-CADHERIN

There is a very high significant positive correlation ($p\leq0.001$), ($R^2 = 0.1429$) between c-MycBP and E-cad in patients and control groups as shown in (Table 4). This result represented for the first time in our study which may reviled the hidden factor affecting both c-MycBP and E-cad causing their down regulation in RPL and this will need more investigations and researches. This demonstrated result conflicting what Liu *et al* has found. They stated that c-Myc oncoprotein is overexpressed in most human cancers and regulates different genes and pathways in different cell types. E-cad expression is supressed by Myc through a post-transcriptional mechanism, but the exact mechanism remains elusive [39]. Likewise, Fonseca-Alves *et al* determined that carcinogenesis of the canine prostatic epithelial cells produced a strong and elevated cytoplasmic c-Myc protein expression associated with a related loss of the tumour suppressor proteins NKX3.1 and E-cad [40]. Another recent paper verified that upregulation of E-cad in PC4-knockdown cells were reversed by overexpression of c-Myc [41]. In an interesting coincidence finding, Miller *et al* has found that Myc activates the expression of miR-9 which inhibits E-cad expression [42]. Present results, in contrary, supported by Liu et al outcome. He and his colleagues concluded that data presented indicated decreasing cellular polyamines represses E-cad transcription, which is prevented by ectopic c-Myc overexpression [43].

Table 4. Correlation between c-Myc and E-cad

Parameter		E-cad	c-Myc
E-cad (ng/ml)	r	1	0.39***
	p		<0.001
c-Myc (ng/ml)	r	0.39***	1
	p	<0.001	
***Correlation is very highly significant at the 0.001 level (2-tailed)			

Conclusion

This study concluded that there is a significant positive correlation between c-Myc and E-cad in control and patients' groups demonstrating for the first time, to our knowledge, that decreasing both c-Myc and E-cad serum level signpost possible hypothesis of these two proteins participate in one way or another in RPL.

Conflict of Interest: we declare that there is conflict of interest

Ethical Approval: the research approved by scientific and ethical committee at our department

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