International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 5, Issue 5 - 2018

Research Article

DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.05.013

Effect of previous scar uterus and sit of placentation on early pregnancy outcome in Iraq

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Abstract

Objectives:
To describe placental location in the first trimester of pregnancy and subsequent placental migration in women with and without a history of previous Cesarean delivery.

Methods:
In this prospective case–control study, placental location was defined according to five anatomical sites in relation to the endometrial cavity. Placental localization was carried out by transabdominal ultrasound between 11 and 14 weeks' gestation. We recruited 150 women who had undergone one or more previous Cesarean sections (CS) and 150 patients without previous Cesarean delivery. Comparative analysis was performed of placental location between the two groups, and to assess placental migration of those classified as being low lying at 20 and 32 weeks' gestation.

Results:
There were significant differences in placental location between the two groups. In the CS group there were significantly more posterior and fewer fundal placentae than in the control group. The number of previous Cesarean deliveries did not have a significant effect on placental location. There was no significant difference in the incidence of anterior low-lying placenta between groups .Placental migration of the low-lying subtypes was similar in both groups .

Conclusion:
The presence of CS scars in the uterus are associated with an increase in the number of posterior placentae and a reduced number that implant in the fundus of the cavity. Migration of a low-lying placenta.

Keywords: pregnancy, placental location, Cesarean sections, CS scars.

1. Introduction

1.1. Anatomy of uterus

The non-pregnant uterus is situated in the pelvic cavity between the bladder anteriorly and the rectum posteriorly, almost the entire posterior wall of the uterus is covered by serosa, that is, visceral peritoneum (fig. 1). Only the upper portion of the anterior wall of the uterus is so covered the peritoneum in this area reflects forward onto the bladder dome to create the vesicouterine pouch. The lower portion of the anterior uterine wall is united to the posterior wall of the bladder by a well defined loose connective tissue layer—the vesicouterine space [1].

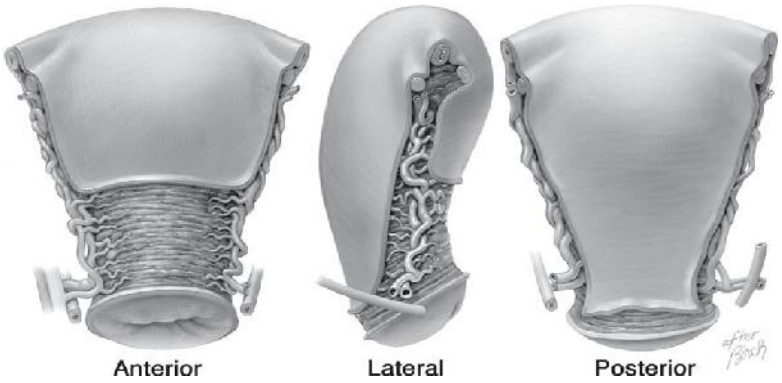

Figure 1: Anterior (A), right lateral (B), and posterior (C) views of the uterus of an adult woman[1].

The uterus is pear shaped and consists of two major but unequal parts. There is an upper triangular portion—the body or corpus, and a lower, cylindrical portion—the cervix, which projects into the vagina. The isthmus is the union site of these two. It is of special obstetrical significance because it forms the lower uterine segment during pregnancy. At each superolateral margin of the body is a uterine cornu, from which a fallopian tube emerges. Also in this area are the origins of the round and uteroovarian ligaments. Between the points of fallopian tube insertion is the convex upper uterine segment termed the fundus. The bulk of the uterine body, but not the cervix, is muscle. The uterus averages 60 g and typically weighs more in parous women. Pregnancy stimulates remarkable uterine growth due to muscle fiber hypertrophy. The uterine fundus, a previously flattened convexity between tubal insertions, now becomes dome shaped. Moreover, the round ligaments appear to insert at the junction of the middle and upper thirds of the organ. The fallopian tubes elongate, but the ovaries grossly appear unchanged [2].

Cervix

The cervical portion of the uterus is fusiform and open at each end by small apertures—the internal and external cervical ora. Proximally, the upper boundary of the cervix is the internal os, which corresponds to the level at which the peritoneum is reflected up onto the bladder. The upper cervical segment—the portio supravaginalis, lies above the vagina's attachment to the cervix (Fig. 2).

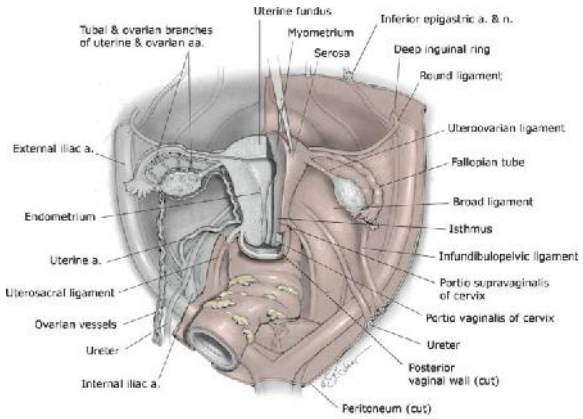

Figure 2: Uterus, adnexa, and associated anatomy [1].

Before childbirth, the external cervical os is a small, regular, oval opening. After labor, especially vaginal childbirth, the orifice is converted into a transverse slit that is divided such that there are the so-called anterior and posterior cervical lips. If torn deeply during labor or delivery, the cervix may heal in such a manner that it appears irregular, nodular, or stellate [1].

Myometrium and Endometrium

Most of the uterus is composed of myometrium, which are smooth muscle bundles united by connective tissue containing many elastic fibers. Interlacing myometrial fibers surround myometrial vessels and contract to compress these. As shown in Figure 2, this anatomy is integral to hemostasis at the placental site during the third stage of labor. The number of myometrial muscle fibers varies by location [1]. Levels progressively diminish caudally such that, in the cervix, muscle makes up only 10 percent of the tissue mass. In the uterine body inner wall, there is relatively more muscle than in outer layers. And, in the anterior and posterior walls, there is more muscle than in the lateral walls. During pregnancy, the upper myometrium undergoes marked hypertrophy, but there is no significant changes in cervical muscle content. The uterine cavity is lined with endometrium, which is composed of an overlying epithelium, invaginating glands, and a supportive, vascular stroma. The endometrium varies greatly throughout the menstrual cycle and during pregnancy. This layer is divided into a functionalis layer, which is sloughed with menses, and a basalis layer, which serves to regenerate the functionalis layer following each menses[1].

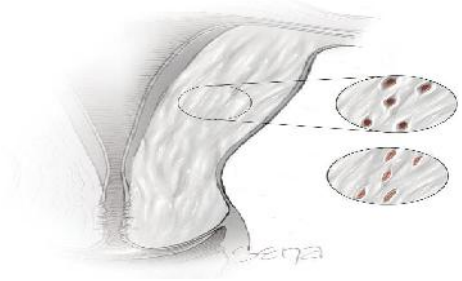

Figure 3: Smooth muscle fibers of the myometrium compress traversing blood vessels when contracted [1].

Blood Supply

During pregnancy, there is marked hypertrophy of the uterine vasculature, which is supplied principally from the uterine and ovarian arteries. The uterine artery, a main branch of the internal iliac artery—previously called the hypogastric artery—enters the base of the broad ligament and makes its way medially to the side of the uterus. Approximately 2 cm lateral to the cervix, the uterine artery crosses over the ureter[1]. Just before the main uterine artery vessel reaches the fallopian tube, it divides into three terminal branches. The ovarian branch of the uterine artery forms an anastomosis with the terminal branch of the ovarian artery; the tubal branch makes its way through the mesosalpinx and supplies part of the fallopian tube; and the fundal branch penetrates the uppermost uterus. In addition to the uterine artery, the uterus receives blood supply from the ovarian artery [1].

Lymphatics

The endometrium is abundantly supplied with lymphatic vessels that are confined largely to the basalis layer. The lymphatics of the underlying myometrium are increased in number toward the serosal surface and form an abundant lymphatic plexus just beneath it [1].

Innervation

The peripheral nervous system is divided in a somatic division, which innervates skeletal muscle, and an autonomic division, which innervates smooth muscle, cardiac muscle, and glands. Pelvic visceral innervation is predominantly autonomic. The autonomic portion is further divided in sympathetic and parasympathetic components [1].

1.2. Decidua

This is a specialized, highly modified endometrium of pregnancy. It is essential for *hemochorial placentation*, that is, one in which maternal blood contacts trophoblast. This relationship requires trophoblast invasion, and considerable research has focused on the interaction between decidual cells and invading trophoblasts. *Decidualization*, that is, transformation of secretory endometrium to decidua, is dependent on estrogen and progesterone and factors secreted by the implanting blastocyst. The special relationship that exists between the deciduas and the invading trophoblast seemingly defies the laws of transplantation immunology. [3]

Decidual Structure

The decidua is classified into three parts based on anatomical location. Decidua directly beneath blastocyst implantation is modified by trophoblast invasion and becomes the *deciduabasalis*. The *decidua capsularis* overlies the enlarging blastocysts and initially separates the conceptus from the rest of the uterine cavity. This portion is most prominent during the second month of pregnancy and consists of decidual cells covered by a single layer of flattened epithelial cells. Internally, it contacts the avascular, extraembryonic fetal membrane—the chorion laeve. The remainder of the uterus is lined by *deciduaparietalis*. During early pregnancy, there is a space between the decidua capsularis and parietalis because the gestational sac does not fill the entire uterine cavity. By 14 to 16 weeks' gestation, the expanding sac has enlarged to completely fill the uterine cavity. The resulting apposition of the deciduas capsularis and parietalis creates the *decidua vera*, and the uterine cavity is functionally obliterated. In early pregnancy, the decidua begins to thicken, eventually attaining a depth of 5 to 10 mm. With magnification, furrows and numerous small openings, representing the mouths outerine glands, can be detected. Later in pregnancy, the deciduas become thinner, presumably because of pressure exerted by the expanding uterine contents[3].

Decidual Reaction

In human pregnancy, the decidual reaction is completed only with blastocyst implantation. Predecidual changes, however, commence first during the mid-luteal phase in endometrial stromal cells adjacent to the spiral arteries and arterioles. Thereafter, they spread in waves throughout the uterine endometrium and then from the implantation site. The endometrial stromal cell enlarge to form polygonal or round decidual cells. The nuclei become round and vesicular, and the cytoplasm becomes clear, slightly basophilic, and surrounded by a translucent membrane. Each mature decidual cell becomes surrounded by a pericellular membrane. Thus, the human decidual cells clearly build walls around themselves and possibly around the fetus. The pericellular matrix surrounding the decidual cells may allow attachment of cytotrophoblasts through cellular adhesion molecules. The cell membrane also may provide decidual cell protection against selected cytotrophoblastic proteases [1].

1.3. Implantation and early trophoblast formation

The fetus is dependent on the placenta for pulmonary, hepatic, and renal functions. These are accomplished through the unique anatomical relationship of the placenta and its uterine interface. Maternal blood spurts from uteroplacental vessels into the placental intervillous space and bathes the outer syncytiotrophoblast. This allows exchange of gases, nutrients, and other substances with fetal capillary blood within the villous core. Thus, fetal and maternal blood are not normally mixed in this hemochorial placenta [1].There is also a paracrine system that links mother and fetus through the anatomical and biochemical juxtaposition of the maternal decidua parietalis and the extra embryonic chorion laeve, which is fetal. This is an extraordinarily important arrangement for communication between fetus and mother and for maternal immunological acceptance of the conceptus[4].

Fertilization and Implantation

Fertilization, which normally occurs in the oviduct, must take place within a few hours, and no more than a day after ovulation. Because of this narrow opportunity window, spermatozoa must be present in the fallopian tube at the time of oocyte arrival. Almost all pregnancies result when intercourse occurs during the 2 days preceding or on the day of ovulation. Thus, postovulatory and postfertilization developmental ages are similar. Steps of fertilization are highly complex. Molecular mechanisms allow spermatozoa to pass between follicular cells; through the zona pellucida, which is a thick glycoprotein layer surrounding the oocyte cell membrane; and into the oocyte cytoplasm. Fusion of the two nuclei and intermingling of maternal and paternal chromosomes creates the *zygote*. Early human development is described by days or weeks post- fertilization, that is, postconceptional. By contrast, clinical pregnancy dating is calculated from the start of the last menses. The follicular phase length is more variable than the luteal phase. Thus, 1 week postfertilization corresponds to approximately 3 weeks from the last menstrual period in women with regular 28-day cycles [5].

Blastocyst Implantation

Six or 7 days after fertilization, the embryo implants the uterine wall. This process can be divided into three phases:

1. Apposition—initial contact of the blastocyst to the uterine wall;
2. Adhesion—increased physical contact between the blastocyst and uterine epithelium; and
3. Invasion—penetration and invasion of syncytiotrophoblast and cytotrophoblasts into the endometrium, inner third of the myometrium, and uterine vasculature. Successful implantation requires a receptive endometrium appropriately primed with estrogen and progesterone by the corpus luteum. Such uterine receptivity is limited to days 20 to24 of the cycle. Adherence is mediated by cell-surface receptors at the implantation site that interact with blastocyst receptors [6].

If the blastocyst approaches the endometrium after cycle day 24, the potential for adhesion is diminished because anti adhesive glycoprotein synthesis prevents receptor interactions. At the time of its interaction with the endometrium, the blastocystis composed of 100 to 250 cells. The blastocyst loosely adheres to the endometrial epithelium by apposition. This most commonly occurs on the upper posterior uterine wall. Attachment of the blastocyst trophectoderm to the endometrial surface by apposition and adherence appears to be closely regulated by paracrine interactions between these two tissues. Successful endometrial blastocyst adhesion involves modification in expression of cellular adhesion molecules (CAMs).The integrins—one of four families of CAMs—are cell-surface receptors that mediate cell adhesion to extracellular matrix proteins [7]. Great diversity of cell binding to several different extracellular matrix proteins is possible by differential regulation of the integrin receptors. Endometrial integrins are hormonally regulated, and a specific set of integrins is expressed at implantation. Specifically, αVβ3 and α4β1integrins expressed on endometrial epithelium are considered a receptivity marker for blastocyst attachment. Aberrant expression of αVβ3 has been associated with infertility. Recognition-site blockade on integrins for binding to extracellular matrix molecules such as fibronectin will prevent blastocyst attachment [8].

The Trophoblast

Human placental formation begins with the trophectoderm, which appears at the morula stage. It gives rise to a trophoblast cell layer encircling the blastocyst. From then until term, the trophoblast plays a critical part at the fetal-maternal interface. Trophoblast exhibits the most variable structure, function, and developmental pattern of all placental components. Its invasiveness promotes implantation, its nutritional role for the conceptus is reflected in its name, and its endocrine organ function is essential to maternal physiological adaptations and to pregnancy maintenance [1].

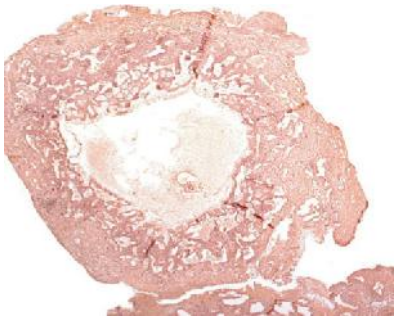

Figure 4: Early implantation of a conceptus [1].

1.4. Placental Organization

Chorionic Villi

With deeper blastocyst invasion into the decidua, the extravillous cytotrophoblasts give rise to solid primary villi composed of a cytotrophoblast core covered by syncytiotrophoblast. These arise from buds of cytotrophoblast that protrude into the primitive syncytium before 12 days postfertilization. As the lacunae join, a complicated labyrinth is formed that is partitioned by these solid cytotrophoblastic columns. The trophoblast-lined labyrinthine channels form the intervillous space, and the solid cellular columns form the *primary villous stalks*. The villi initially are located over the entire blastocyst surface [1].

They later disappear except over the most deeply implanted portion, which is destined to form the placenta. Beginning on approximately the 12th day after fertilization, mesenchymal cords derived from extraembryonic mesoderm invade the solid trophoblast columns. These form *secondary villi*. Once angiogenesis begins in the mesenchymal cores, *tertiary villi* are formed. Although maternal venous sinuses are tapped early in implantation, maternal arterial blood does not enter the intervillous space until around day 15. By approximately the 17th day, however, fetal blood vessels are functional, and a placental circulation is established. The fetal–placental circulation is completed when the blood vessels of the embryo are connected with chorionic vessels. In some villi, angiogenesis fails from lack of circulation. They can be seen normally, but the most striking exaggeration of this process is seen with hydatidiform mole [1].

1.5. Placental and chorion development

Chorion and Decidua Development

In early pregnancy, the villi are distributed over the entire periphery of the chorionic membrane (Fig. 5). As the blastocyst with its surrounding trophoblasts grows and expands into the decidua, one pole faces the endometrial cavity. The opposite pole will form the placenta from villous trophoblasts and anchoring cytotrophoblasts. Chorionic villi in contact with the decidua basalis proliferate to form the chorion frondosum—or leafy chorion—which is the fetal component ofthe placenta. As growth of embryonic and extraembryonic tissues continues, the blood supply to the chorion facing the endometrial cavity is restricted. Because of this, villi in contact with the decidua capsularis cease to grow and then degenerate [1].

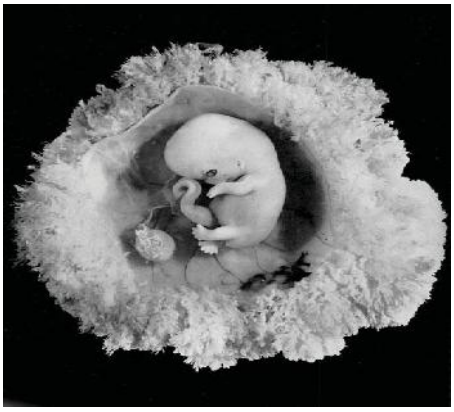

Figure 5: Photograph of an opened chorionic sac. An early embryo and yolk sac are seen. Note the prominent fringe of chorionic villi [1].

This portion of the chorion becomes the avascular fetal membrane that abuts the decidua parietalis, that is, the chorion laeve—or smooth chorion. This smooth chorion is composed of cytotrophoblasts and fetal mesodermal mesenchyme that survives in a relatively low-oxygen atmosphere. Until near the end of the third month, the chorion leave is separated from the amnion by the exocoelomic cavity. Thereafter, they are in intimate contact to form an avascular amniochorion. The chorion laeve is generally more translucent than the amnion and rarely exceeds 1-mm thickness. These two structures are important sites of molecular transfer and metabolic activity. Moreover, they constitute an important paracrine arm of the fetal–maternal communication system [1].

Maternal Regulation of Trophoblast Invasion and Vascular Growth

During the first half of pregnancy, decidual natural killer cells (dNK) accumulate in the decidua and are found in direct contact with trophoblasts. These cells lack cytotoxic functions and are able to dampen inflammatory T (H) 17 cells. These along with other unique properties distinguish dNK cells from circulating natural killer cells and from natural killer cells in the endometrium before pregnancy [9]. Recent studies suggest that decidual macrophages play a regulatory role in inhibiting NK cell killing during pregnancy [10]. This importantly prevents them from recognizing and destroying fetal cells as “foreign.”

Hanna and colleagues (2006)[11] have elucidated the ability of dNK cells to attract and promote trophoblast invasion into the deciduas and promote vascular growth. Decidual NK cells express both IL-8 and interferon-inducible protein-10, which bind to receptors on invasive trophoblast cells to promote their decidual invasion toward the spiral arteries. Decidual NK cells also produce proangiogenic factors, including VEGF and placental growth factor (PlGF), which promote vascular growth in the decidua. In addition, trophoblasts secrete specific chemokines that attract the dNK cells to the maternal-fetal interface. Thus, both cell types simultaneously attract each other [11].

Trophoblast Invasion of the Endometrium

Extravillous trophoblasts of the first-trimester placenta are highly invasive. They form cell columns that extend from the endometrium to the inner third of the myometrium. Recall that hemochorial placental development requires invasion of endometrium and spiral arteries. This process occurs under low-oxygen conditions, and regulatory factors that are induced under hypoxic conditions contribute in part to invasive trophoblast activation [12]. Invasive trophoblasts secrete numerous pro- teolytic enzymes that digest extracellular matrix and activate proteinases already present in the endometrium. Trophoblasts produce urokinase-type plasminogen activator, which converts plasminogen into the broadly acting serine protease, plasmin. This in turn both degrades matrix proteins and activates matrix metalloproteases. One member of the MMP family, MMP-9, appears to be critical for human trophoblast invasion. The timing and extent of trophoblast invasion is regulated by a balanced interplay between pro- and antiinvasive factors. The relative ability to invade maternal tissue in early pregnancy compared with limited invasiveness in late pregnancy is controlled by autocrine and paracrine trophoblastic and endometrial factors. Trophoblasts secrete insulin-like growth factor II, which acts in an autocrine manner. It promotes invasion into the endometrium, whereas decidual cells secrete insulin-like growth factor binding-protein type 4, which blocks this autocrine loop. Thus, the degree of trophoblast invasion is controlled by matrix degradation regulation and by factors that cause trophoblast migration. Low estradiol levels in the first trimester are critical for trophoblast invasion and remodeling of the spiral arteries. Recent studies in nonhuman primates suggest that the increase in secondtrimester estradiol levels suppresses and limits vessel remodeling by reducing trophoblast expression of VEGF and specific integrin receptors [13]. As the extravillous trophoblast differentiates, it gains expression of integrin receptors that recognize the extracellular matrix proteins collagen IV, laminin, and fibronectin. Binding of these extracellular matrix proteins to specific integrin receptors initiates signals that promote trophoblast cell migration and differentiation. As pregnancy advances, increasing estradiol levels repress and thus control the extent of uterine vessel transformation via downregulation of VEGF and integrin receptor expression [13].

1.6. Placental Growth

Placental Growth

In the first trimester, placental growth is more rapid than that of the fetus. But by approximately 17 postmenstrual weeks, placental and fetal weights are approximately equal. By term, placental weight is approximately one sixth of fetal weight[1].Lobes are incompletely separated by grooves of variable depth that overlie placental septa, which arise from folding of the basal plate. The total number of placental lobes remains the same throughout gestation, and individual lobes continue to grow—although less actively in the final weeks [1]. Although grossly visible lobes are commonly referred to as cotyledons, this is not accurate. Correctly used, lobules or cotyledons are the functional units supplied by each main stem villus.

Cesarean Section

Background

The first modern cesarean section was performed by German gynecologist Ferdinand Adolf Kehrer in 1881. Cesarean section is often performed when a vaginal delivery would put the baby's or mother's life or health at risk. Many are also performed upon request [14].An analysis of global, regional, and national cesarean section (CS) rates shows that an estimated 15% of all deliveries worldwide occur by CS [15]. This general prevalence masks an uneven distribution and wide variations by continent, region and country. Regional CS rates, for example vary from 0-40% [16]. According to the Iraq Multiple Indicator Cluster Survey 2006 (Iraq MICS 2006) [17], about 20% of births were delivered by C-section. Cesarean sections have jumped in Iraq in recent years accounting for 79 percent of births at private hospitals. The rate of C-sections in Iraq has climbed from 18 percent in 2008 to 32 percent in 2010 [18].

Definition

A Caesarean section is a surgical procedure in which one or more incisions are made through mother's abdomen and uterus to deliver one or more babies . A Caesarean section is often performed when a vaginal delivery would put the baby's or mother's life or health at risk. Some are also performed upon request without a medical reason to do so. The World Health Organization recommends that they should only be done based on medical need. Established guidelines recommend that caesarean sections not be used before 39 weeks without a medical indication to perform the surgery [19]

Types of uterine incision:

A. Low-transverse uterine incision should be made through the thin, non contractile portion of the lower uterine segment in a curvilinear fashion. Also pictured is a low-vertical incision, which is made through the non contractile lower uterine segment in a vertical fashion. B. J-extension of the low-transverse incision. When additional exposure to the uterine cavity is required to deliver the fetus, the low-transverse incision can be extended laterally and cephalad to increase the length of the incision without endangering the uterine arteries. C. Another option in this situation is to use a T-extension in the midline. D. The classical uterine incision is made through the contractile portion of the myometrium above the bladder [20].

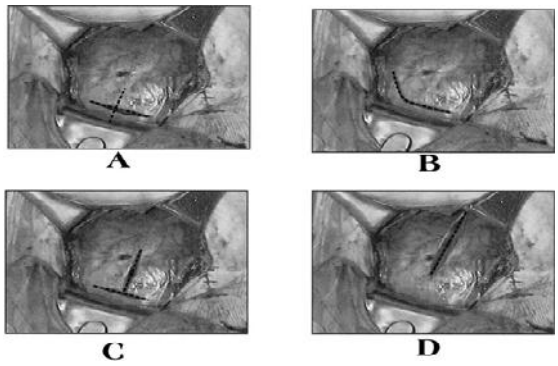

Figure 6 Types of uterine incision [20].

Risks of CS

The maternal mortality is higher than that associated with vaginal birth (5.9 for elective cesarean delivery v. 18.2 for emergency cesarean v. 2.1 for vaginal birth, per 100 000 completed pregnancies in the United Kingdom during 1994–1996) [21]. Cesarean section also requires a longer recovery time, and operative complications such as lacerations and bleeding may occur, at rates varying from 6% for elective cesarean to 15% for emergency cesarean [22]. Having a cesarean delivery increases the risk of major bleeding in a subsequent pregnancy because of placenta previa (5.2 per 1000 live births) and placental abruption (11.5 per 1000 live births) [23]. Among term babies, the risk of neonatal respiratory distress necessitating oxygen therapy is higher if delivery is by cesarean (35.5 with a prelabour cesarean v. 12.2 with a cesarean during labour v. 5.3 with vaginal delivery, per 1000 live births) [24]. It has reported that the risk of unexplained stillbirth in a second pregnancy is somewhat increased if the first birth was by cesarean rather than by vaginal delivery (1.2 per 1000 v. 0.5 per 1000) [25]. Lastly, birth by cesarean section were 3.6 times more likely to die as women in the vaginal delivery group [26]. Deneau-Tharaux and her colleagues [26] studied 65 maternal deaths over birth by cesarean is not generally considered “natural” or “normal. Kim (2010) reports a significant increase in maternal deaths in California from 5.6 per 100,000 in 1996 to an astounding 16.9 per 100,000 live births in 2006. Morton of the California Maternity Quality Care Collaborative says that the rise in mortality rates may be related to the increase in maternal request c-sections [27]. Lui and her colleagues (2007) used information from a Canadian database to study 46,776 women in the planned cesarean group and over 2.2 million in the planned vaginal group. Severe morbidity rates were reported as 27.3% in the planned cesarean group compared to 9% in the planned vaginal birth group. Complications associated with cesarean deliveries included hemorrhage requiring hysterectomy, anesthetic complications, thromboembolism, major puerperal infection, wound disruption, and wound hematoma [28].

Declercq et al. (2007) using a Massachusetts database of 244,088 women, found that mothers who underwent planned cesarean sections had a significant statistical increased rate of rehospitalization within 1 month after delivery compared to mothers who delivered vaginally (19.2 vs. 7.5 per 1,000 live births for the vaginal group). Rehospitalizations were primarily due to wound related complications, especially infection. Therefore, with the increasing cesarean section rate, the incidence of repeat cesarean sections will increase [29]. With each subsequent cesarean section, there is an increasing risk of placenta previa, a condition where the placenta grows over the opening of the uterus. When the cervix starts to dilate with labor, significant bleeding can occur endangering the mother as well as the infant, and necessitating a c-section. The risk of placenta previa in the next birth is 50% higher than with the first cesarean birth [30]. Placenta accreta, where the placenta grows into the uterine musculature, also increases in subsequent pregnancies. Placenta accreta is treated by removal of the uterus resulting in subsequent sterility [31]. In subsequent pregnancies after the initial c-section, there is also a risk of uterine rupture if labor ensued. This complication is life threatening for both mother and fetus. In a systematic review Guise et al. (2004) reported a risk of uterine rupture rate of 7.8 per 1,000 live births in one large study [32].

Figure 7: CS scar [1].

Cesarean scar pregnancy

The first case of a CS ectopic pregnancy was reported in English medical literature in 1978 [33]. Since then, there are only 19 cases published until 2001 [34]. But over the past 5 years, there has been a substantial increase in the number of CSP published in the English language literature. This may reflect a 'true' increase in its incidence because of the rising caesarean section rate worldwide or an 'apparent' one as result of better detection of the CSP by liberal use of transvaginal ultrasound scan.

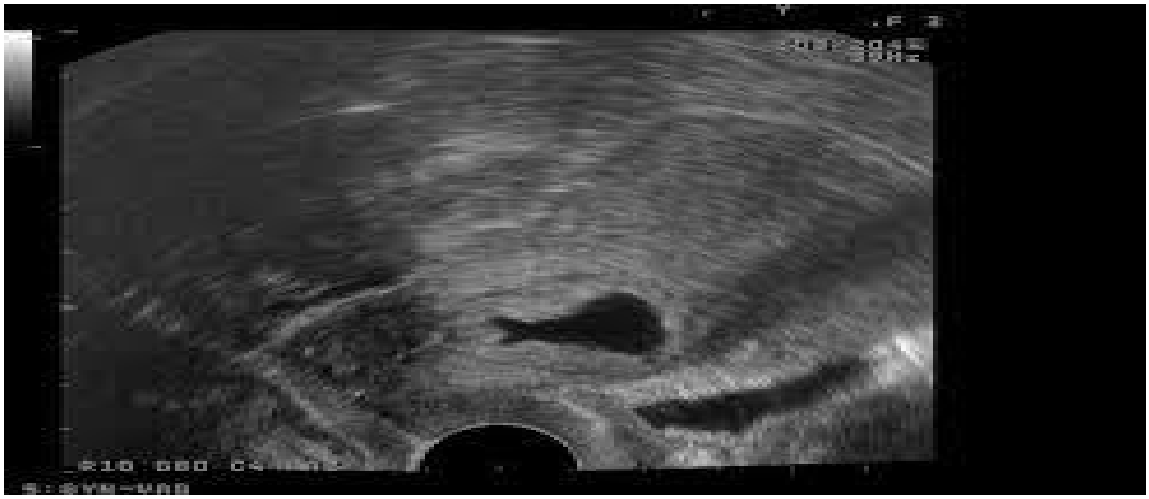

Figure 8: Ultrasound of an early pregnancy in a caesarean section scar [1].

The incidence of CSP is unknown, as very few cases have been reported in the literature. Jurkovicet al.[35] have estimated a prevalence of 1:1800 in their local population of women attending the early pregnancy assessment unit. A case series [36] estimates an incidence of 1:2226 of all pregnancies, with a rate of 0.15% in women with a previous CS and a rate of 6.1% of all ectopic pregnancies in women who had at least one caesarean delivery. The gestational age at diagnosis ranged from 5+0 to 12+4 weeks (mean 7.5 ± 2.5 weeks), and the time interval between the last caesarean section and the CSP was 6 months to 12 years in this series[37]. CSP has been described in spontaneously conceived pregnancy as well as after in vitro fertilization (IVF) and embryo transfer. IVF associated heterotopic CSP, a rare event, has also been described, both with twins [38] and triplets [39]. No particular predilection has been reported for maternal age or parity.

Predisposing factors, mechanism and pathophysiology

The exact cause and mechanism is not well understood. Implantation of a pregnancy within the scar of a previous caesarean section is different from an intrauterine pregnancy with placenta accrete [34]. Placenta accreta is characterized by the absence of decidua basalis and varying degrees of invasion of the myometrium by trophoblastic tissue. The pregnancy is essentially within the uterine cavity. In CSP, the gestation sac is completely surrounded by myometrium and the fibrous tissue of the scar, quite separate from the endometrial cavity [40]. The most probable mechanism that can explain scar implantation is that there is invasion of the myometrium through a microtubular tract between the caesarean section scar and the endometrial canal [41]. Such a tract can also develop from the trauma of other uterine surgery, e.g. curettage, myomectomy, metroplasty, hysteroscopy and even manual removal of placenta [42]. Damage to the decidua basalis during uterine surgery can persist in the endometrium in the form of tiny dehiscent tracts or minute wedge defects. A CSP is more aggressive in its behavior than placenta praevia accreta because of its early invasion of the myometrium.Pathological findings after a total hysterectomy suggest that the villi are not merely penetrating the myometrium but are bound with or implanted in it [43]. Vial et al. [44] proposed two different types of CSPs. The first is an implantation on the prior CS with progression towards the cervicoisthmi space or the uterine cavity. Such a CSP may progress to a viable birth but with the risk of a life-threatening bleeding (see below, Expectant Treatment). The second is a deep implantation into a CS defect growing towards the bladder and abdominal cavity, a type that is more prone to rupture. It is uncertain whether the risk of CSP is related to the number of previous caesarean sections. Some case series have reported that between 50 and 72% of CSPs occur after two or more prior caesarean sections [45]. Some believe multiple CSs are a strong risk factor for CSP because of increased scar surface area, but others [46, 47] argue against such a correlation. A systematic review found that 52% cases followed one previous caesarean section, 36% after two and 12% after three or more previous caesarean sections [48].No particular order or sequence between the previous caesarean sections and subsequent pregnancies for any risk of CSP has been reported in the literature. Data on any correlation between the CSP and the indication of the caesarean delivery that preceded this abnormal implantation are inadequate, but, interestingly, breech presentation is the most frequent (31%) among the publications that documented the indications [48]. The impact of the time interval between the previous caesarean sections and the subsequent CSP implantation is also not clear. Some CSPs occurring within a few months of a caesarean section suggest that an incomplete healing of the caesarean sections scar may contribute to scar implantation, but this theory cannot explain the CSP that has been reported as late as 12 years after a prior caesarean sections [24].

Placenta previa caused by CS

Placenta previa is a form of impaired placentation when placenta lies low in the uterine cavity covering completely or partially the internal cervical ostium. It is one of the main causes of vaginal bleeding in the third trimester. This is not a common pregnancy complication as about one in every 250 pregnancies may have placenta previa. A trend of increasing placenta previa was observed in past decade, mainly because of increasing c-section and advancing maternal age at conception. Although the clinical course of placenta previa is highly suggestive, the etiology of this condition still remains obscure. The strongest connection was found with previous history of c-section, high parity, advanced maternal age[9] history of previous spontaneous or induced sections, previous placenta previa, child sex at birth (more in baby boys). Placenta previa is a form of obstetrical problem associated with considerable fetal and maternal morbidity. Many studies conducted

around the world confirm a 2 to 5 fold increase risk of placenta previa with previous history of c-section showing up to 37.5% increased risk with previous c-section [49].

Placenta Accreta

Placenta accreta is a rare but serious obstetric condition that is associated with considerable maternal morbidity and mortality. In women with placenta previa, an abnormally adherent placenta is suspected when there is an absent decidual interface between the placenta and the myometrium. Another sign is the presence of unusually dilated vessels at the placental site. Although the reported accuracy of sonographic diagnosis in the third trimester is reasonably high, late detection is of limited value because it does not prevent the serious complications of placenta accrete [50].In 60% to 70% of cesarean scar pregnancies, there is clear evidence of trophoblast penetrating the endometrial-myometrial junction. It has been postulated that firsttrimester cesarean scar pregnancies that invade the myometrium may develop into placenta previa/accrete if the pregnancy is allowed to progress [51].

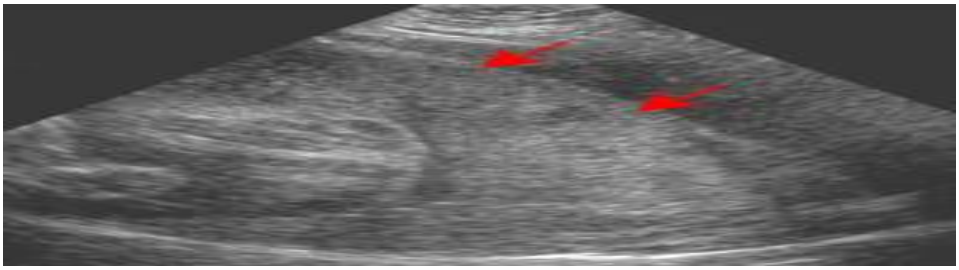

Figure 9:Ultrasonography of placenta accreta [52].

Aim of study

To highlight if there is association between the presence of scar of c/s and implantation site and early pregnancy complications in next pregnancy.

Patients and Methods

Study design

A prospective observational study.

Time of Data collection:

Carried out during the period from the 1st of January 2015 to the 1st of December 2015.

Setting of study:

The study was conducted at AL- Elwiya Maternity Teaching Hospital- Baghdad. The study protocol was approved by Obstetrical and Gynecological Committee of Iraqi Board of medical specialization, Baghdad - Iraq.

Sampling:

Pregnant ladies visiting consultancy clinic at Elwiya Maternity Teaching Hospital in their first (6-14) weeks gestation with and without history of previous caesarean section were included in the study. The patients attended the consultancy clinic for antenatal care or for treating early pregnancy symptoms and complications (as pain, morning sickness, bleeding and abortion). All patient were fully assessed by full history (medical, surgical, obstetrical, family, drugs and social hx.), full examination (general, vital signs, cardiovascular, respiratory system and obstetrical examination) was done, all patients were sent for routine antenatal investigations (CBC, blood group & RH, serum glucose, GUE, VDRL screening –viral screening) and other investigations as lupus anticoagulant, anticardiolipin antibodies, GTT and thyroid function test according to patients' conditions. All patients were sent for abdominal or vaginal ultrasonography by using Philips (HD11.XE wieh frequencies 2-5 MHz). The sample was collected by researcher in consultancy clinic of Elwyia maternity teaching hospital by direct interview on Monday and Tuesday every week and fulfilling of prepared questionnaire.

The sample size was 300 pregnant ladies were included in our study (150 with previous history of C/S and 150 without previous history of C/S) they fulfilled the inclusion criteria.

The follow up of pregnant ladies started from 1st visit till 14th week gestation by direct interview with researcher. The schedule of visits was according to the condition of the patient, most of the cases were assessed every four weeks.

-Inclusion Criteria

Pregnant women in their first (6-14) weeks gestation with and without history of previous cesarean section.

-Exclusion Criteria

1- Medical diseases.
2-Pregnancy resulting from assisted fertilization and multiple pregnancy.
3-Leiomyoma or other gynecopathy that might potentially affect the uterine flow.
4-Uterine surgery other than cesarean section (myomectomy, D&C, meteroplasty,….etc).

Data Collection

The data was collected through direct interview with participants, after explaining the purpose of the study using a questionnaire. ,

The questionnaire included the followings [appendix 1]:

- Demographic information: age and occupation.
- Obstetrical & Gynecological history: gravidity, parity, abortion, mode of delivery and last menstrual period.
- US findings: gestational age, viability, implantation site and distance between GS and IO.
- Follow up findings: Complications: pain, threatened abortion (vaginal bleeding), abortions.

Ethical considerations

1. Approval of the study proposal was obtained from Elwiya Maternity Teaching Hospital Authority.
2. Objectives of the study were clarified and informed consent had been taken from the patients written on ethical paper with privacy.
3. Confidentiality of the data was maintained throughout the study.

Statistical Analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 20 was used. Descriptive statistics presented as (mean ± standard deviation), frequencies, and percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test was used when expected variables were less than 20%) and t-test for continuous variables. In all statistical analysis, level of significance (*P* value) set at ≤ 0.05 and the results presented as tables and/or graphs.

Results

A total of 300 pregnant women were included in present study with mean age as 30.4±5.5 years, 50% of them were aging 30-39 years. More than half (64%) of pregnant women were housewives and 36% of them were employed. All these findings were shown in table 1.

Antenatal care was given for 70% of pregnant women and 30% of them did not receive care. Mean gravida of women was 3±1, 48.3% of studied women had two previous pregnancies. Mean para of pregnant women was 1±1, 56.3% of pregnant women had one child. Fifty two women had history of abortion. All these findings were shown in table 1.

Half of studied women had cesarean section scar (CS) and half of them had no CS. Mean number of cesarean sections was 1±1, 68% of women had one previous cesarean section and 32% of them had more than one cesarean section. All these findings were shown in table 2 and figure1.

Ultrasound examination revealed that mean gestational age (GA) of studied women was 10±1 weeks, 182 women had GA ≥ 10 weeks and 118 women had GA of < 10 weeks. The viability was present for 251 women and implantation sites were distributed as followings; fundal (56.4%), posterior (39.3%) and anterior (4.3%). Mean distance between gestational

sac (GS) and internal os of cervix (IO) was 3.2±0.7 cm, 86.7% of women had the distance as more than 2.5 cm. All these findings were shown in table 2 and figure 2.

Table 1: General characteristics of pregnant women.

Variable	No.	%
Age mean±SD (30.4±5.5 years)		
20-29 years	122	40.7
30-39 years	150	50.0
≥ 40 years	28	9.3
Total	300	100.0
Occupation		
Housewife	192	64.0
Employed	108	36.0
Total	300	100.0
Antenatal care		
Yes	210	70.0
No	90	30.0
Total	300	100.0
Gravida mean±SD (3±1)		
1	19	6.3
2	145	48.3
3	101	33.7
4	12	4.0
5	13	4.3
6	10	3.3
Total	300	100.0
Para mean±SD (1±1)		
0	19	6.3
1	169	56.3
2	82	27.3
3	20	6.7
4	10	3.3
Total	300	100.0
Abortion		
No	248	82.7
Yes	52	17.3
Total	300	100.0

Table 2: Cesarean section number and scars of studied pregnant women.

Variable	No.	%
Cesarean section scar		
Yes	150	50.0
No	150	50.0
Total	300	100.0
Number of cesarean sections mean±SD (1±1)		
1	97	64.7
>1	53	35.3
Total	150	100.0
Gestational age mean±SD (10±1 weeks)		
< 10 weeks	118	39.3
≥ 10 weeks	182	60.7
Total	300	100.0
Viability		
Yes	251	83.7
No	49	16.3
Total	300	100.0
Site of implantation		
Fundal	169	56.4
Posterior	118	39.3
Anterior	13	4.3
Total	300	100.0
Distance between GS and IO mean±SD (3.2±0.7 cm)		
≤ 2.5 cm	40	13.3
> 2.5 cm	260	86.7
Total	300	100.0

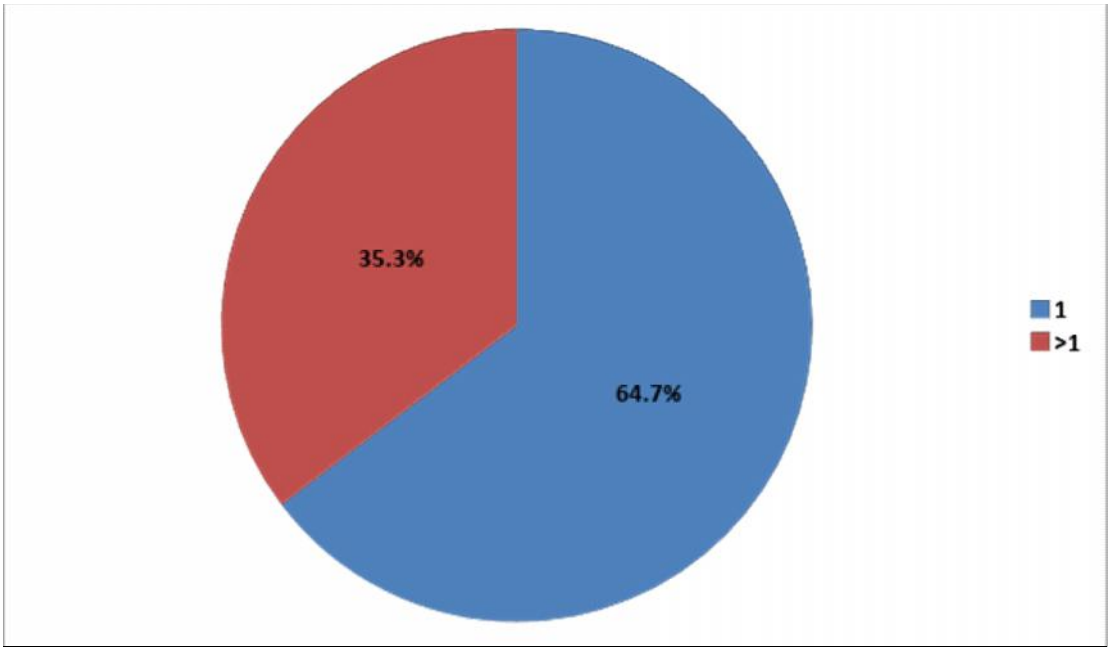

Figure 10: Cesarean sections distribution.

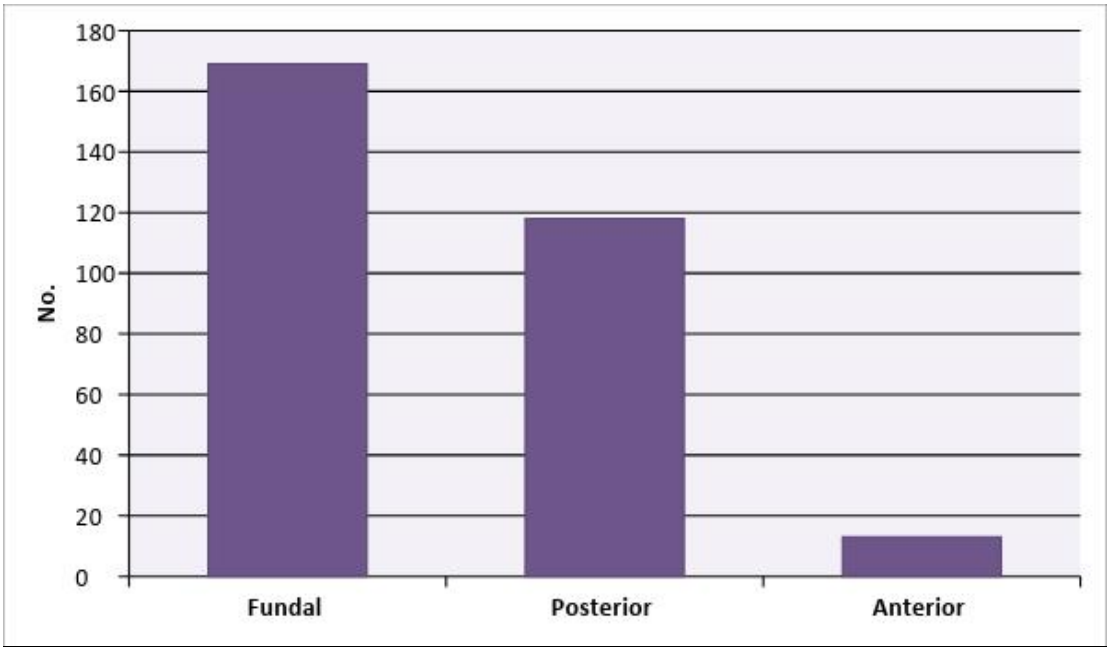

Figure 11: Implantation sites of pregnant women.

Early complications were present for 39.7% of studied women; abortion (26%), pain (39.7%) and bleeding (36%). All these findings were shown in table 3 and figure 3.

Table 3: Early pregnancy complications of pregnant women.

Variable	No.	%
Complications		
Yes	119	39.7
No	181	60.3
Total	300	100.0
Abortion		
Yes	78	26.0
No	222	74.0
Total	300	100.0
Pain		
Yes	119	39.7
No	181	60.3
Total	300	100.0
Bleeding		
Yes	108	36.0
No	192	64.0
Total	300	100.0

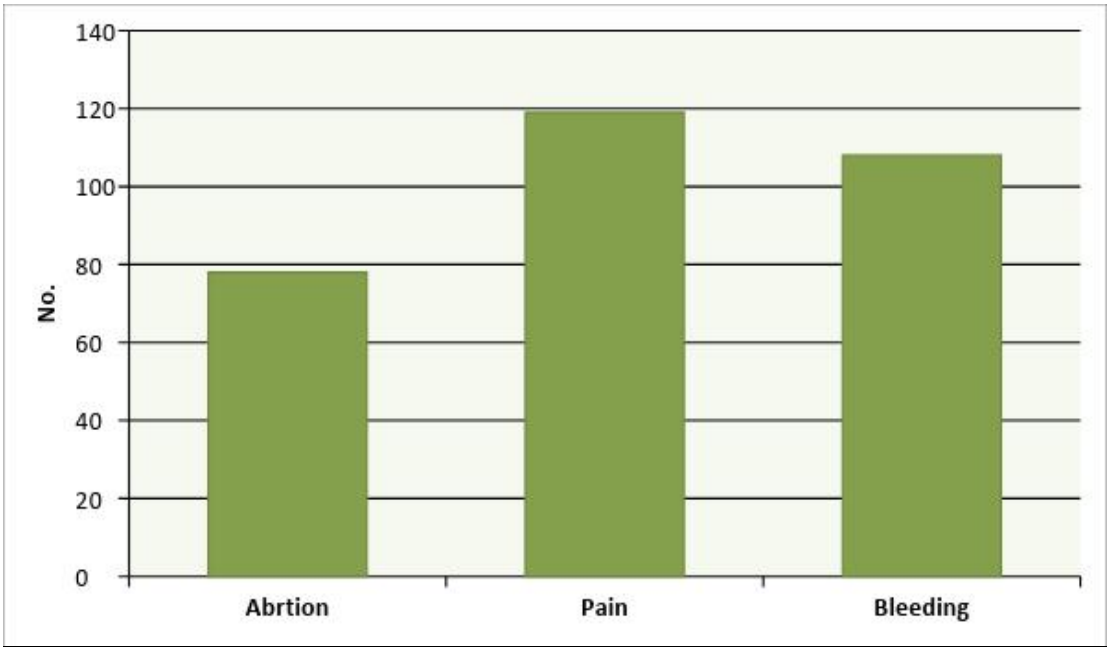

Figure 12: Early complications.

There was a significant association between increased women age and Cesarean section scars ($p<0.001$). No significant difference was observed between women with CS and those without regarding occupation ($p>0.05$). There was a significant association between high gravidity history of women and CS ($p<0.001$). A significant association was observed between high parity history and CS ($p<0.001$). No significant difference was observed between women with CS and those without regarding antenatal care and abortion history ($p>0.05$). All these findings were shown in table 4 and figures 4, 5.

Table 4: Distribution of general characteristics for pregnant women according to presence of CS.

Variable	CS		No CS		χ^2	P
	No.	%	No.	%		
Age					24.3	**<0.001**
20-29 years	40	26.7	82	54.7		
30-39 years	93	62.0	57	38.0		
≥ 40 years	17	11.3	11	7.3		
Occupation					0.5	0.4
Housewife	93	62.0	99	66.0		
Employed	57	38.0	51	34.0		
Antenatal care					1.0	0.3
Yes	109	72.7	101	67.3		
No	41	27.3	49	32.7		

Gravida					44.8	**<0.001**
1	0	-	19	12.7		
2	84	56.0	61	40.7		
3	49	32.7	52	34.7		
4	0	-	12	8.0		
5	7	4.7	6	4.0		
6	10	6.7	0	-		
Para					32.5*	**<0.001**
No	0	-	19	12.7		
1	93	62.0	76	50.7		
2	40	26.7	42	28.0		
3	7	4.7	13	8.7		
4	10	6.7	0	-		
Abortion					0.01	0.9
No	124	82.7	124	82.7		
Yes	26	17.3	26	17.3		

**Fishers exact test.*

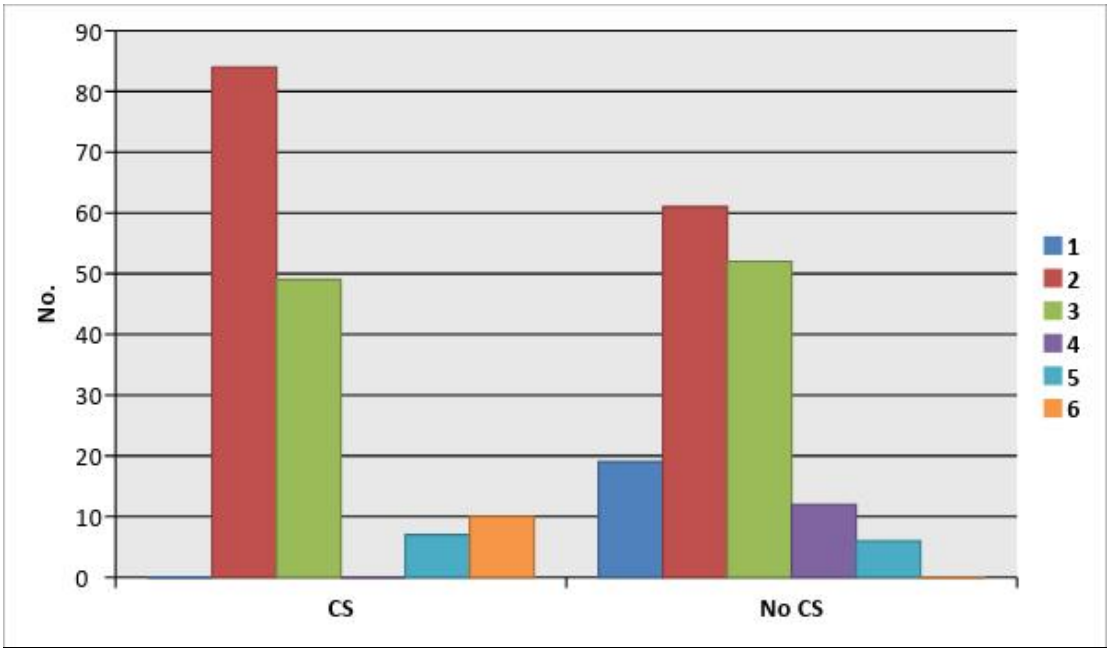

Figure 13: Distribution of woman's gravida according to CS presence.

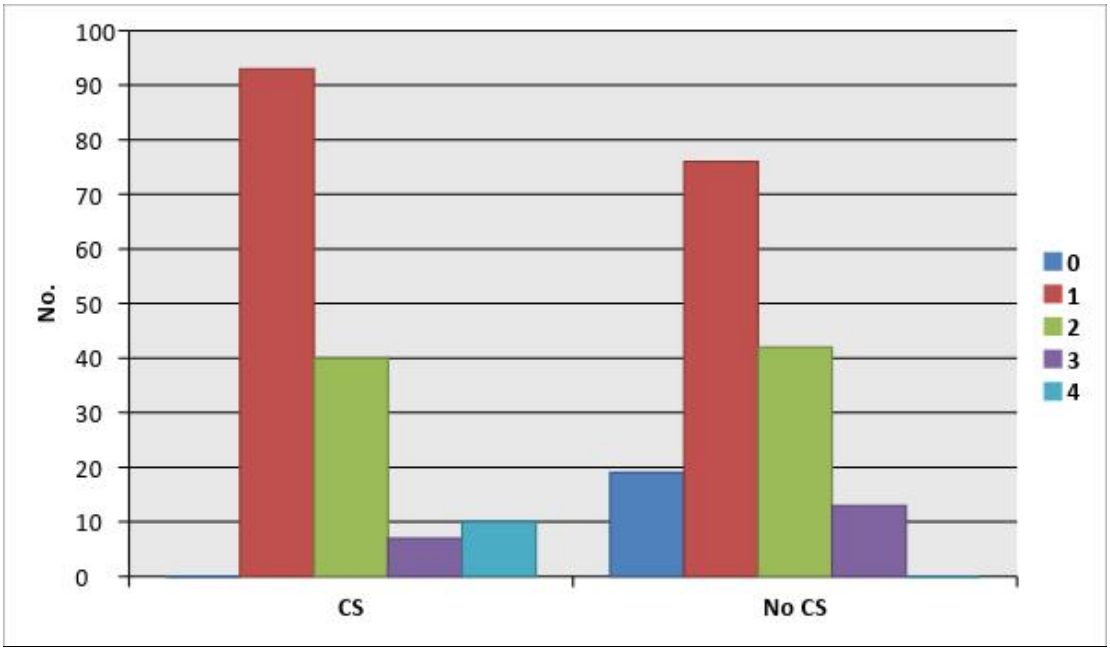

Figure 14: Distribution of woman's parity according to CS presence.

There was a significant association between women with CS and each of posterior and anterior sites of implantation (p<0.001). A significant association was observed between women with CS and small distance between GS and IO (p=0.004). There was a significant association between low viability and women with cesarean scar (p=0.04). No significant difference was observed between women with CS and those without regarding gestational age (p=0.4). Early pregnancy complications were significantly higher among women with CS (p<0.001). Abortion, pain and bleeding were significantly higher among women with CS (p<0.05). All these findings were shown in table 5 and figures 6,7, 8.

Table 5: Distribution of ultrasound findings and complications for pregnant women according to presence of CS.

Variable	CS		No CS		χ^2	P
	No.	%	No.	%		
Gestational age					0.5	0.4
< 10 weeks	62	41.3	56	37.3		
≥ 10 weeks	88	58.7	94	62.7		
Viability					4.1	**0.04**
Yes	119	79.3	132	88.0		
No	31	20.7	18	12.0		
Site of implantation					82.7	**<0.001**
Fundal	46	30.7	123	82.0		
Posterior	91	60.7	27	18.0		
Anterior	13	8.7	0	-		

Complications					25.7	**<0.001**
Yes	81	54.0	38	25.3		
No	69	46.0	112	74.7		
Abortion					9.7	**0.002**
Yes	51	34.0	27	18.0		
No	99	66.0	123	82.0		
Pain					25.7	**<0.001**
Yes	81	54.0	38	25.3		
No	69	46.0	112	74.7		
Bleeding					42.1	**<0.001**
Yes	81	54.0	27	18.0		
No	69	46.0	123	82.0		

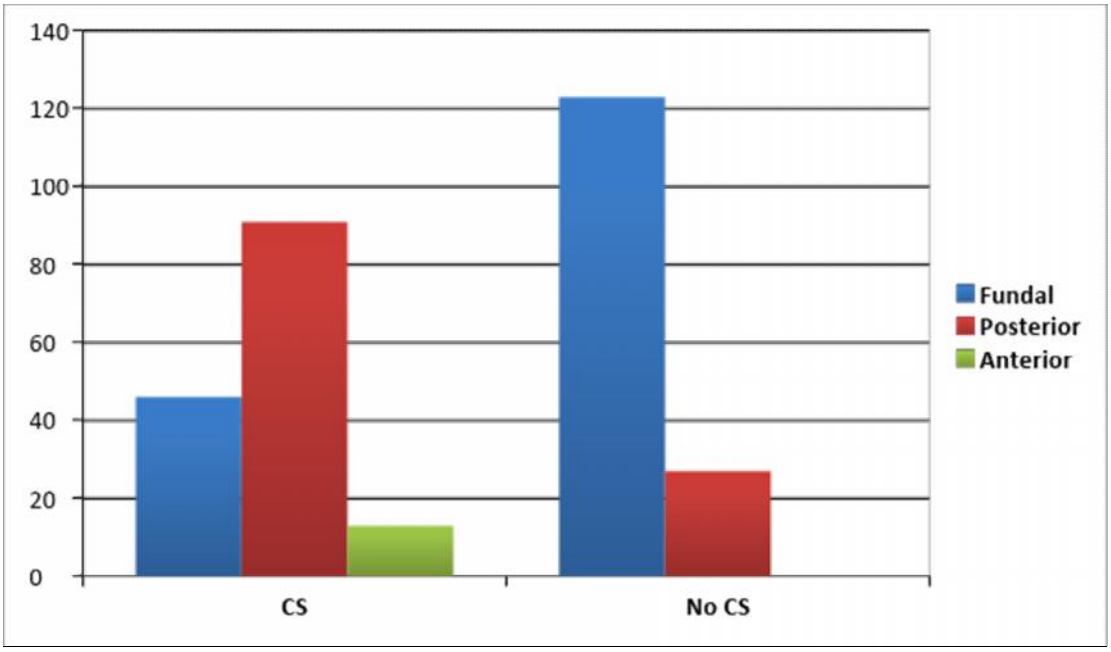

Figure 15: Distribution of implantation sites according to CS presence.

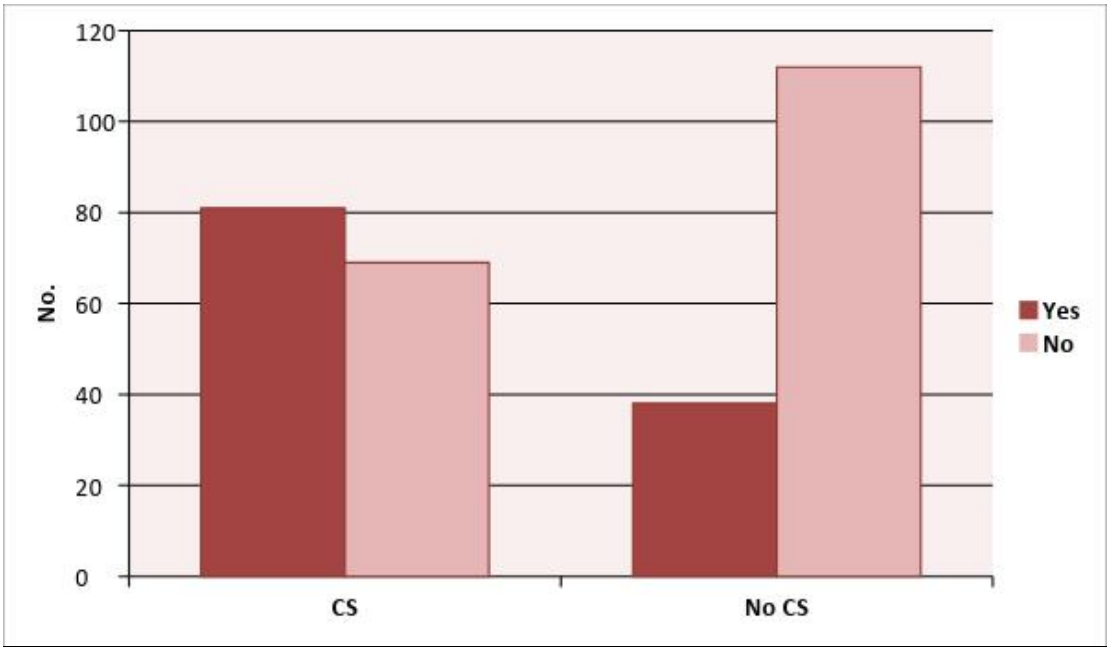

Figure 16: Distribution of early complications according to CS presence.

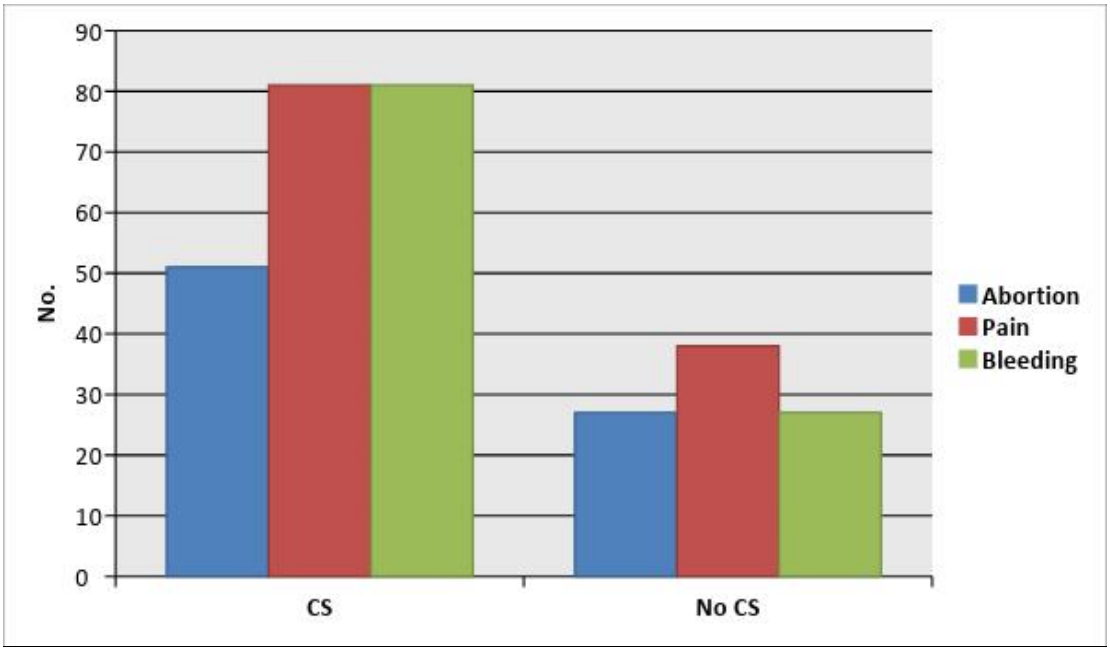

Figure 17: Distribution of abortion, pain and bleeding according to CS presence.

Mean age of women with scar was significantly higher than mean age of women without scar ($p<0.001$). Mean distance between GS and IO was significantly lower among women with CS ($p<0.001$). All these findings were shown in table 6 and figure 9.

Table 6: Distribution of age, gestational age and distance between GS an IO means for pregnant women according to presence of CS.

Variable	CS	No CS	t-test	P
	Mean±SD	Mean±SD		
Age (years)	31.6±5.1	29.2±5.6	3.7	**<0.001**
Gestational age (years)	9.7±1.1	9.9±1.2	1.0	0.3
Distance between GS and IO (cm)	2.9±0.6	3.4±0.5	8.5	**<0.001**

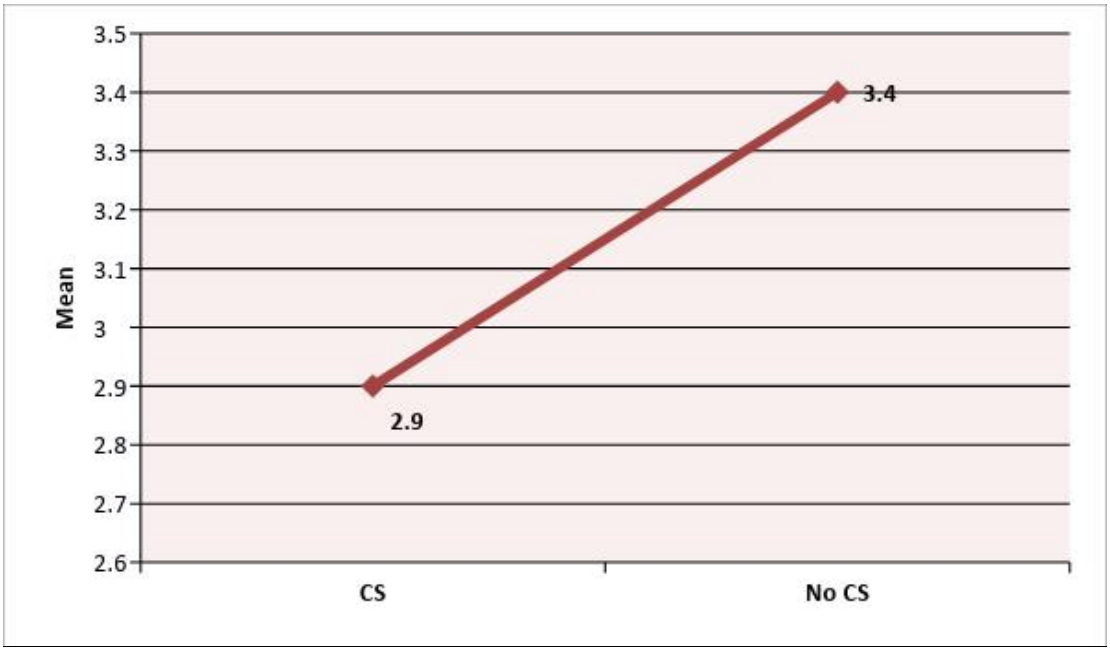

Figure 18: Distribution of distance mean according to CS presence.

Discussion

The rate of cesareans is constantly increasing, reaching more than 30% of births in several countries. Although millions of cesareans are performed worldwide, poor uterine scar healing is associated with complications, such as uterine rupture, in subsequent pregnancies [53].

Present study found that pregnant women with previous hx. ofCS were significantly older than women without previous hx. of CS (p<0.001). This finding coincided with results of Timofeev J, et al study in USA (2013) which was a large prospective study in 12 obstetric centers that reported association of previous cesarean section scar with increased age of women [54]. Higher rates of pre-existing medical conditions and obstetric complications were found with increasing maternal age, but the absolute risks were low. Notably, the overall risk of cesarean delivery was significantly higher in an older parturient woman (driven primarily by the indication of previous uterine scar) [54].

The gravida and parity of pregnant women with CS were significantly higher than those with no CS (p<0.001). This is similar to results of Al-Rowaily MA, et al study in Saudi Arabia (2014) which revealed high rates of cesarean among pregnant women with history of multiple pregnancies and high parity [55]. Gravidity, preeclampsia and preterm delivery were identified as significant risk factors for adverse maternal outcomes. Gravida 4 females were threefold more likely to experience adverse maternal outcomes, when compared with gravida 1 females. Pregnant women with preeclampsia were also threefold more likely to suffer adverse maternal outcomes. With preterm delivery, females were more than two times more likely to suffer from adverse maternal outcomes than with term delivery [55]. Another study done by Balachandran L, et al in UAE (2014) showed that

increasing parity was noted to be associated with an increase in vaginal birth after cesarean rate. This again emphasizes the fact that increases in the number of vaginal deliveries increases the chances of having a successful trial of scar [56].

Posterior implantation in uterus was significantly prevalent among pregnant women with CS (p<0.001). This finding agreed with results of Naji O, et al study in UK (2013) who showed implantation was most frequently posterior (53%) in the CS group and fundal in the non-CS group (42%). Gestational sac implantation was 8.7 mm lower in the CS group (95% confidence interval (CI) 6.7–10.7, P, 0.0001) compared with non C/S group[57]. A deleterious effect of the presence of a CS scar on the uterus was further supported by Ben-Nagi et al who suggested there might be a link between altered uterine immunobiology, CS and embryo implantation [58]. They studied the effect of CS on the endometrium in premenopausal women with a history of CS; endometrial samples were taken from both the CS scar site and posterior uterine wall and the results were compared with samples obtained from the posterior uterine wall in women who had spontaneous vaginal deliveries only. The most significant difference was that fewer leukocytes and less vascularization were found at the scar site than in the endometrium of the unscarred uterus. In addition, they found a delay in endometrial maturation at the scar area, and this delay might have been a result of disruption in steroid receptor expression [58]. Distinguishing between CSP, cervical pregnancy and an intrauterine gestation sac implanted low in the cavity may be difficult [59]. A recent review reported that the diagnosis was missed in 107 out of the 751 cases reviewed [60]. Just as concerning is the possibility of a false-positive diagnosis of CSP, leading to the termination of a viable, correctly located pregnancy [58].

In general, early pregnancy complications reported for pregnant women were significantly more common among women with CS in current study (p<0.001). This is similar to results of Naji O, et al study in UK (2013) [57], Ash A,et al study in USA (2007) [61] and Rizk B, et al study in Egypt (2013) [62]. Rate of abortion among pregnant women with CS was significantly higher in present study (p=0.002). This is similar to results of Naji O, et al study in UK (2013) [57] who concluded that cesarean section scars was significantly associated with spontaneous abortion. It is possible that this complication is related to the poor healing of the cesarean section scar and the implantation of the gestational sac into it. It may also result from a defect in the endometrium caused by trauma created by minor procedures as embryo transfer in the assisted reproductive techniques [63]. The natural history of this abnormal implantation is not clear but it may result in a pregnancy that grow towards the uterine cavity and loses its vascular connection causing spontaneous abortion. Or it may continue to grow to near term gaining new stronger vascular connections ending into a low-lying adherent placenta with or without invasion of surrounding organs.Vaginal bleeding and pain were significantly more common among pregnant women with CS in our study (p<0.001). This finding agreed with results of previous case report study by Aldakhil LO in Saudi Arabia which sowed higher chance of uterine bleeding associated with cesarean section scar [64].

Most bleeding cases usually occur during labor. Most of the reported early uterine scar dehiscence and rupture causing severe bleeding occurs during the second trimester termination of pregnancy. Uterine scar dehiscence in the first trimester is rare and usually asymptomatic [65].

Strength and limitations

Strength of our study is that it was comparative study and carried out on a relatively appropriate sample size. Perhaps a limitation lies in the initial scan being undertaken at around 12 weeks, when the placenta is known to subsequently migrate [66]. Furthermore, we did not perform a formal interobserver variability analysis of our definition of placental implantation site, which highlights the fact that there is no gold standard against which to judge ultrasound- based assessment of placental location in addition to inability to assess temporal relationship as it is a cross sectional study.

Conclusion

Pregnancy complications were frequently counted in pregnant women with previous history of cesarean scar. Cesarean section scar is more likely to cause pain, vaginal bleeding and abortion among pregnant women. Placental implantation was commonly at posterior part of uterus in pregnant women with history of cesarean scar. Distance between GS and IO among women with history of previous CS is less than those with no CS.

Recommendations

- Heightened awareness amongst obstetricians regarding the possibility of scar pregnancy in those with prior caesarean section and early ultrasound in these women may lead to early diagnosis and hence a chance of conservative management.
- Excision of previous scar in the uterus and anatomical repair is the surgical choice of treatment.
- More research on cesarean scar and its effects on pregnant women should be encouraged.

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DOI:10.22192/ijarbs.2018.05.05.013	

How to cite this article:
Dunya Younus Mohamedsalih, Nisreen Rashid Hameed, Shatha Faisal Abdulla. (2018). Effect of previous scar uterus and sit of placentation on early pregnancy outcome in Iraq. Int. J. Adv. Res. Biol. Sci. 5(5): 100-125.
DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.05.013