In The Name Of God

Islamic Azad University

College of Medicine

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Role of paternal age in spontaneous abortion among pregnant women admitted in hospitals of Azad University

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بررسی تأثیر سن پدر در بروز سقط خودبخودی در خانم های باردار بستری شده در بیمارستانهای وابسته به دانشگاه آزاد اسلامی

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LIST

Role of paternal age in spontaneous abortion among pregnant women admitted in hospitals of Azad University

Role of maternal age in pregnancy outcomes is an established one; but there are some controversies about role of paternal age. Current study was performed as a descriptive-analytical cross-sectional survey to determine the role of paternal age in spontaneous abortion among pregnant women admitted in hospitals of Azad University. Four-hundred 20-30-years-old women were evaluated in two groups of 200 subjects with abortion and term labor. One-hundred and sixty-seven subjects (41.8%) were aged lower than 30 years, 177 women (44.3%) 30-40 years, and 56 subjects (14%) were older than 40 years of age. Wives of men that had an age of less than 30 years 80 subjects (47.9%), in those with 30-40 years 76 women (42.9%), and in those older than 40 years 44 patients (78.6%) had spontaneous abortion with a statistically significant association (P=0.0001).

Keywords: Paternal Age, Spontaneous Abortion

INTRODUCTION

Introduction

About half of all spontaneous abortions occurring after the sixth gestational week carry a chromosomal anomaly. [1, 2] The proportion of spontaneous abortions with chromosomal anomalies is likely to be higher for first trimester than for second trimester spontaneous abortions; it appears to peak around gestational week 11.[2, 3]

Chromosomal anomalies in the zygote may result from errors during gametogenesis in either parent, during fertilization, or during the first cellular divisions of the zygote.[2] Thus, a male factor causing chromosomal anomalies in the spermatozoa may induce spontaneous abortion. Male age could be such a factor, as the frequency of sperm chromosomal anomalies, such as aneuploidy or DNA strand breaks, has been suggested to increase with age.[4, 5] Similarly, paternally inherited genetic mutations in the embryo, which may also cause spontaneous abortion, may be more frequent with increasing paternal age because of the continuous replication of male stem cells after puberty.[6]

When examining the effect of paternal age, one must control for the effect of maternal age, because of its association with both spontaneous abortion risk [7, 8] and paternal age. Increases in the risk of spontaneous abortion with increasing paternal and maternal ages have been reported in a retrospective study.[9] In another retrospective study spanning over a 15-

year period, we reported that, after controlling for female age at conception, the risk of spontaneous abortion was increased when the male partner was aged 35 years or more, compared with less than 35 years. However, this was seen only among couples in which the woman was less than 30 years.[10] An effect of paternal age for only a limited range of a woman's age did not agree with our a priori hypothesis. An a posteriori explanation of this result was that a weak effect of paternal age may be easier to identify in couples in which the woman is in her twenties than in couples in which the woman is in her thirties or forties. This is because younger women constitute a relatively homogeneous population as far as maternal biologic risk factors for spontaneous abortion are concerned, whereas among older women many biologic maternal factors, not all controlled for by an adjustment for female age, may influence the risk of spontaneous abortion and mask an effect of paternal age. Retrospective studies on spontaneous abortion are, moreover, potentially limited by recall bias. In a study comparing prospective records and data from a retrospective questionnaire spanning more than 20 years, women recalled only 80 percent of the spontaneous abortions that occurred in the 20 years prior to interview; for 20 percent of the recalled spontaneous abortions, the date of occurrence of the spontaneous abortion was recalled with an error greater than 1 year.[11] For these reasons, it is important to have a

prospective study confirming a possible paternal age effect on the risk of spontaneous abortion.

The main aims of this prospective study were to examine the effect of male age on the risk of spontaneous abortion and to test whether an effect exists independently of the age of the female partner. The secondary and more exploratory aim was to describe the relation between paternal age and risk of spontaneous abortion as a function of gestational age.

REVIEW OF LITERATURES

Review of Literatures

Spontaneous abortion refers to pregnancy loss at less than 20 weeks' gestation in the absence of elective medical or surgical measures to terminate the pregnancy. The term "miscarriage" is synonymous and often is used with patients because the word "abortion" is associated with elective termination. "Spontaneous pregnancy loss" has been recommended to avoid the term "abortion" and acknowledge the emotional aspects of losing a pregnancy.[12] Another emotionally neutral term is "early pregnancy failure."[13]

For clinical purposes, spontaneous abortion often is subdivided into threatened abortion, inevitable abortion, incomplete abortion, missed abortion, septic abortion, recurrent spontaneous abortion, and complete abortion (Table 1).

TABLE 1
Spontaneous Abortion: Definitions of Subcategories

Complete abortion: all products of conception have been passed without the need for surgical or medical intervention
Incomplete abortion: some, but not all, of the products of conception have been passed; retained products may be part of the fetus, placenta, or membranes
Inevitable abortion: the cervix has dilated, but the products of conception have not been expelled
Missed abortion: a pregnancy in which there is a fetal demise (usually for a number of weeks) but no uterine activity to expel the products of conception
Recurrent spontaneous abortion: three or more consecutive pregnancy losses
Septic abortion: a spontaneous abortion that is complicated by intrauterine infection
Threatened abortion: a pregnancy complicated by bleeding before 20 weeks' gestation

Incidence

Approximately 20 percent of pregnant women will have some bleeding before 20 weeks' gestation, and roughly one half of these pregnancies will end in spontaneous abortion.[14] Up to 20 percent of recognized pregnancies will end in miscarriage. However, when women were followed with serial serum human chorionic gonadotropin (hCG) measurements, the actual miscarriage rate was found to be 31 percent.[15] Many pregnancies are lost spontaneously before a woman recognizes that she is pregnant, and the clinical signs of miscarriage are mistaken for a heavy or late menses.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
The possibility of ectopic pregnancy should be considered when transvaginal ultrasonography reveals an empty uterus and the quantitative serum human chorionic gonadotropin level is greater than 1,800 mIU per mL (1,800 IU per L).	C	5
Transvaginal ultrasound should be performed in the first trimester of pregnancy when incomplete abortion is suspected and is extremely reliable in identifying intrauterine products of conception.	C	7, 8
Expectant management should be considered for women with incomplete spontaneous abortions. It has an 82 to 96 percent success rate without the need for surgical or medical intervention.	A	17-22, 24
When misoprostol (Cytotec) is used to treat women with a missed spontaneous abortion, it should be given vaginally rather than orally.	B	27
Patients who have had a spontaneous abortion should be given the opportunity to choose a treatment option.	B	28
A 50-mcg dose of $Rh_0(D)$ immune globulin (Rhogam) should be administered to Rh-negative patients who have a threatened abortion or have completed a spontaneous abortion.	C	5

Physicians should be alert to the development of psychologic symptoms that frequently occur following spontaneous abortion (e.g., depression, anxiety).	C	31-34

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

Diagnosis

Threatened abortion is defined by vaginal bleeding in a woman with a confirmed pregnancy. First-trimester bleeding in a pregnant woman has an extensive differential diagnosis (Table 2) and should be evaluated with a full history and physical examination. Laboratory tests should include potassium hydroxide and "wet prep" microscopy of any vaginal discharge, complete blood count, blood typing and Rh testing, and quantitative serum hCG testing. Gonorrhea and chlamydia testing also should be considered. Ultrasonography is crucial in identifying the status of the pregnancy and verifying that the pregnancy is intrauterine. When transvaginal ultrasonography reveals an empty uterus and the quantitative serum hCG level is greater than 1,800 mIU per mL (1,800 IU per L), an ectopic pregnancy should be considered.[16] When transabdominal ultrasonography is performed, an empty uterus should raise suspicion of an ectopic pregnancy if quantitative hCG levels are greater than 3,500 mIU per mL (3,500 IU per L). A uterus found to be empty on ultrasound examination may signal a completed spontaneous abortion, but the

diagnosis is not definitive until ectopic pregnancy is excluded. If an ultrasound examination finds an intrauterine pregnancy, ectopic pregnancy is unlikely, although heterotopic pregnancy has been reported (i.e., simultaneous intrauterine and ectopic pregnancies).[16] The risk for spontaneous abortion decreases from 50 to 3 percent when a fetal heartbeat is identified on ultrasound examination.[12]

When the clinical examination reveals a dilated cervix, spontaneous abortion is inevitable. However, cervical evaluation is not reliable for distinguishing between complete and incomplete abortion.[17,18] Transvaginal ultrasonography should be performed and is extremely reliable for finding products of conception, with a 90 to 100 percent sensitivity and 80 to 92 percent specificity.[18,19]

TABLE 2
Differential Diagnosis of First-Trimester Vaginal Bleeding

Cervical abnormalities (e.g., excessive friability, malignancy, polyps, trauma)
Ectopic pregnancy
Idiopathic bleeding in a viable pregnancy
Infection of the vagina or cervix
Molar pregnancy
Spontaneous abortion
Subchorionic hemorrhage
Vaginal trauma

A missed spontaneous abortion usually is diagnosed by routine ultrasonography or when an ultrasound scan is obtained because the symptoms and physical signs of pregnancy are regressing. Figure 1 presents an algorithm for diagnosing spontaneous abortion.[12]

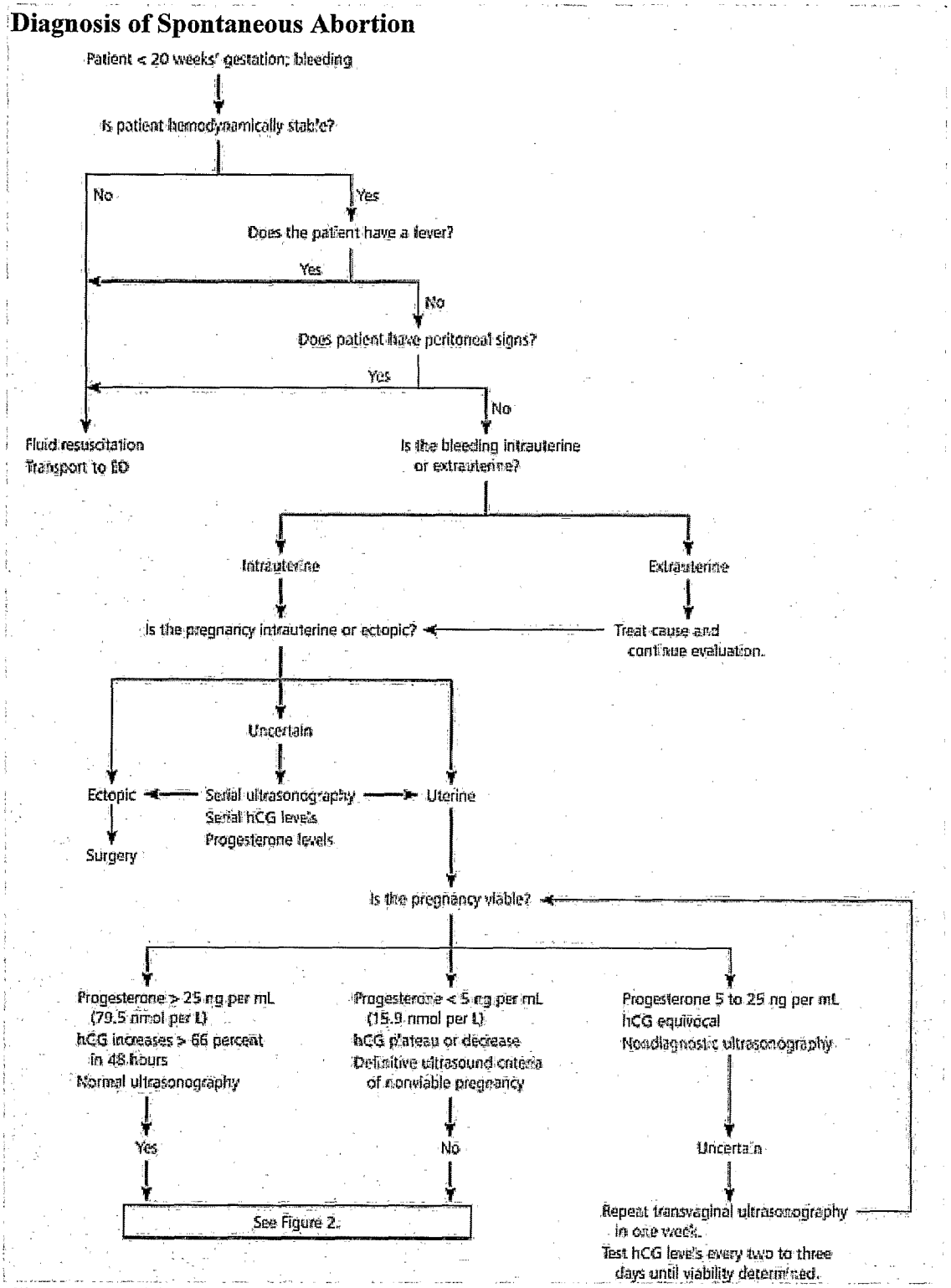

Figure 1. Algorithm for the diagnosis of spontaneous pregnancy loss. (ED = emergency department; hCG = human chorionic gonadotropin.)

Etiology and Risk Factors

Chromosomal abnormalities are a direct cause of spontaneous abortion. One meta-analysis[20] found that a chromosomal abnormality occurs in 49

percent of spontaneous abortions. Autosomal trisomy was the most commonly identified anomaly (52 percent), followed by polyploidy (21 percent) and monosomy X (13 percent).[20] Most chromosomal abnormalities that result in spontaneous abortion are random events, such as maternal and paternal gametogenesis errors, dispermy, and nondisjunction. Structural abnormalities of individual chromosomes (e.g., translocations, inversions) were reported in 6 percent of women who had spontaneous abortions, and approximately one half of these abnormalities were inherited.[9] Chromosomal abnormalities are more likely to be associated with recurrent spontaneous abortion, but are uncommon even in that instance (4 to 6 percent).[20]

Risk factors for spontaneous abortion are listed in Table 3.[12,21-25] However, other factors are notable for their lack of association with miscarriage. One study[26] that examined the influence of stress on early pregnancy loss failed to find a clear association. Marijuana use, likewise, has not been proven to increase the risk for spontaneous abortion.[22] Sexual activity also does not elevate risk in women with uncomplicated pregnancies.

Treatment

Dilatation and curettage is the traditional treatment for spontaneous abortion; manual vacuum aspiration is another surgical option. Prompt surgical evacuation of the uterus has been recommended in the past

because of the risk for infection and concerns about coagulation disorders that result from retained products of conception.[12,13] However, the need for immediate surgical evacuation in all patients with a spontaneous abortion has been questioned. Many recent studies[27-35] have examined the outcomes of expectant and medical management for women with spontaneous abortions.

TABLE 3
Risk Factors for Spontaneous Abortion

Advanced maternal age
Alcohol use
Anesthetic gas use (e.g., nitrous oxide)
Caffeine use (heavy)
Chronic maternal diseases: poorly controlled diabetes, celiac disease, autoimmune diseases (particularly antiphospholipid antibody syndrome)
Cigarette smoking
Cocaine use
Conception within three to six months after delivery
Intrauterine device use
Maternal infections: bacterial vaginosis; mycoplasmosis, herpes simplex virus, toxoplasmosis, listeriosis, chlamydia, human immunodeficiency virus, syphilis, parvovirus B19, malaria, gonorrhea, rubella, cytomegalovirus
Medications: misoprostol (Cytotec), retinoids, methotrexate, nonsteroidal anti-inflammatory drugs
Multiple previous elective abortions
Previous spontaneous abortion
Toxins: arsenic, lead, ethylene glycol, carbon disulfide, polyurethane, heavy metals, organic solvents
Uterine abnormalities: congenital anomalies, adhesions, leiomyoma

Prompt surgical evacuation of the uterus is the treatment of choice when the patient is unstable because of heavy bleeding or has evidence of a

septic abortion. Patient choice is another reason to proceed with surgical evacuation.

Some women may have already completed a spontaneous abortion by the time they present for clinical evaluation. If the ultrasound examination shows an empty uterus and evaluation of the expelled tissue confirms the presence of products of conception, no further action is needed; in these instances, patients have a completed spontaneous abortion and can be managed expectantly.[27] If the products of conception are not physically confirmed when the uterus is empty, an ectopic pregnancy must be ruled out.

Many studies[17-24] have compared expectant management, medical therapy, and surgical management for women with incomplete spontaneous abortion. Expectant management proved to be successful, with no need for surgical intervention in 82 to 96 percent of women.[28-33,35] Most patients who had surgical intervention were followed expectantly for two weeks before intervention was recommended.[17,19,21] Medical therapy with misoprostol (Cytotec) or mifepristone (Mifeprex) does not confer significant additional benefit.[34] The average time to completion of the miscarriage was nine days.[31]

In women with missed spontaneous abortions, expectant management has a variable but generally lower success rate than medical therapy, ranging from 16 to 76 percent.[28,31,36,37] In contrast, medical therapy for missed

spontaneous abortion results in high success rates for completion of a spontaneous abortion without surgical intervention. One study[36] found that patients had an 80 percent success rate after using 800 mcg of misoprostol, administered intravaginally and repeated after four hours, if necessary. Intravaginal administration of misoprostol causes less diarrhea than oral administration.[38]

Patient preferences should be considered when choosing a treatment for spontaneous abortion. Physicians should discuss the available options and the evidence to support each option with the patient. There is evidence to suggest that women who are given the opportunity to choose a treatment option have better subsequent mental health than women who are not allowed to choose their therapy.[39] However, patients express less happiness with the mode of treatment they receive and are less willing to have the same care again when they begin with noninvasive management and later require surgical intervention.[40] When patients are allowed to choose their therapy, 38 to 75 percent choose expectant management.[31,37,41]

An algorithm for managing women with spontaneous abortion is presented in Figure 2.[12] A 50-mcg dose of Rh_o(D) immune globulin (Rhogam) should be given to patients who are Rh-negative and have a threatened abortion or have completed a spontaneous abortion.[16]

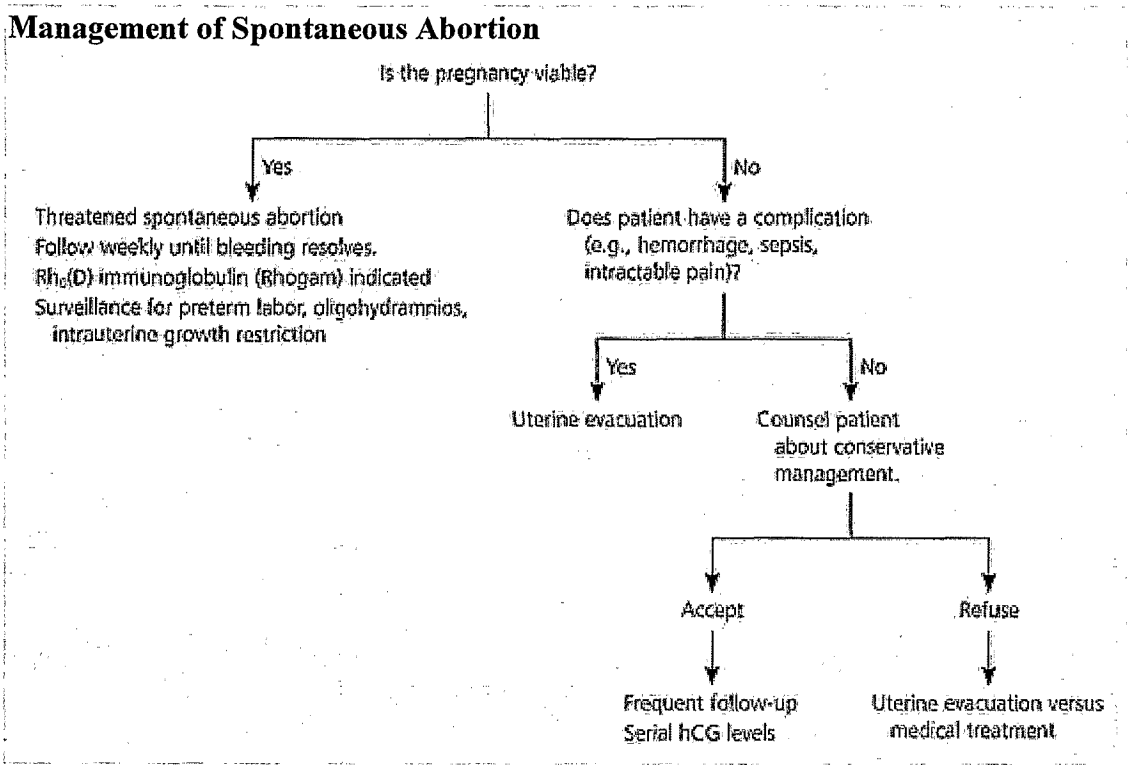

Figure 2. Algorithm for the management of spontaneous pregnancy loss. (hCG = human chorionic gonadotropin.)

Psychologic Issues After Spontaneous Abortion

Physicians should recognize the psychologic issues that affect a patient who experiences a spontaneous abortion. Although the literature lacks good evidence to support psychologic counseling for women after a spontaneous abortion, it is thought that patients will have better outcomes if these issues are addressed. The patient and her partner may be dealing with feelings of guilt, and they typically will go through a grieving process and have symptoms of anxiety and depression.