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Mini Review

The Importance of the Aneuploidy Screening in Pregnancy

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Abstract

The human genome is delicately balanced, and for the most part perturbations in the chromosome complement are often incompatible with embryonic development. Aneuploidy is a state of abnormal and highly variable DNA and chromosome content found in both hereditary disorders and human malignancy. Aneuploidy is one of the most important reason of reproductive biology and reproductive diseases. Many people are exposed to environmental genotoxic agents. Studies have shown that genotoxic agents and late marriages induce aneuploidy and polyploidy. The importance and clinical relevance of paternally derived aneuploidy is very important. Therefore, the aneuploidy screening is important in pregnancy. Prenatal aneuploidy screening has changed dramatically in recent years with increases in the types of CAs reliably identified and in the proportion of aneuploid fetuses detected. The findings of our studies confirm that in many cases a poor prognosis condition is associated with CAs. The newborns of smoking and mobile phone exposure of mothers have elevated frequencies of chromosome translocations and DNA strand breaks. It is known that cigarette smoking has genotoxic effects and causes mutations. The toxic substances from cigarette and mobile phone exposure induce structural and numerical CAs *in vitro* and could potentially increase levels of aneuploidy in the fetus. We concluded that mobile phone risks to human chromosomes and health.

Keywords: Aneuploidy; Chromosomes; Amenorrhea

Introduction

Nowadays, it is inevitable that people will be more exposed to the mutagenic and carcinogenic effects of genotoxic agents in their daily life or work environments due to the technological advances that are going on rapidly. Therefore, the human population is chronically exposed to natural and man-made sources. In the general population, there is growing concern of possible adverse genetic damage due to increasing exposure to the mutagenic and carcinogenic effects of genotoxic agents, and late marriages. The acute toxicity of genotoxic agents and the longer-term exposure has adverse effects on reproductive health, lung growth and development, neurocognitive function and cognitive decline, psychiatric morbidity, immune function, cancer risk, and cardiovascular disease. The human genome is delicately balanced, and for the most part perturbations in the chromosome complement are often incompatible with embryonic development. The number of baby abortion is increasing worldwide. Miscarriage is a common clinical problem and may be due to CAs in the fetus. Aneuploidy is the presence of chromosome number that is different from the simple multiple of the basic chromosome number and can include gain or loss of genetic material. In other words, aneuploidy is a state of abnormal and chromosome content found in both hereditary disorders and human malignancy. Because each chromosome consists of hundreds of genes, the loss or gain of large chromosomal segments disrupts significant amounts of genetic material and often results in a nonviable pregnancy or offspring that may not survive after birth. Together, aneuploidy is also a well recognised feature of human tumours.

In our study, we investigated the CAs in a total of 1725 pregnancies with risk according to triple test screening. CAs was detected in 3.2% of patients with high risk in triple test, and about 44.6% of these CAs were numerical aberrations. Our datas indicate that maternal serum triple marker screening is an effective method of detecting fetal CAs in Türkish women. It is also an effective screening tool for non-Down's CAs. Therefore, this screening method gives the advantage of early counselling and of diagnosis quite as early as in the second trimester of pregnancy. All women in whom serum screening indicates an increased risk for fetal CAs should be offered genetics counseling and chorionic villus sampling or amniocentesis. At the same time, we found CAs at 4% of the 1725 pregnant women who came to genetic screening with the risk of amniotic synthesis. The 2.6% of these CAs was numerical aberrations. The distributions of the numerical irregularities were as follows; 29% trisomy 21, 9% trisomy 18, 3% trisomy 13, 9% sex chromosomes, 10% mosaicism and 2% triploidy. Our datas indicate that second trimester triple marker testing is an effective screening tool for detecting fetal Down's syndrome in Turkish women [1].

We do not know the exact causes of aneuploidies during pregnancy but know some harmful factors that can cause aneoploidies. Our previous studies showed that the rate of aneuploidy increases with age, maternal smoke, the exposure of electromagnetic fields and cancers. The CAs associated with pregnancy losses and recurrent miscarriages are mostly numerical ones, with trisomy being the most frequent, followed by polyploidy and monosomy X. Recurrent miscarriage is a health problem involving 2 to 5% of

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couples. About 50-70% of all sporadic miscarriages are caused by a CA [2]. In one of our two studies related to spontaneous abortion, the proportion of numerical CAs was 11% in 1510 couples with a history of recurrent spontaneous abortion. Numerical chromosome aberrations (aneuplodies) were identified in seven couples, including three women and four men. An additional marker chromosome was identified in one woman and three men. One woman and one man had an extra X and Y chromosomes in mosaic form [3]. In other study, we also found major CAs in 51% of miscarriages. The most common abnormalities were fetal sex chromosome aneuploidies. They include 17.4% with 45, X karyotype and 8.7% with 47, XXY karyo type. Triploidy was found to be the second most common abnormality in our study. The frequency of triploidy was 12.2% of all miscarriages and 21.7% of all CAs (69, XXX or XXY). The mean age of mothers carrying a fetus with triploidy was 25.2 years (range 20-36), and the mean of their gestational ages was 10 weeks (8-13 years). The cytogenetic results of the two pregnancies were trisomy 21. There was not an increase in maternal age in trisomy conceptions. The frequency of mosaics was 4.9% of all miscarriages and 8.7% of all CAs [4]. Thus, cytogenetic analyses should be recommended in couples with recurrent miscarriages, when clinical data fail to clarify the cause.

CAs is one of the most important reasons of reproductive diseases. We found CAs in 4.4% of the patients with Bad Obstetric History (BOH). Aproximately, 0.7% of individuals with BOH have the numerical CAs and aneuploidies [5]. Also, our findings confirm that chromosomal evaluation can have a diagnostic value in couples with BOH. In our other study, we found the CAs frequencies surprisingly high in infertile couples and individuals with reproductive problems. The 50% of these was numerical CAs. Aneuploidies were present in 1.1% of all infertile individuals. Therefore, we suggest that chromosomal analysis should be performed routinely in both males and females of infertile couples [6]. Amenorrhea is one of the important reasons for patient referral to an endocrine or gynecologic clinic. Its etiology is heterogeneous. Cytogenetic investigations have shown the importance of CAs as a major cause of amenorrhea. In our work related amenorrhea, we detected numerical and structural abnormalities of X chromosome in 39.3% in Turkish women with amenorrhea. Among X CAs, monosomy and mosaic were the most frequent X aneuploidy [7].

Despite the damages explained above of nicotine it is estimated that about 20-25% of women still smoke during pregnancy [8]. For example, women who smoke during pregnancy are more likely to be depressed, anxious, or to have other mental health problems that could affect parent-child interactions and/or impose a genetic influence on the development of the child. From a public health perspective, it is vital to know whether smoking is harmful to the fetus in the first trimester when wom. The toxic substances from cigarette smoke induce structural and numerical CAs *in vitro* and could potentially increase levels of aneuploidy in the fetus. Moreover, increased levels of aneusomy in fetus are correlated with low implantation rates, spontaneous abortions and fetal losses. This possibility is consistent with the genotoxic effects in fetal cells from smoking during pregnancy are most likely caused by cigarette constituents, providing a potential mechanism for polyploidies and aneuploidies in fetal cells or embryo. According to our findings, tetraploidy and aneuploidy were found to be the most frequent abnormalities in our study. In our work, on the genotoxic effects of nicotine in smoking mothers, we provide the evidence that nicotine exposure *in vitro* has detrimental effects on fetal cells, and the most common numerical aberrations were chromosome 21 aneuploidies, followed by monosomies and trisomies 22, X, 8, 10, 15 and 20, respectively [9]. In particular, there is a significant excess of non disjunction in G group chromosomes, and G group chromosomes are more sensitive to nicotine in terms of non-disjunction events. Our findings indicate that smoking can be a confounding factor when assessing aneuploidy and tetraploidy in human fetal cells. The prenatal exposure to nicotine increases the frequencies of premature centromere separation and premature anaphase, in agreement with the results of our study which suggested that nicotine elevates aneuploidy levels in human fetal cells. This data indicates that nicotine expresses significant direct genotoxic effects on human fetal-cells *in vitro*. This possibility is consistent with the genotoxic effects in fetal cells from smoking during pregnancy are most likely caused by cigarette constituents, providing a potential mechanism for polyploidies and aneuploidies in fetal cells or embryo.

In an unpublished work was to evaluate the possible effects of *in vitro* 900 and 1800 MHz GSM-like (radiation from cell phones) exposure on chromosomes of human fetal cells. We found CAs in 25.9% of cells exposed to RF radiation, and non-thermal RF-EMF caused delays in chromosome condensation, and a significant rise in CAs with increasing exposure time. Structural changes were observed usually consisted of ragilities and gaps in various chromosomes, not observed numerical aberrations. In the exposed cells treated with 1800 MHz, the most damages were seen in chromosome 1, 3, 2, 5, 6, 7, 10, X and 4, respectively. We concluded that mobile phone risks to human chromosomes and human health. However, we confirm that RF-EMR affects negatively the condensation of chromosomes.

Aneuploidy is a well recognised feature of human tumours, and there is a significant correlation between aneuploidy and melanoma thickness. We observed aneuploid not only in gestation but also in different types of cancer. Because, aneuploidy is a well recognised feature of human tumours, and has been proposed to drive tumor development by enhancing genomic instability [10]. Aneuploidy in human cells is considered to be age and cancer-related [11]. We was observed the chromosome 22, X, 3, 17 and 18 aneuploidies to be the most frequent among all numerical aberrations in the women with uterine myomas [12], especially chromosome 22. The increased incidence of aneuploidy, could contribute to the progression of the disease along with other chromosomal alterations.

In another cancer study, we was observed the aneuploidies in chromosomes X, 22, 3, 17 and 18 to be most frequently observed in children with neuroblastoma [13]. Aneuploidy is a commonly observed feature in neuro blastic tumours. Our findings indicated that loss and/or gain of chromosome X, 22, 3, 17 and 18 was important in development of neuro blastic tumours, especially chromosome X. Loss of sex chromosome is the largest source of aneuploidy, and efforts have been made to better understand its role in these processes. However, the function of sex chromosome aneuploidies is not yet fully known. The loss or gain of an X chromosome in women with aging is much more frequent than that of the Y chromosome in males [14]. In our study, sex aneuploidies were found in 28.4% of sarcoma tissue, and ın the blood, were found in the 5.6% of cells analyzed. The most

damages were seen in loss of one or more extra X or Y chromosomes in cancer tissue, respectively [15]. Our findings suggest that the Y and X aneusomies play a role in the pathogenesis of sarcoma tissue. The genetic instability associated with sex chromosome polysomies and the loss of one Y may account for the considerable potential for risk of sarcoma tumors.

In our study related to lung and bladder cancers, 78.9 % of the patients had monosomy X and Y. The Y aneuploidies were observed as common. In particular, the Y chromosome losses were found in 77.8 % of the male patients, with the second most common karyotype seen among males being the XXY, XXYY and XYY chromosome structures [16]. There are also several reports that suggest that structural and numerical sex chromosome changes were seen frequently in patients with lung cancer [17,18]. Our results may suggest that SCAs may be contributing factors in the development of lung and bladder cancers, and aneuploidies of the X and Y chromosomes play a role in the pathogenesis of cancers, thus it may be a diagnostic criterion for lung and bladder cancers.

As seen in our studies above, aneuploidies are causing the fetal development, spontaneous abortions, congenital phenotypic defects, and cancers development. Among the reasons for avoiding these genetic damages are advanced maternal age and avoidance of genotoxic damage that will affect gametogenesis in parents. At the same time, combined data of our study suggested that CAs are associated with pregnancy losses and are required for the etiological investigation of true genetic counseling. These findings could be used widely in the clinical genetics and will be an effective tool for genetic counseling and reproductive guidance. Because, CAs occur in approximately 1 in 150 live births, the prevalence is greater earlier in gestation because aneuploidy accounts for a large proportion of early pregnancy loss. The incidence of fetal aneuploidy increases as a woman ages but can affect any woman regardless of age and is not related to race or ethnicity. It is well known that women over 35 are also at increased risk for fetal trisomies. Other factors that increase the risk of fetal aneuploidy include a history of a prior aneuploid fetus and the presence of fetal anomalies. Autosomal trisomies are the most common aneuploidies. Mechanisms leading to aneuploidy are still not entirely understood even though, e.g., the loss of spindle checkpoint functions, altered proteins of the mitosis spindula, and alterations in the kinetochore components have been suggested to cause DNA aneuploidy [19]. We know some of the causes that trigger the development of the aneoploidies, but some of them do not know. We know that main cause of aneoploidie is the result of chromosomal non disjunction and anafaz lagging in the anaphase. For this reason, all toxic damages must be avoided which will cause damage to the loss of spindle checkpoint functions in cell division. Among these harmful toxic factors, we can refer to advanced maternal age, smoking, harmful rays, toxic substances and eating style. Because, embryonic aneuploidy results from genomic errors at one or more stage(s) of development—oocyte meiosis I, oocyte meiosis II, fertilization, and mitosis [20]. Understanding when and how genomic errors occur is essential to the field of reproductive medicine. Genomic errors that occur during oocyte meiosis are a well-established cause of embryonic aneuploidy. Such errors occur as a result of whole chromosome or chromatid segregation failure in meiosis I or II [20,21] with error rates directly related to maternal age. In addition to errors in meiosis, genomic errors may occur during the post-fertilization mitotic divisions, resulting in embryonic mosaicism [22,23]. Therefore, it should not be exposed to harmful effects that affect chromosomal distribution in meiosis.

Because of this, screening in pregnancy is very important. Because, we cannot correct genetic diseases, but we can eliminate abnormal fetuses before birth with early diagnosis and genetic counseling. Screening in pregnancy is the process of surveying a population, using a specific marker or markers and defined screening cut-off levels, to identify the individuals in the population at higher risk for a particular disorder. Screening for a disorder should be undertaken only when the disorder is considered to be serious enough to warrant intervention. Pregnancy screening for fetal aneuploidy started in the mid 1960s, including Down syndrome, using maternal age as the screening test. Historically, women 35 years or older at the time of delivery and women with an abnormal screening test were offered prenatal genetic counseling and the option of a diagnostic test such as amniocentesis or chorionic villus sampling. Indeed, we are also more often detected the trisomy 21,18 and 13 in amniocentesis analysis of elderly mother. However, screening tests to identify women at risk for fetal aneuploidy such as trisomies 21, 18, 13 or X are routinely offered to all women during pregnancy regardless of maternal age. A number of screening strategies are available, which utilize both biochemical and ultrasonography to achieve high detection rates. Aneuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy, ideally at the first prenatal visit. The choice of whether to perform screening or diagnostic testing for aneuploidy depends on the woman's goals and values and her desire for informational accuracy. Although maternal age may be helpful in adjusting an individual woman's risk of having a fetus with aneuploidy, it should not be used as the sole determinant of whether aneuploidy screen- ing or diagnostic testing is offered. Nowadays, second trimester maternal serum biochemical testing helps identify women at risk for neural tube defects, trisomy 21 and trisomy 18. Evaluation of the severity and the etiology of the anomaly is an important prognostic factor [24].

Conclusion

After all this information, miscarriage is a common clinical problem and may be due to CAs in the fetus. Our results strongly suggest that nicotine, mobile phone, bad obstetric history, amenorrhea and cancers are leading to numerical chromosomal irregularities of mother and human fetal cells. There is a positive correlation between the frequency of aneuploidy and the effect of nicotine, mobile phone and cancers to induce numerical chromosome damage. Cigarette abuse during pregnancy increases maternal health risks as well as mental and physical problems for the fetus, contributing to multiple adverse outcomes such as preterm delivery and stillbirth. We concluded that mobile phone risks to human chromosomes and health. The findings of our studies confirm that in many cases a poor prognosis condition is associated with CAs. It is well understood that the fetal environment is of tremendous importance during the developmental period in determining health throughout the life of the individual. Despite the high frequency and clinical relevance of aneuploidy in humans, surprisingly little is known about factors that modulate the risk of meiotic non-disjunction, the only factor incontrovertibly linked to human aneuploidy being represented by increasing maternal

age. The mechanisms underlying the predisposition to aneuploidy still need to be elucidated. There is increasing evidence supporting the fact that each aneuploidy event is dependent not on a specific variable, but on groups of variables. Therefore, fetal aneuploidy risk can be evaluated on the basis of a combination of maternal age, prior affected pregnancy or family history, maternal serum biochemical tests and fetal ultrasound markers. Recently, new non-invasive prenatal testing based on massively parallel sequencing of circulating free fetal DNA (cfDNA) in maternal plasma has been shown to be highly effective for aneuploidy detection. But cfDNA is not routinely used in all countries. Therefore, all women with indications should have the option of invasive diagnostic testing for fetal aneuploidy by amniocentesis or CVS. Invasive prenatal diagnosis would be offered to women who screen above a set risk cut-off level on non-invasive screening or to pregnant women whose personal, obstetrical, or family history places them at increased risk. For women who do not initially want a diagnostic test, screening for aneuploidy should be offered to those who present for prenatal care before 20 weeks' gestation regardless of maternal age. Women should be informed of the adjusted risk for aneuploidy and allowed to make individual decisions regarding diagnostic testing based on the numerical risk. Screening in pregnancy should be considered if the woman or her partner has a history of a previous child or fetus with a chromosomal abnormality or is a carrier of a chromosome rearrangement that increases the risk of having a fetus with a chromosomal abnormality.

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