Toward a New Era of Fetal Tobacco Syndrome

Toshihiro Ino* and Kazuo Kurosawa

Gunma Paz College, Faculty of Health Science, 1-7-1 Tonyamachi, Takasaki, Gunma, 370-0006, Japan

Abstract: Fetal tobacco syndrome (FTS) was first reported in early 1986. However, since that time, neither the name nor diagnostic criteria of the disease have been applied. One reason for this is that bronchial asthma, sudden infant death syndrome, attention deficit hyperactive syndrome and obesity as delayed symptoms of FTS, are not found at birth. The initial diagnostic criteria include: (1) maternal smoking with a cigarette consumption of more than five cigarettes/day during pregnancy, (2) symmetrical developmental delays with no other causes (gestational age ≧37 weeks and birth weight< 2,500 g), (3) no maternal hypertension. However, a low birth weight at a gestational age of less than 37 weeks, congenital malformations and delayed symptoms should also be included in these diagnostic criteria. In this review, FTS is compared with fetal alcohol syndrome and new diagnostic criteria are proposed based on previous reports.

Keywords: Congenital malformation, Diagnostic criteria, Alcohol, Tobacco, Pregnancy.

INTRODUCTION

Maternal smoking during pregnancy seriously affects fetal development. According to recent reports from the USA, maternal smoking during pregnancy is a cause of 5-8% of early deliveries, 13-19% of cases of low-birth-weight infants at full term, 5-7% of deaths related to early delivery and 23-34% of cases of sudden infant death syndrome [1-4]. Fetal alcohol syndrome is well known in the field of pediatrics, and the details of its symptoms and diagnostic criteria are described in text books [5-8]. In contrast, fetal tobacco syndrome (FTS) generally remains unknown. Our impression is that the nomenclature of FTS is not often employed although this condition has been assessed in numerous studies showing that maternal smoking during pregnancy has harmful effects on the fetus.

In this review, we consider whether FTS has been established as a clinical entity and describe the original report of FTS, with a focus on the diagnostic criteria of this condition based on previous studies.

FETAL ALCOHOL SYNDROME

Concept of Fetal Alcohol Syndrome (FTS)

FTS is a congenital neuro-cerebral disorder of the fetus involving malformations induced by habitual alcohol consumption in the pregnant mother. The degree of mental retardation in the baby is dependent on the amount and frequency of the mother's alcohol intake during pregnancy. Reports of FAS have been published since the late 1960's, and studies regarding the effects of alcohol on the fetus have accumulated since the 1970's [5, 6].

Prevalence of FAS

Approximately 40% of mothers with alcohol dependency give birth to babies with FAS. In Japan, the prevalence of FAS is estimated to be 0.05-0.1/1,000 births according to a survey performed in 1991. This percentage is lower than that of the 0.2-2.0/1,000 births reported in the USA (in particular, the prevalence of FAS in Alaska is 5-6/1,000 births due to the high frequency of alcohol consumption) [9]. However, the rate of drinking among females who may become pregnant has increased annually in Japan in recent years, and the frequency of drinking during pregnancy is higher than that observed in other countries. As a result, there is concern that the incidence of FAS will continue to increase.

Relationship with the Amount and Period of Alcohol Intake

The direct cause of FAS is alcohol intake in pregnant females. Whether the mother has a history of FAS or her parents exhibited alcohol dependency are not directly related to the incidence of FAS. Therefore, this condition appears to be unrelated to hereditary factors, and there is no risk of FAS if the mother does not drink during pregnancy. FAS may be induced by the consumption of two glasses per day of any kind of alcohol (including beer and wine) or four glasses of alcohol at a time. FAS may also be induced via the intake of breast milk from a mother who drinks, as breast milk is derived from blood. This phenomenon is the same as if the baby drank alcohol directly. In fact, drinking during lactation increases the risk of developmental disabilities in children. Therefore,

*Address correspondence to this author at the Ino Clinic, 1-12-24 Hakoda, Kumagaya, Saitama, 360-0014 Japan; Tel: 048-528-8300; Fax: 048-526-3900; E-mail: ino-t@sk9.so-net.ne.jp

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formula milk is recommended if the mother drinks during this period. In the first trimester, particularly a gestational age of 2 months, which is a critical period, maternal drinking affects the development of the brain and other organs in the fetus. In addition, maternal drinking in the second and third trimesters may result in a low birth weight and developmental delays in the brain and neurological system. A higher maternal age is also associated with a greater incidence of FAS. If one or both parents drink regularly for a long period between 10 to 20 weeks of age, germ cell damage is likely. In addition, long-term alcohol drinking increases tolerance to alcohol, encouraging an individual to drink more over time, thus increasing the risk of having a FAS baby, even in young mothers.

Physique and Nutrition of the Mother

The efficiency of alcohol excretion is lower in lean mothers than in mothers with a typical physique. One glass of alcohol in females is equivalent to two glasses of alcohol in males, as females are generally smaller than males and female hormones inhibit the activity of catabolic enzymes that degrade alcohol. Additionally, females have more subcutaneous fat than males, which prolongs the long time required to clear alcohol from the body. Furthermore, problems in mother's health status, such as eating disorders, anemia, liver dysfunction or malnutrition, affect fetal development. Drinking before eating and/or while fasting is more harmful than drinking with a meal including carbohydrates. The dehydration of alcohol in the liver depends on the form of drinking, for example swigging or relishing the drink, as well as the duration between drinks. Alcohol is effectively dehydrogenated in the liver when drinking one cup of alcohol slowly.

Main Symptoms of FAS

The symptoms of FAS include evident morpho-logical abnormalities, cerebral palsy, epilepsy, learning disabilities and severe behavioral disorders without external malformations. Three major symptoms are as follows:

(1) *Neurological abnormalities*: subtle or excessive behavioral (hyperactive) or learning disabilities

(2) *Maldevelopment*: a low birth weight (5-10% lighter than a healthy baby), intrauterine growth retardation

(3) *Specific facial features*: as follows

FAS is associated with three diagnostic facial features, including a short palpebral fissure length, smooth philtrum and thin upper lip. The ratio of the distance from the endocanthion to exocanthion (palpebral fissure length)/distance between the endocanthion sites is less than 80% in Asians and some American Indians and less than 90-95% in Caucasians and blacks. The smaller the value, the more accurate the diagnosis of FAS. The philtrum or distance between the nose and upper lip is long and the philtrum groove is not clear and smooth. The upper lip is very thin with a straight line.

Microcephaly is evident, with a head circumference less than 5% than normal. Extreme epicanthal folds are also observed. The nose is small and short, and the bridge is not evident. Micrognathia with a sharp and small chin is detected, with consequent occlusion of the teeth that worsens with growth as the teeth jostle each other. In contrast, the lower chin may become too big. Ear malformation is also evident, with the ear bending backward in a low-set position. Ruggedness of the auricle is the reverse of normal (Railroad track ear). Other malformations may be found rarely, including awkward occlusion of the teeth, an abnormal amount of facial and body hair in infants, webbed fingers, small nails, a simian crease, scoliosis, sacrococcygeal or sacral dimples, facing forward palms, articular abnormalities, hemangiomas and nevi. In addition, strabismus, myopia, deafness and congenital heart malformations are also detected rarely.

Diagnostic criteria for FAS were recently proposed by Watkins and colleagues, as shown in Table **1**.

FETAL TOBACCO SYNDROME (FTS)

The literature search of "Fetal tobacco syndrome" was performed by PubMed and the scope of reviewing was ranged from 1980 to 2014.

Classical Criteria for FTS

The concept of FTS was first reported by Nieburg in JAMA in 1985 [9]. The diagnostic criteria include:

1) Maternal smoking of more than five cigarettes/day during pregnancy

2) Symmetrical developmental delays without other causes (gestational age $\geqq$37 weeks and birth weight less than 2,500 g)

3) No maternal hypertension

Since that time, there have been no substantial discussions regarding these criteria.

Table 1: Recommended Australian FASD Diagnostic Categories and Criteria

Diagnostic criteria[#]	Fetal Alcohol Syndrome (FAS)	Diagnostic category	Neurodevelopmental Disorder-Alcohol Exposed (ND-AE)
		Partial Fetal Alcohol Syndrome (PFAS)	
Requirements for diagnosis	Requires all 4 of the following criteria to be met:	Requires confirmed prenatal alcohol exposure, the presence of 2 of the 3 characteristic FAS facial anomalies at any age, and CNS criteria to be met:	Requires confirmed prenatal alcohol exposure and CNS criteria to be met:
Prenatal alcohol exposure	Confirmed or unknown	Confirmed	Confirmed
Facial anomalies	Simultaneous presentation of all 3 of the following facial anomalies at any age: i. short palpebral fissure length (2 or more standard deviations below the mean) ii. smooth philtrum (Rank 4 or 5 on the UW Lip-Philtrum Guide[†]) iii. thin upper lip (Rank 4 or 5 on the UW Lip-Philtrum Guide[†])	Simultaneous presentation of any 2 of the following facial anomalies[°] at any age: i. short palpebral fissure length (2 or more standard deviations below the mean) ii. smooth philtrum (Rank 4 or 5 on the UW Lip-Philtrum Guide[†]) iii. thin upper lip (Rank 4 or 5 on the UW Lip-Philtrum Guide[†])	No anomalies required[*]
Growth deficit	Prenatal or postnatal growth deficit indicated by birth length or weight≤10th percentile adjusted for gestational age, or postnatal height or weight≤10th percentile	No deficit required[*]	No deficit required[*]
Central Nervous System (CNS) abnormality	At least 1 of the following: i. clinically significant structural abnormality (e.g. OFC≤3rd percentile, abnormal brain structure), or neurological abnormality (seizure disorder or hard neurological signs); and/or ii. severe dysfunction (impairment in 3 or more domains of function, 2 or more standard deviations below the mean)[‡]		

Symmetrical developmental delays indicate that the head, body, arms and legs are undergrown to the same degree. This is an early trimester disability caused by chromosomal abnormalities, congenital malformations and drugs. On the other hand, in patients with asymmetrical developmental delays, the arms and legs are undergrown despite normal development of the head, resulting in imbalances. The causes of this developmental delay are primarily considered to be placental dysfunction and gestational toxicosis. Several reports have suggested relationships between maternal smoking during pregnancy and premature delivery at less than 37 weeks of age, respiratory disorders, obesity and neurological developmental disorders [2,3]. Eventually, the diagnosis of FTS at birth became regarded as inaccurate. Tanaka and colleagues proposed the concept of the fetal tobacco effect in which a gestational age less than 37 weeks should be added to the classical criteria [10]. However, there have been no subsequent discussions or follow-up studies on this issue. Therefore, it is necessary to develop new diagnostic criteria for FTS in order to establish this disorder as a clinical entity.

The major issues related to FTS are as follows.

Prevalence of Smoking in Pregnant Females

The prevalence of smoking among pregnant females is 15-25%, a rate that has tended to decrease from a global standpoint. In Japan, the rate is 6-7%, which is relatively low compared to the 30% observed in Australia and 22% noted in Germany. In contrast, the rate of maternal smoking among females less than 20 years of age has gradually increased over the past 10 years [11-13]. Based on the report of the Japan Ecology and Children (Echo-Chil) Study conducted by the Ministry of the Environment, the proportion of pregnant mothers of less than 25 years of age who smoke is 10%, while that among their husbands is 63%, the highest rates in this age group worldwide [14].

Fetal-Placenta Unit

Pathological abnormalities in the fetal-placenta unit are induced by maternal smoking during pregnancy. The fetal-placenta unit participates in the exchange and transport of substances and is a functional unit of hormone production. Morphological studies using electron microscopy have revealed that maternal smoking during the first trimester interferes with the proliferation and differentiation of cytotrophoblasts, increases the thickness of the basement membrane of cytotrophoblasts, alters the production of collagen in the villi and decreases the number of vessels. It has been previously reported that these morphological abnormalities are induced primarily by the nicotine and cadmium present in tobacco smoke [12]. As a result, the prevalence of premature separation of the placenta

increases significantly, with an odds ratio of 1.4-4.0, in correlation with the degree of cigarette consumption in the mother during pregnancy. This rate decreases if the mother stops smoking in early pregnancy.

Low-Birth-Weight Infants

It is well-known that birth weight is significantly decreased by smoking in the pregnant mother [15-17]. The weight of such infants is low and their length is short for their gestational age, the so-called SFD (small-for-date) type, which is considered to be a form of intrauterine growth retardation. Previous studies have shown an odds ratio of SFD of 1.5-2.9 and that the birth weight decreases 10-12 g for each increase in the number of cigarettes/day smoked by the mother [12]. This effect is doubled by maternal smoking in the third trimester. On the other hand, smoking cessation within the first trimester can eliminate the risk of SFD. It has recently been reported that some types of the CYP1A1 (an enzyme that decomposes benzo(a) pyrene) and GSTT1 (a glutathione-related gene as a carcinogen) genes increase the risk of SFD [12].

Fetal Death

The prevalence of spontaneous abortion may be higher in cases of maternal smoking, with an odds ratio of approximately 1.2-1.8, although some reports have shown no significant differences. The risk ratio for stillbirth (death at more than 20 weeks of gestation) is 1.2-1.8 and has been reported to be dependent on the level of cigarette consumption in the mother [16, 17].

Premature Delivery

It is also well known that the risk of premature delivery is increased by maternal smoking. A majority of studies have demonstrated a significantly elevated risk, with an odds ratio of 1.2-1.6, strengthening the relationship between cigarette consumption and premature delivery at less than 32 weeks of gestation. The cause of premature delivery is thought to be associated with a higher risk of premature rupture of membranes, with an odds ratio of 2.0-3.0.

Sudden Infant Death Syndrome (SIDS)

Previous meta-analyses have reported consistent results showing risk ratios of 2.0-3.0 and a dose-response relationship between cigarette consumption and the incidence of SIDS. Regarding the prevalence of sudden infant death syndrome, the mortality rate increases by 4% in cases in which the mother smokes 10 cigarettes/day. In most epidemiological studies, however, it is difficult to distinguish fetal from postnatal exposure to secondhand smoke in terms of the underlying cause.

Bronchial Asthma and Wheezing

Meta-analyses have revealed that maternal smoking during pregnancy increases the incidence of both bronchial asthma and wheezing in the infant, with an average odds ratio of 1.8. In addition, there is a dose-response relationship between dyspnea in the baby and cigarette consumption in the pregnant mother.

Obesity

According to the results of our previous meta-analysis, the incidence of obesity (a BMI above 95%) in the infant is associated with an average odds ratio of 1.5.

Cleft Lip and Palate

The results of a previous meta-analysis showed a fixed risk ratio for cleft lip and palate of 1.2-1.3, regardless of the type of epidemiological study. The incidence of these malformations is 1.7 times higher in cases in which the mother smokes more than 20, versus less than 20, cigarettes/day [23]. Cleft lip and palate are well-known malformations induced by fetal exposure to tobacco smoke; however, other malformations are also important.

Congenital Malformations

Hackshaw and colleagues previously reported the results of 50 meta-analyses, as shown in Table **2**. Their analysis included 173,687 malformations among 11,674,332 control cases in 172 epidemiological studies. Consequently, significantly increased odds ratios were found for congenital heart disease (OR:1.09), musculoskeletal malformations (OR:1.16), limb defects (OR:1.26), digital defects (OR:1.18), clubfeet (OR:1.28), craniosynostosis (OR:1.33), facial defects (OR:1.19), eye abnormalities (OR:1.25), cleft lip and palate (OR:1.25), gastrointestinal malformations (OR:1.27), anal atresia (OR:1.20), gastroschisis (OR:1.50), urogenital malformations (OR:1.05) and central nervous malformations (OR:1.10).

Attention Deficit Hyperactive Disease

A meta-analysis of 13 studies of attention deficit hyperactive disease demonstrated a significantly

Table 2: Odds Ratios of Congenital Malformation in FTS (Summary of Meta-Analysis)

		Study number	Pooled odds ratio	95% C.I.	
Cardiovascular system		25	1.09	1.02	1.17
	Cardiac malformation	19	1.09	1	2.18
Musculoskeletal system		25	1.16	1.05	1.27
	Limb reduction	8	1.26	1.15	1.39
	Finger anomaly	6	1.18	0.99	1.41
	Clubfoot	12	1.28	1.1	1.47
	Diaphragmatic hernia	4	0.94	0.72	1.22
Craniosynostosis		5	1.33	1.03	1.73
Facial anomalies		12	1.19	1.06	1.35
	Eye anomaly	8	1.25	1.11	1.4
	Oral cleft	38	1.28	1.2	1.36
Gastrointestinal anomalies		35	1.27	1.18	1.36
	Gastroschisis	12	1.5	1.28	1.76
	Omphalocele	7	1.19	0.95	1.48
	Anal atresia	7	1.2	1.06	1.36
	Hernia	4	1.4	1.23	1.59
	Esophageal fistula	7	0.93	0.81	1.07
Genitourinary system		40	1.05	0.98	1.12
	Any anomay	32	1.01	0.93	1.1
	Cryptorchidism	12	1.13	1.02	1.25
	Hypospadias	15	0.9	0.85	0.95
	Renal/urinary tract	9	1.15	0.95	1.39
Central nervous system		29	1.1	1.01	1.19
	Anencephaly/spina bifuda	17	0.97	0.86	1.1
Respiratory system		6	1.11	0.95	1.3
Skin		5	0.82	0.75	0.89
All defect together		38	1.01	0.96	1.07

elevated odds ratio of 2.4 [24, 25]. Emotional and behavioral disorders, delayed speech and attention deficits are found in infancy, while symptoms of attention deficit hyperactive disease become evident in adolescence. MRI findings show abnormalities of the cerebral cortex and gray matter, and the prevalence of nicotine dependency in such cases is high.

DIAGNOSTIC CRITERIA FOR FETAL TOBACCO SYNDROME

The diagnostic criteria reported by Nieburg and colleagues include only the level of cigarette consumption in the mother and the birth weight of the infant, and the diagnosis is made at birth. There are currently no descriptions regarding symptoms that may become evident postnatally over time. In addition, the criteria do not include sudden infant death syndrome, bronchial asthma or obesity, which appear a few years after birth. Therefore, there is concern that a diagnosis made after the appearance of late symptoms is retrospective. In contrast, it is possible to predict and prevent subsequent symptoms if an exact diagnosis can be obtained at birth. Premature delivery should also be added to the diagnostic criteria due to its higher risk ratio in infants with symptoms of FTS. In such cases, premature delivery without other causes may be added to the criteria, regardless of the birth weight for gestational age, including a small-for-date status or

Table 3: Diagnostic Criteria of FTS which we Proposed

Diagnostic criteria	Diagnostic classifications		
	Strict FTS	Extended FTS	SIDS, asthma, ADHD, obesity
Requirements for diagnosis	Requires all of the following criteria except No.3 to be met.		It is possible to diagnose retrospectively if above disorders are found. In this occasion, but requires all of the following criteria except 3
1. Prenatal tobacco exposure	Maternal smoking during pregnancy with cigarette consumption of more than 5 pieces/day		
2. Growth deficit	Requires more than 37 gestational weeks and all of the following 3 items. a. Symmetrical growth deficit b. Birth weight less than 2500g c. Kaup index >11.3	Requires less than 37 gestational weeks and all of the following 3 items. a. Symmetrical growth deficit b. Less than -1.5SD for appropriate birth weight c. Kaup index>11.3	Requires either of left columms
3. Congenital malformations	The possibility of FTS is considered high if anomalies described below exist. Oral and cleft palates, gastroschisis, limb reduction, clubfoot, craniosynostosis, hernia		
4. Maternal hypertension (included pregnancy induced hypertension)	No existence is prerequisite.		
5. Intrauterine growth retardation	No other obvious causes are prerequisite.		

SIDS: Sudden infant death syndrome, ADHD: Attention deficit hyperactive disorder

intrauterine growth retardation. Table **3** shows the new diagnostic criteria for FTS proposed by the authors.

In cases of fetal alcohol syndrome, it is feasible to obtain a clinical diagnosis at birth or soon after, as this syndrome presents with the specific facial features mentioned above. In patients with FTS, on the other hand, no specific facial features, except for cleft lip and palate, are evident; therefore, making a definitive diagnosis can be difficult. In this report, we described a new set of diagnostic criteria including the addition of congenital malformations, with an odds ratio of more than 1.25, as evident in a meta-analysis by Hackshaw and colleagues. In the classical diagnostic criteria for FTS, the ponderal index (obesity index: body weight (kg)/height (m^3)>2.32, similar to the Rohrer index, used in older children) is used to assess the balance of body weight and height. However, the Kaup index is employed in the new criteria because it has recently become a more popular assessment tool in early infancy. There are no other changes to the criteria, in which the absolute requirements are the lack of maternal hypertension, including pregnancy-induced hypertension syndrome, and intrauterine growth retardation without an obvious cause.

SUMMARY

The diagnostic nomenclature of FTS is not frequently used, compared to fetal alcohol syndrome. The reason for this is because it is difficult to use the classical diagnostic criteria, as bronchial asthma, sudden death syndrome, attention deficit hyperactive syndrome and obesity manifest after birth. We herein proposed new diagnostic criteria in both the strict and broad sense that include delayed symptoms. However, these new criteria are not well supported by evidence, but rather were developed in consideration of the previous literature. Hence, substantial discussion regarding the diagnostic criteria for FTS is mandatory in the future

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DECLARATION OF INTERESTS

The authors report no declarations of interest.

Mr. Kazuo Kurosawa: I would like to declare that I conceived of the study, collected the data, and contributed to writing the paper.

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