Environmental factors for the development of fetal urinary malformations

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Background: **The development of the kidneys and other organs of the urinary tract also follow the natural rule of gene-environment-lifestyle interaction. Both intrinsic and extrinsic factors may be associated with the etiology of various kinds of urinary malformations. The environmental factors belong to extrinsic factors, which have attracted increasing attention from researchers.**

Methods: **Publications about urinary malformations were searched from databases such as PubMed, Elsevier, Chemical Abstract, Excerpta Medica, Chinese Hospital Knowledge Database and Wanfang Database.**

Results: **Urinary malformation is associated with low birth weight, maternal diseases, placental insufficiency, maternal drug exposure, and maternal exposure to environmental pesticides. Living environment and socioeconomic factors may also influence the incidence of urinary malformation.**

Conclusion: **It is important to understand the association of environmental factors with the development of the renal system and urinary malformation in order to decrease the incidence of urinary malformations.**

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Review article

Introduction

Urinary malformations are the congenital anomalies of the kidneys and/or urinary tract. Human nephrogenesis completes at around 34-36 weeks of gestation.[1,2] Potter[3] divided urinary malformations into four types based on the anatomical and histological characteristics: renal agenesis, dysplastic kidneys, hypoplastic kidneys, and associated lower urinary tract anomalies. Both intrinsic and extrinsic factors may be associated with the etiology of urinary malformations. The development of the urogenital system also follows the natural rule of gene-environment-lifestyle interaction. In this article, we systematically reviewed the publications in databases including PubMed, Elsevier Web of Science, Chemical Abstract, Excerpta Medica , Chinese Hospital Knowledge Database and Wanfang Database about the environmental aspects of maternal and fetal factors involving in urinary malformations.

Low birth weight and urinary malformations

Human nephrogenesis completes at around 36 weeks of gestation. Low birth weight and/or prematurity is associated with various measures of kidney disease, including congenital urinary malformations.[4] The reduced number of nephrons is an increased risk of progressive renal disease.[5] An animal study found that despite the similar sizes of the kidney, intrauterine growth restriction (IUGR) piglets had fewer glomeruli (nephron) (43%), which was correlated with birth weight.[6] Hughson et al[7] reported that birth weight is a strong determinant of glomerular number (Nglom) and, thereby, glomerular size in the postnatal kidney can be detected by using human autopsy tissue. The Nglom in individuals is dependent upon maternal diseases affecting the kidney, and the nephron number is varied at birth and is therefore developmentally determined. An increase of per kg in birth weight was associated with an addition of 260 000 nephrons per kidney. The same group later investigated the relationship between maternal obesity, birth weight race, and hypertension-related renal structural changes in the United States; they found that

birth weight and gender, but not race, predicted the Nglom of the newborns.[8] A similar study[9] also showed that the kidneys of low birth weight neonates contained fewer glomeruli per unit area of kidney cortex than neonates with normal birth weight. It should be noted that part of the congenital urinary malformations could have resulted in the decrease in the glomerular number, and due to technological limitations, it is very difficult to clarify the direct relation between IUGR and the reduced number of nephrons. Hypospadias, a kind of urinary tract malformation, was found to be more common in infants with uniformly poor intrauterine growth. It was reported that the incidence of hypospadias in the NICU population increased by 10 folds from 0.4% in 1987 to 4% in the first quarter of 2000.[10] This increasing frequency of hypospadias and its association with poor intrauterine growth originating in early gestation suggests that common environmental factor(s) that have an impact on both conditions may be involved.

Low birth weight can be caused by various endocrine dysfunctions such as environmental thyroid dysfunction. There has been clinical evidence that environmental iodine deficiency causes environmental thyroid dysfunction, which is commonly observed in newborns with low birth weight. In humans, thyroid hormone (TH) plays many roles in different tissues at different developmental times,[11] and TH deficiency during development is associated with irreversible damage to virtually all organ systems. Pregnant women, developing fetuses, and newborns are the sensitive populations particularly at risk for TH disruption induced by environmental contaminants. A number of environmental contaminants with diverse structures have shown to decrease circulating levels of TH,[12] and human exposure to some of these chemicals is associated with altered serum profiles of TH.[13] Iodine is an essential element for the biosynthesis of TH. Environmental iodine deficiency causes endemic goiter, resulting in thyroid dysfunction and low birth weight in children born in regions of the world where dietary iodine deficiency is prevalent.[14]

Fetal environment and urinary malformations

Maternal nutritional status and amniotic fluid

Fetal growth and development is sensitive to fetal environment preliminary determined by maternal physiology and placental function. Barker[15] hypothesized in early years that environmental cues during fetal development could permanently alter the functions of the developing fetus and affect adult renal function, which is termed "fetal programming". About 80%-90% of the human incidence of IUGR is due to impaired nutrient perfusion through the placenta, leading to low birth weight in offspring as well as altered organ development, including reduced nephron number and impaired renal function.[16] Animal studies have proved that maternal nutritional deficiency leads to alterations in cell turnover and gene expression in the metanephros of the offspring, which is associated with a deficit in the final nephron number.[17]

Clinically, 1%-2% of women have significant malformation of the uterus, such as didelphic uterus or bicornuate uterus. It should be noticed that many genetic factors that cause bicornuate uterus also affect renal morphogenesis, leading to renal dysplasia and resultant oligohydramnios as well as further increasing the chances of other fetal malformations.[18] Fetal kidneys begin to develop around 5 weeks of gestation in humans, and fetal urination is the major source of amniotic fluid. Fetal anuria is one of the common causes of oligohydramnios. Renal tubular dysgenesis involves incomplete differentiation of proximal tubular nephron segments, often showing fetal anuria and subsequent oligohydramnios.[19,20] In this condition, marked hypotrophy of all nephron segments from the glomerulus to the connecting tubule can be observed under microscopy.[21]

Placental insufficiency

Vascular placental insufficiency is considered to be a common pathogenic factor in human IUGR, resulting in small-for-gestational-age (SGA) asymmetric newborns. It was proved that the glomeruli number was significantly reduced in the asymmetric IUGR rabbit fetuses, probably due to decreased renal vascular supply.[22] The kidney has been reported to be particularly sensitive to the effects of placental insufficiency during the late gestation when it undergoes rapid growth.[23] A number of studies have shown that placental insufficiency affects the embryonic patterning of the kidney.[24-26] Human fetuses with IUGR have increased renal medullary echogenicity that could result from decreased tissue oxygenation.[24] This is of clinical importance because patients with congenital renal malformations have unexplained renal medullary dysplasia,[25] which could result from IUGR-dependent effects on growth and patterning of the kidney medulla. Mice with placental insufficiency associated with genetic loss of Cited1 in the placenta were found to have renal medullary dysplasia caused by decreased oxygenation and increased apoptosis in the renal medulla.[26] This is possibly an evidence showing that placental insufficiency promotes renal medulla dysplasia. In rats, uteroplacental insufficiency induced by uterine vessel ligation was noted to result in nephron deficit in offspring, suggesting that perinatally growth-restricted offspring

may be susceptible to the onset of renal injury and renal insufficiency with aging in the absence of concomitant hypertension.[27]

Gestational diabetes

Congenital malformations occur more frequently in the offspring of diabetic mothers. However, gestational diabetes is known to play a controversial role in the development of urinary tract malformations. *In vivo* and *in vitro* studies on the potential adverse effects of hyperglycemia on kidney development in rats[28] revealed that exposure to hyperglycemia *in utero* can cause nephron deficit, which in turn may have renal consequences after birth. A prospective case control survey conducted in France assessed the role of insulin-requiring gestational diabetes in the development of ureteric malformations after adjustment (an odds ratio: 5.1; 95% confidence interval: 1.1-24.5)[29] and found that gestational diabetes is a risk factor for urinary tract malformations. A previous study[10] reported that infant growth parameters at birth (weight, head circumference, and length), along with maternal risk factors, are associated with changes in fetal growth, including maternal age, race, gestational diabetes, and maternal use of alcohol or tobacco or substance abuse during pregnancy. Furthermore, the study found a significant association between hypospadias and poor intrauterine growth. The growth restriction could be probably due to early gestation because there is a relative involvement of somatic (weight and length) and brain growth (head circumference). Nevertheless, this study did not find evidence of the association between gestational diabetes and hypospadias. Environmental factors associated with gestational diabetes include exposure to tobacco smoke *in utero*[30] and pregnant women's ability to follow a healthy lifestyle.[31]

Maternal drug exposure

Nowadays, more and more pregnant women are receiving medications due to either complication of pregnancy or maternal diseases that existed prior to pregnancy. Some drugs may cross the placenta barrier, enter the fetal circulation, and alter the development of the kidneys. Fetal exposure to certain medications due to maternal diseases is another cause of urinary tract malformations; for example, abnormalities developed after intrauterine exposure to non-steroid anti-inflammatory drug (NSAIDs) such as indomethacin, ibuprofen, piroxicam, naproxen sodium, and aspirin. Maternal intake of NSAIDs may cause renal tubular dysgenesis (RTD) with incidences as high as 5.5%-8.3%.[19] In addition, the toxic effect of angiotensin-converting enzyme (ACE) inhibitors on the fetus during the second and third trimesters of pregnancy can lead to congenital abnormalities and renal failure. The incidence of RTD after exposure to ACE inhibitors was 10% of all published RTD cases.[32] *In utero* exposure to NSAIDs, ACE inhibitors, and specific angiotensin II receptor type 1 antagonists may affect renal structure and produce renal congenital abnormalities, including cystic dysplasia, tubular cystic dysplasia, tubular dysgenesis, and reduced nephron number.[33]

Other drugs may also cause fetal urinary tract malformations. It was reported that sons of women exposed to diethylstilbestrol *in utero* in a cohort of women with fertility problems had 21 times increased hypospadias risk, when compared with the control.[34] Adriamycin is an anthracycline antibiotic produced by the fungus *Streptomyces peucetius*, and an adriamycin rat model has been established for different organ anomalies, including urinary tract malformations such as congenital obstructive uropathy. A previous study[35] reported that maternal exposure to adriamycin resulted in urinary tract anomalies. The higher frequency occurred as the dose of adriamycin was increased (1.5 mg/kg of adriamycin per day yielded the highest number of hydronephrotic viable fetuses in rats).

Maternal exposure to environmental pesticides

Pregnant women's exposure to pesticides is unavoidable in agricultural countries. The occupational exposure of pregnant women to pesticides has been reported to result in placental insufficiency by reducing the synthesis of progesterone, lactogen, estriol as well as changes of placental tissue.[36] Studies[37-41] on the association between environmental pesticides and urinary tract malformations have focused on neonatal hypospadias. Hypospadias is a common congenital malformation of male urinary genitalia, and most of the cases have mixed etiology of monogenic and multifactorial forms, implicating both genes and environmental factors. In a number of developing countries, the use of pesticides is unavoidable. The cause-result relation between maternal exposure of pesticide and urinary tract malformation is contradictory. Being involved in agricultural activities, which increases the chance of being exposed to pesticides, seems to increase the risk of hypospadias.[38] Another study[39] has also reported that the prevalence of hypospadias seems to be higher in areas of intensive pesticides use or in agricultural areas. However, other studies[40,41] have found that both paternal exposure to pesticides before pregnancy and maternal occupational exposure to pesticides do not appear to be associated with hypospadias. Maternal exposure to water disinfection byproducts has been suggested to increase hypospadias risk, but most studies have provided little evidence for this association.[42,43]

Natural/socioeconomic factors and urinary malformations

Ethic factors

The relationship between oligohydramnios and urinary tract malformations has been discussed earlier. Interestingly, one retrospective population-based study had focused on the influence of season on oligohydramnios, and two distinct ethic groups (Jewish *vs.* Bedouin) living in the same area sharing the same level of healthcare services were compared.[44] It was concluded that oligohydramnios is significantly more common during the summer months than the rest of the seasons of the year, and Bedouin ethnicity was noted as an independent risk factor for oligohydramnios. Although the study did not report the incidence of urinary tract malformations based on its close association with oligohydramnios, it was reasonable to deduce that the congenital malformations including urinary tract malformation occurred more frequently in summer season and in Bedouin population.

There are countries with a comparatively high rate of consanguinity marriage in the world due to social reason or ethic traditions. It has been reported that there is an increased incidence of renal tubular dysgenesis in Galilee, which is considered to be associated with high consanguinity among parents.[19] The prevalence of lower urinary tract obstruction has been found to be significantly associated with the maternal ethnic group and deprivation, and is highest in the most deprived quintile.[45]

Environmental anoxia may cause glomeruli malformation

An animal study[46] demonstrated that renal development at birth in the mouse was similar to that of the mid-trimester human fetus when nephrogenesis remains incomplete. After systemic exposure of anoxia, the function of proximal tubular mitochondria was markedly impaired;[47] this probably caused progressive tubular destruction and widespread formation of atubular glomeruli.[48] A fetal lamb model of urinary tract obstruction also revealed that within 48 hours after urinary tract obstruction, ampullae in the nephrogenic zone dilated.[49] This dilatation distorted the ampullae, inhibiting their normal division, effectively preventing nephrogenesis, causing no formation of nephrons, and, hence, resulting in renal hypoplasia or aplasia.

In utero tobacco or alcohol exposure

Smoking is common in both developing and developed countries, and is associated with certain socioeconomic factors such as nationality, single *vs.* non-single, and status of employment. Smoking is persistently the leading cause of IUGR in developed countries.[50] During pregnancy, smoking rates were higher in young women who lived in single households, were unemployed and white.[51] There was a significant correlation between IUGR infants and placental insufficiency and maternal smoking, and the SGA rate was very high in women who smoked excessively.[52] In Canada, higher odds of preterm birth and SGA were noted to be associated with socioeconomic factors such as lower average income, lower level of education, and high alcohol intake.[53] Urinary tract malformations are more common in fetuses of mothers with high alcohol intake[54] and diabetes mellitus.[55]

Epidemiologic studies[56,57] have reported that pregnant women are more likely to consume alcohol in acute doses rather than in a chronic capacity. Fetal growth restriction has previously been demonstrated in animal models of prenatal ethanol exposure and in human patients with fetal alcohol syndrome.[58-60] However, the mechanism through which alcohol disrupts renal development is not very clear. It has previously been identified that altered ureteric branching morphogenesis is correlated with the changes in the levels of expression of genes critically involved in kidney development.[61] It has been reported that prenatal alcohol exposure impairs kidney development, resulting in reduced nephron number.[62] The underlying mechanism might be that the ethanol-induced inhibition of ureteric branching morphogenesis and glomerular development in the cultured rat kidney could have been ameliorated by co-culture with exogenous RA. A study on the effects of acute ethanol exposure during pregnancy on nephron endowment and renal function in offspring[63] showed that at one month of age, the nephron number was 15% and 10% respectively, in ethanol-exposed males and females, when compared with the controls, possibly due to inhibited ureteric branching morphogenesis. Prenatal ethanol exposure is known to influence the activity of the hypothalamic-pituitary-adrenal axis, resulting in elevated maternal glucocorticoid levels.[64] Thus, it is plausible to suggest that the above-mentioned findings may be mediated at least in part by the actions of glucocorticoids. In addition, fetal ethanol exposure during the latter half of gestation has been reported to result in 11% reduction in nephron endowment without affecting the overall growth of the kidney, fetus, or the expression of key genes involved in renal development or function.[65]

Assisted reproductive technology (ART)

Assisted reproductive technologies (ARTs) usually involve hormonal stimulation. Studies[40,66] have shown that ARTs increase the risk of hypospadias. Furthermore, ART has been reported to be associated

Table. Environmental factors and the related perinatal diseases and type of urinary malformations

Environmental factors	Perinatal diseases	Kidney/urinary malformations
Environmental contaminants[12]	Environmental thyroid dysfunction	Renal dysplasia
Environmental iodine deficiency[14]	Thyroid dysfunction	Renal dysplasia
	Low birth weight (LBW)	
Maternal uterus malformation[18]	LBW	Renal dysplasia
	Intrauterine growth retardation (IUGR)	Renal tubular dysgenesis
Placental insufficiency[22-26]	IUGR/LBW	Decreased glomerular number of newborns
		Renal medulla dysplasia
Maternal drug exposure		
Non-steroid anti-inflammatory drug[19,33]		Renal tubular dysgenesis
Angiotensin-converting enzyme inhibitors[32]		Congenital abnormalities and renal failure
Aangiotensin II receptor type 1 antagonists[33]		Cystic dysplasia
		Tubular cystic dysplasia
		Tubular dysgenesis
		Reduced nephron number
Diethylstilbestrol[34]		Hypospadias
Adriamycin[35]		Congenital obstructive uropathy
Environmental pesticides[36-43]	Placental insufficiency	Hypospadias
Summer season[44]	Oligohydramnios	Urinary tract malformation
Bedouin ethnicity[44]	Oligohydramnios	Urinary tract malformation
Social reason or ethic traditions[19]	Consanguinity marriage	Renal tubular dysgenesis
	Maternal ethnic group and deprivation	Lower urinary tract obstruction
Environmental anoxia[47-49]		Renal hypoplasia or aplasia
In utero tobacco or alcohol exposure[50-55]	IUGR	Various urinary tract malformations
	Placental insufficiency	
Assisted reproductive technologies[68,69]	Genomic imprinting disorders	Hypospadias

with genomic imprinting disorders,[67] which could be another mechanism to increase hypospadias in ART. Vottero et al[68] reported that alterations in the methylation pattern of the androgen receptor gene leads to the abnormal expression of the gene in the foreskin tissue from hypospadias children, which may contribute to the development of hypospadias. With respect to ART, hypospadias appears to occur more frequently after microinsemination than after conventional IVF. Furthermore, with regard to microinsemination, the rate of hypospadias seems to be higher when epididymal or testicular sperms are used; when compared with ejaculated sperms,[69] it may be due to the fact that couples undergoing microinsemination usually suffer from severe male infertility, which is associated with hypospadias.

Human evolution involved exposure to physically demanding environment where infection, thermal stress, periods of food deprivation, and requirement to be physically active predominated. The development of the kidneys and other organs of the urinary tract also follows the natural rule of gene-environment-lifestyle interaction. The environmental factors mentioned in this review, which may be associated with urinary malformations, are summarized in Table. Urinary malformations also have a genetic basis[70] and may be inherited in a Mendelian manner, especially in multiorgan syndromes involving malformations of the renal system.[71,72] Over 30 specific genes have been identified in the development of the mammalian kidney and urinary tract.[73]

Conclusions

This review addressed the environmental factors related to urinary malformations, not genetic factors. It is important to understand the association of environmental factors with the development of the renal system and urinary malformation.

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