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REVIEW ARTICLE

Potential facet for prenatal arsenic exposure paradigm: linking endocrine disruption and epigenetics

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Abstract

Environmental exposure to toxicants/heavy metals during critical periods of development can influence changes in embryo and germline of the offspring; and later on affect the disease susceptibility in adults. Exposures to toxic metals or endocrine disruptors are particularly harmful during fetal development. Arsenic, a well-known toxic metalloid and reproductive toxicant is one the major concern because of its adverse and delayed health effects. Considering the complex and numerous adverse health effects of prenatal arsenic exposure, it is very difficult to identify the one single mechanism for arsenic-induced toxicity. This is further complicated due to biphasic response reported where arsenic has very different effects at low and high doses particularly during early life exposure scenario. In this review, we are focusing on prenatal arsenic exposure and its lifelong adverse effects, and their association with endocrine disruption and epigenetic changes. We provide evidence that developmental arsenic exposure alters the functional fetal epigenome in a tissue-specific manner by alterations in DNA methylation patterns, histone modifications and changes in micro RNA. Arsenic as an endocrine disruptor also affects the reproductive potential of the organism. These adverse effects of arsenic could manifest directly through classical hormone imprinting or through irreversible epigenetic modulation. Thus, understanding the association of epigenetic changes and endocrine disruption by prenatal arsenic exposure may help unravel the crucial mechanism for the development of disease later in life.

Keywords Arsenic · Prenatal exposure · Epigenetics · Endocrine disruption · Fetal reprogramming

Introduction

Environmental factors such as heavy metals, dietary macro and micro-nutrients, xenochemicals and endocrine disruptors are known to affect human health. It was established early in the last century that polluting chemical compounds such as pesticides and heavy metals had multifaceted effects on the health and wellbeing of animals and humans. The first comprehensive report on this phenomenon was from Silent Spring by Rachel Carson [21]. The book explored various ill effects of organic pesticides, herbicides and other persistent organic pollutants (POPs) in ecological niches, creating a huge public sensation. Nonetheless, the observations opened up a window for scientific community to explore the side effects of organic pesticides. Several evidences suggested serious side effects such as cancer of various organs, metabolic disorders and endocrine disruption through estrogen or gestagen mimicking compounds. Among this class of compounds, perhaps the most studied endocrine disrupting chemical is BPA, which acted as a xenoestrogen, and disrupted the various cellular signalling pathways associated

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with estrogen signalling in the responsive tissues. Previously only estrogen mimetic compounds were the focus of scientific research, but recent experimental evidences link a wide array of environmental pollutants including heavy metals (e.g. cadmium and lead) and metalloid (arsenic) contaminants with endocrine disruption. These compounds act upon the endocrine system either directly or indirectly in synergy with other EDCs. Toxic effects of heavy metals have been proven to be a major threat and there are several health risks associated with them [65, 124]. Among the heavy metals, arsenic is the twentieth most abundant element on earth and its inorganic forms are lethal to the living creatures at moderately high concentrations. Arsenic is also known as a protoplasmic poison [52] and teratogen [32, 41]. Inorganic Arsenic is classified as a group-1 human carcinogen by the International Agency for Research on Cancer (IARC) and its association have been found with several types of cancer [27, 31, 43]. Several non-carcinogenic effects, including cardiovascular disease [126], hypertension [1] and diabetes [138, 139] have also been observed in chronic exposure victims. Arsenic is also known to cross the blood-placenta barrier and hence is responsible for adverse birth and developmental outcomes after prenatal exposure [3, 33, 95, 113, 133].

At low doses, arsenic can disrupt the hormonal homeostasis by direct or indirect interactions and cause reproductive toxicity thus, it can also function as an endocrine disruptor [13, 14, 80]. The body of scientific literature regarding this phenomenon is constantly growing, but the existing research shows that arsenic acts on gonadal, adrenal and thyroid endocrine systems, which are vital for development and metabolic function. Most studies focus on the adult exposure aspect when observing endocrine disrupting properties of arsenic but an emerging body of scientific literature suggests that arsenic can also cause endocrine disruption during gestational exposure. Although, it has been well established that arsenic acts as a transplacental carcinogen [135] or co-carcinogen along with environmental carcinogenic agent i.e. UV-radiation [62], there are only a handful of reports on gestational or developmental endocrine disrupting properties of arsenic.

The environmental exposure during critical periods of development can influence development of the offspring and disease susceptibility later on in adults. This aspect has been integrated in developmental origins of health and disease (DOHaD) hypothesis [10, 47]. The classical example of the unfortunate Dutch famine suggested that maternal nutrient stress during gestation influenced the disease susceptibility in adulthood [94]. Embryonic environmental exposure, endocrine disruptors and nutrition influence the phenotype of F1 generation. Prenatal exposure to environmental insults (heavy metals, diet, xenochemicals, endorcrine disruptor) can modify the epigenetic regulation of the genome and hence can change the response of organism towards the adaptation in that particular environment. Thus, a single genotype to produce a broad range of adult phenotypes, as a consequence of the developmental plasticity occurs when environmental influences affect cellular pathways during gestation. The paradigm of adult-onset disease following prenatal exposure is rooted in the process of developmental plasticity. Developmental perturbations due to prenatal exposure of arsenic may lead to severe diseases [145]. Inorganic arsenic can pass the placental barrier and alter the different epigenetic marks in the foetus and further can increase the chances of early onset of disease [67]. Alteration in the maternal environment could adversely affect the functionality of epigenetic regulators which later on increase the disease susceptibility in adults [9]. Cellular memory modules play an important role in the reprogramming of genetic imprint and any amendment in this process leads to disruption of various signalling pathways and lead to disease conditions [36]. In the light of the above mentioned studies, present review is an attempt to summarize the role of prenatal arsenic exposure and its effect on alteration of epigenetic machinery or disruption of the endocrine system and its relation to adult onset diseases.

Adverse effects of prenatal exposure to arsenic

Both arsenic and its methylated metabolites can cross the blood-placenta barrier and thus prenatal arsenic exposure can lead to impaired fetal growth, fetal loss during pregnancy, or even increased post-birth infant mortality (reviewed in [102]). Arsenic is considered as reproductive toxicant in animals since early 90's when low level arsenate exposure were found to cause various developmental anomalies in chick embryos [101]. The teratogenic effects of arsenic were explained by various groups in late 90's [12, 50, 79]. These studies showed various developmental impairment, congenital malformation and adverse reproductive outcomes after prenatal exposure to arsenic.

Numerous epidemiological studies suggested that gestational arsenic exposure lead to significant increase in mortality and several adverse health effects [36, 37, 113, 105, 108] Various population cohort studies suggest prenatal arsenic associated diseases include disruption of immune system [38–40, 77]; heart disease [41, 118]; lung disease [42,120]; metabolic related disease [43] and nervous system related diseases [44–49, 97, 128] These adverse effects of prenatal arsenic exposure suggested that maternal/fetal environment is involved in the regulation of some transgenerational effects that are translated into disease phenotypes later in life of the offspring. For example, late-onset alterations and tumors in the livers of the F_2 males arose after maternal arsenite exposure

to pregnant mice [50]. Studies both in animal as well as population cohorts suggest that male infertility occurred after prenatal arsenic exposure [51–54]. Several reports suggest that the maternal exposure to endocrine disrupting chemicals during gestation also alter the growth and development of foetus [15, 55, 56, 83]. Thus, it would be interesting to delineate the associations of arsenic as an endocrine disruptor and epigenetic regulator after in utero exposure.

In utero arsenic exposure has long-term adverse effects on human health (supported by both animal and human population associations study). Detrimental effects of developmental arsenic exposure have been found in lower organisms e.g. chick [57] and in killfish—*Fundulus heteroclitus* [58] to higher animal model and humans. Various studies in different model systems suggested that there is an association of alteration in the gene expression and adverse effects i.e. reduced growth, placental angiogenesis, early onset of puberty, and deficiencies in cognitive development, early onset of atherosclerosis and learning and memory deficit later in life (Table 1). Prenatal arsenic reduced growth of the embryo by increasing both insulin-like growth factors (*IGF-1* and *IGF-1R*) levels in skeletal muscle in Killifish—*F. heteroclitus* [58]. Placental angiogenesis pathway is linked to arsenic induced reduced birth weight [60]. Correlation of maternal exposure to As during gestational period with early onset of puberty in offspring females has been shown by altered mRNA expression of signalling genes [84] (Table 1). In utero exposure to arsenite altered development of the mammary gland by increased expression of the ERα transcripts [96]. Altered GR signaling following gestation arsenic exposure is linked to induce glitch in cognitive development [18, 86]. Transplacental arsenic exposure alters transcriptome of liver and about 16% of the differential expressed genes have active SREBP1 (3 sterol regulatory element binding protein isoforms) which regulates lipid homeostasis in vertebrates [119]. These amendments in developmental programming of liver functions might be enough to induce pro-inflammatory response later in life and may contribute to early onset of atherosclerosis. Further, gestational arsenic exposure mimicked stress condition in liver which can later develop liver disease in mice [92].

Adult hippocampal neurogenesis and related gene expression during development had shown in arsenic exposed animals [84, 127, 143]. Arsenic targets the central nitrergic system, decreased the nitric oxide markers and altered brain structure [110]. Differential expression of behaviour and neurobiological markers with prolonged adverse effects has been shown in mice exposed to low level of arsenic [84]. Thus, differential gene expression and adverse health effects after prenatal exposure is associated (Table 1).

Arsenic and endocrine disruption

Due to its worldwide distribution and carcinogenic toxicity, arsenic is considered as a global health threat. A wide range of pathological symptoms has been defined for chronic arsenic exposure in human populations from the endemic areas. The symptoms of chronic exposure to arsenic in drinking water include the progression of various malignant and non-malignant skin lesions [66, 98]; peripheral neuropathy [40, 70] and cancers of liver, lung and urinary bladder [81, 121, 137, 138]. It has also been established that arsenic acts to attenuate the immune system following chronic exposure, rendering the individual susceptible towards pathogenic invasion [39, 90, 107]. Arsenic induced toxicity have been very well documented and reviewed in animal systems by various research groups across the globe, resulting in strict quality control measures by authorities, which limited the maximum tolerable level of inorganic arsenic in drinking water to 10 parts per billion (10 µg/L) in the developed countries. However, in India, the maximum tolerable limit of arsenic in drinking water is 50 parts per billion (50 µg/L). Although the advent of advance water purification systems and strict regulatory measures have curbed the exposure levels significantly, emerging evidence suggests that inorganic arsenic exposure in very low doses may induce harmful effects on mammalian endocrine systems. The reports published by various groups on the role of Arsenic as an endocrine disruptor after gestational exposure of arsenic are listed in Tables 2 and 3.

Arsenic toxicity on gonadal endocrine system

Gonadal endocrine system is an important player in regulating the reproductive behavior of living organisms through regulating gonadal hormones by Hypothalamus–pituitary–Gonadal (HPG) axis [57]. Hypothalamic–pituitary–ovarian (HPO) axis in females and hypothalamic–pituitary–testicular (HPTT) in males regulate gonadal gametogenesis [117]. Accumulation and inhibitory effect of arsenic in the gonadal glands has been reported in animal model [142]. Further, arsenic might interact with the hormone receptor, and induces inhibitory effects on gametogenesis in both sexes.

Despite all of these evidences, there are only a handful of studies that indicate gestational endocrine disruption of gonadal endocrine system by arsenic (Table 2). These changes are shown to be perceived during the exposure period but established later in life. The effects of gestational exposure to arsenic in both male and female gonadal endocrine system is diverse while some researchers demonstrate proliferative lesions of ovary, oviduct hyperplasia in offspring females and testicular lesions and interstitial cell tumors in male offspring [125], others have reported early

Table 1 Compilation of the studies of differential expression of genes after prenatal arsenic exposure and its association with the onset disorders at different doses in both human population cohort and animal model

S. no.	Model/sample	Arsenic dose	Alteration in gene expression	Associations with onset disorders	References
1	New Hampshire Cohort (cord blood samples)	0.5–5 µg/L	Alteration in Fetal immune repertoire; Over expression of IL1 β	Immune system	[90]
2	Flanders, Belgium (cord blood)	Very lower	Increased expression of sFLT1 (soluble fms-like tyrosine kinase-1) gene	Reduced Birth weight	[55]
3	Bangladesh Children	< 1–510 µg/L	Enrichment of arsenic toxicity related genes i.e. ArsB and Asrc genes	Alteration in the gut microbiota	[35]
4	Thailand Population (cord blood samples)	503.5 µg/L	Activation of Inflammation and NF-kB signalling	Altered Immune System	[45]
5	C57BL/6 mice (brain tissue)	50 ppb	Alternation of Rest and Rcor1 (CoREST) gene expression in a sex and time dependent manner	Impaired development of brain	[130]
6	C57BL/6J mice Embryonic mouse brain	50 ppb	Higher levels of GSH/GSSH in females Age and sex specific alternations in GR signaling	Learning and memory deficit	[4]
7	C57BL/6J mice (Placenta and Fetal Brain)	50 ppb	Decreased mRNA levels of GR and the 11β-HSD1 and increase expression of 11β-HSD2	Impaired learning and memory	[18]
8	C57BL/6J mice (dentate gyrus tissue)	50 ppb	Upregulation of genes involved in neurogenesis, proliferation and differentiation	Deficits in learning and memory	[127]
9	C57BL/6 mice (Hippocampus)	50 ppb	Reduced expression of MAPK/ERK genes	Learning deficits	[86]
10	C57BL/6 mice (brain and serum)	50 ppb	Elevated level of serum corticosterone levels, dorsal hippocampal serotonin 5HT 1A receptor binding and reduced dorsal hippocampal serotonin 5HT 1A receptor binding	Alters neuroendocrine markers and long-lasting adverse effects on Behavior	[84]
11	C3H mice	85 ppm	Upregulation of (CTNNB1) and interleukin-1 receptor genes	Increased Liver tumors in F2 males	[93]
12	Female ICR mice	15 mg/L	Increase in mRNA expression levels of kiss-1, GnRH1, Oct2 and Ttf1	Early onset of puberty in females	[78]
13	Wistar rats	0, 10, 50, and 100 mg/L	Overexpression of Neurotransmitter metabolic enzymes levels	neurobehavioral, learning and memory changes	[143]
14	Wistar rats	3 ppm	Upregulation of nNOS-mRNA level while all Nitregenic markers downregulated	Altered brain structural organization	[110]
15	Sprague-Dawley rats	5 g/kg	Over-expression of estrogen receptor-alpha (ERα)	Defective mammary gland development, breast cancer	[96]
16	Apolipoprotein E-knockout mice (Liver tissue)	49 ppm	Hepatictranscriptome analyzed hsp70 upregulated and active SREBP1	Diabetes mellitus and Rheumatoid arthritis	[119]
17	BALB/c, C57BL/6, and C3H/HeARC mice (lung tissue)	100 µg/L	Up-regulation of genes involved in mucus production (Clca3, Muc5b, Scgb3a1), innate immunity (Reg3γ, Tff2, Dynlrb2, Lplunc1), and lung morphogenesis (Sox2).	Impaired respiratory health	[107]

Table 1 (continued)

S. no.	Model/sample	Arsenic dose	Alteration in gene expression	Associations with onset disorders	References
18	Killifish Embryos	0, 50, 200, 800 ppb	Increased levels of skeletal muscle IGF-1 and IGF-1R	Reduction in growth during development	[122]
19	Zebrafish Embryos	0, 50, 500 ppb With or without Zn	Altered Expression of Oxidative stress and Insulin Production (Zip1, Znt2, Nrf2 etc)	Harmful effect on the development and may increase the risk for developing chronic diseases like diabetes.	[11]

onset of puberty in the female offspring as judged by vaginal opening time and estradiol levels [78]. Elevated gonadotrophin-releasing hormone (GnRH), FSH and testosterone in female offspring has been reported only once [16] (Table 2).

Effects of arsenic on estrogen and glucocorticoid signaling

Among other endocrine disrupting effects, arsenic exposure modulates the estrogen signaling pathway in a number of tissues (Table 3). Reproduction and development in males and females are regulated by endogenous estrogens [75]. The action of estrogens are activated by binding to nuclear receptors i.e. estrogen receptor alpha [54] and beta [72] as well as the membrane-bound receptor, GPR30 [20]. Kumar et al. explored the binding of arsenic trioxide to 17-β-estradiol in cancerous epithelial cell line of the breast (MCF-7) [73]. The binding titrated the natural activity of estrogen in these cells and promoted cell survival, proliferation and migration. In other words, this report demonstrated the estrogenic properties of arsenic trioxide which may explain numerous other disorders associated with low level exposure to arsenic. However, the studies in this area are often contradictory e.g. one report demonstrated the ability of arsenic and cadmium to bind the membrane bound estrogen receptor as well as G-protein coupled estrogen receptors in human lung adenocarcinoma cell line [61]. In their study, this group observed that exposure to environmentally relevant concentration of arsenic and cadmium resulted in increased proliferation of these cells like the exposure of these cells to physiologically relevant concentrations of 17-β-estradiol. In contrast, in the MCF-7 cells, arsenic at low concentrations (0.25–1 μM) inhibited cell proliferation [28]. The findings in these reports suggest that chronic exposure to low levels of arsenic can disrupt the estrogen signalling via interacting with estrogen receptor as well as the hormone itself. In the uterus of rat, disruption of circulating levels of gonadotropins and estradiol; degeneration of luminal epithelial, stromal and myometrial cells; and downregulation of the downstream components of the estrogen signaling pathway were found after exposure of high dose (4 ppm arsenic) of arsenic [22] Although, there are evidences of arsenic mediated disruption of estrogen signalling in vitro and in adult exposure models, there are only a handful of reports on the prenatal exposure to arsenic and its effects on estrogen signaling. In hepatocellular carcinoma of mice exposed to prenatal arsenic increased mRNA levels of ER-α and cyclin D1 has been observed (42.5 and 85 ppm of arsenic) [134]. Further, study by the same group targeting global alteration of gene expression profiles by gestational arsenic exposure suggested a case of "liver feminization" in in utero arsenic exposed male C3H mice, which showed upregulation of estrogen receptor mediated signaling in their liver and consequently, higher incidence of hepatocellular carcinoma [82]. Parodi

Table 2 Arsenic as an endocrine disputer after gestation exposure at different doses and duration

As dose	Duration	Experimental subjects	Toxicity	Target organ	References
0.15–15 ppm As III	Gestational day 0–21	Female ICR mice	AsIII induced early onset of puberty in female offspring	–	[78]
5 and 50 ppm $NaAsO_2$	Gestational + adult	Female rats	AsIII induced compromised cyclicity, decreased estradiol, increased follicle-stimulating hormone (FSH), less preovulatory follicles and presence of ovarian cysts after lactation. Female offspring showed elevated GnRH, testosterone and FSH	Ovary	[16]
12.5 and 25 ppm MMA(III)	Gestational GD8–GD18	Pregnant female CD1 mice	Increased frequency of Proliferative lesions of ovary, adrenal cortex, oviduct hyperplasia in offspring females Testicular lesions, interstitial cell tumors in male offspring	–	[125]

et al., suggested early onset of mammary gland development, early vaginal opening (collectively, early onset of puberty) in rats, potentially increasing susceptibility of the exposed animals (5 µg As/kg bodyweight) towards breast cancer [96]. Waalkes et al. suggested that transplacental exposure to arsenic led to exacerbated postnatal urogenital carcinogenesis induced by diethylstilbestrol treatment [136] (Table 3).

Another endocrine pathway which is particularly vulnerable to arsenic toxicity, is the glucocorticoid signalling pathway (GR signaling—Table 3). Glucocorticoids are steroid hormones secreted from the adrenal gland in response to stress. Once in circulation, the glucocorticoids can exert a wide array of tissue specific effects. They are traditionally seen as anti-inflammatory molecules, but emerging evidence suggests more towards a dual mode of action of glucocorticoids [30]. An aberrant expression of glucocorticoid receptor or any disruption in GR signalling may get translated into a wide range of health effects including impaired reproduction [141], stress response [89] and adipogenesis and the induction of central obesity [76]. It was reported by several groups that arsenic modulates GR function both in vitro and in vivo. Moderate dose of arsenic has been shown to perturb the GR signalling in in vitro studies leading to a complex dose–response relationship. An interesting study illustrated that lower doses of arsenic (< 1 µM) cause stimulation of GR and tyrosine aminotransferase (TAT) genes, whereas higher concentrations (1–3 µM) cause repression across GRs under human, mouse and rat promoter control, suggesting a role of arsenic interference in the DNA binding domain of these receptors [13]. This study, conducted on the EDR3 cell line, also inferred that arsenic may also modulate the intracellular progesterone, mineralocorticoid and aldosterone receptor, as they all share a common/similar DNA binding domain. Thus, the exposure to arsenic in critical developmental periods may induce a hormonal imprinting, which persists throughout adult life. Several studies indicated the modulation of hormonal imprinting by arsenic, e.g. altered GR signaling following gestational arsenic exposure have been observed throughout adulthood [18] and in another study, arsenic exposure has been shown to induce glitches in cognitive development via transcriptional alteration in MAPK/ERK pathway [86]. Further, additional research work is required to explore estrogen receptor/signaling and its interaction to arsenic.

Developmental arsenic exposure and epigenetic modulations

Considering the complex and numerous adverse health effects of prenatal arsenic exposure, it is very difficult to identify the one single mechanism for the arsenic induced toxicity. Mechanisms pertaining to arsenic toxicity have been reviewed by many authors [60, 76, 115, 116, 123]. The mechanism of arsenic induced carcinogenesis has been the most intensely studied facet of arsenic toxicity, in which several molecular mechanisms are predicted to play a role. There are several recent reviews which suggested the epigenetic mechanisms for arsenic induced carcinogenesis after chronic or long term exposure [5, 23, 25, 59, 112, 140] but little is known about the gestational exposure. The interplay between genes and environment modulate disease susceptibility through epigenetic reprogramming at early development which could be possible cause of origins of adult onset disease. A heritable change (transgenerationally inheritable) in gene expressions without alteration in the DNA sequence is defined as epigenetics [6, 106]. Disease development is well characterized by disruption of the epigenome [34, 48]. There is a complex interplay between one's genetic architecture and epigenetic marks "imprinted" by endogenous or exogenous factors which can be responsible for the disease susceptibility [64]. Regulation of the "epigenome" occurs by intertwined mechanisms of small-interfering RNAs, DNA

Table 3 Arsenic as an endocrine disrupter and associated altered signalling pathways

Arsenic dose	Model system	Endocrine pathway(s) affected	References
Arsenic trioxide (10nM)	MCF-7 (breast epithelial carcinoma cell line)	Direct binding interaction with 17-β estradiol resulted in titration of its effect in vitro	[73]
Sodium arsenite (1–200 μM)	MCF-7 (breast epithelial carcinoma cell line), T47D cell line (human breast tumor cells) MDA-MB-231(human breast adenocarcinoma; only express ERβ)	NaAsO2 dose-dependently increased viability of hormone-dependent breast cancer MCF-7 and T47D cells expressing both ERα and ERβ but not hormone-independent MDA-MB-231 cells expressing ERβ. The study suggested that arsenite induces rapid nongenomic signal transduction through estrogen dependent ERK1/2 pathway which may contribute to its proliferative effect on hormone-dependent breast cancer cells	[91]
Sodium arsenite (100 nM)	NCl-H1793 (human non-small cell carcinoma cell line)	Arsenic at the specified concentration, increased cellular proliferation through the activation of MAPK/ERK signalling by binding to membrane bound GPER	[61]
Arsenic trioxide (5–20 nM)	MCF-7 (breast epithelial carcinoma cell line), T47D cell line (human breast tumor cells)	higher doses of arsenic trioxide (ATO) dramatically reduced the survival of these two breast cancer cell lines while lower doses of ATO significantly inhibited the expression of ERα, but did not affect ERβ expression. The ERα expression is totally restored when ATO is absent for 24 h	[24]
Arsenic trioxide (ATO) (0.1–10 μM)	Ishikawa and ECC-1 endometrial cancer cell line	ATO inhibited ER- mRNA and protein expression in a dose-dependent manner in both the Ishikawa and ECC-1 endometrial cancer cell lines. Treatment with ATO resulted in rapid phosphorylation of the p42/p44 MAPK which could be abolished by addition of the MAPK inhibitor, U0126	[7]
Arsenic trioxide (2μM)	MCF-7 (breast epithelial carcinoma cell line)	Arsenic trioxide at the specified dose showed antiestrogenic property, inhibiting proliferation of cells	[28]
Sodium arsenite (4 μg/ml for 28 days)	Adult wistar albino female rats	The results indicated that arsenic disrupted the circulating levels of gonadotropins and estradiol, leading to degeneration of luminal epithelial, stromal and myometrial cells of the rat uterus and downregulated the downstream components of the estrogen signaling pathway	[22]
Sodium arsenite (42.5 and 85 ppm; gestational exposure)	Pregnant C3H mice	The results suggested increased mRNA levels of ER-α and cyclin D1 in hepatocellular carcinoma of male mice that were exposed prenatally to arsenic. Indicating HCC proliferation through estrogenic activity	[134]
Sodium arsenite (5μg/kg bw; intraperitoneal injection; gestational day 12–17)	Pregnant female sprague–Dawley rat	Early onset of puberty in the offspring females, characterized by early vaginal opening, mammary gland development	[96]
85 ppm arsenic in drinking water. Gestational day 8–18	Pregnant female CD1 mice	The results indicated prenatal arsenic exposure aggravated the response toward xenoestrogens (DES) in the development of uterine cancer in female offspring	[136]

Table 3 (continued)

Arsenic dose	Model system	Endocrine pathway(s) affected	References
85 ppm arsenic in drinking water (gestational day 8–18)	Pregnant female C3H mice	Transplacental arsenic exposure at a carcinogenic dose produced aberrant estrogen-linked pulmonary gene expression. ERα activation was specifically associated with arsenic-induced lung adenocarcinoma and adenoma	[114]
Sodium arsenate (50 ppb; from 7 to 10 days prior to mating till birth)	Pregnant c57BL/6j mice	At E14 arsenic exposure significantly decreased expression of both GR and the 11β-HSD protein and mRNA in brain of exposed offspring, while 11β-HSD2 enzyme protein levels were increased but mRNA levels were decreased in the brain. These changes in brain protein continued into the E18 time point, but mRNA levels were no longer significantly altered. Suggesting a role of developmental programming of the GR system	[18]
Sodium arsenate (50 ppb; from 7 to 10 days prior to mating till birth)	Pregnant c57BL/6j mice	Decreased GR and MR receptor levels in the hippocampus of prenatally exposed offspring. This led to deregulation of MAPk/ERK signalling pathway providing a link between GR deregulation induced by arsenic and learning/memory deficits	[86]
Arsenic (iAS^{3+}) (7.5 ppb for in ovo and 1, 2 or 5μM for in vitro midbrain micromass culture assay)	*In silico* approach to identify novel pathways regulated by moderate exposure to arsenic. Chick embryo model was used to evaluate the effect of GR blocking and further studied in vitro midbrain micromass culture	The glucocorticoid receptor pathway predicted to be a key mediator of multiple metal-induced birth defects. In the chick embryo model, structural malformations induced by inorganic arsenic prevented when signaling of the glucocorticoid receptor pathway was inhibited. Further, glucocorticoid receptor inhibition demonstrated partial to complete protection from both iAs- and cadmium-induced neurodevelopmental toxicity in vitro	[2]
Sodium arsenate (50 ppb; ad libitum)	C57BL/6j females. Exposed from 7 to 10 days prior to mating till weaning of the pups	Prenatal arsenate exposure produced sex specific effects on the glucocorticoid system. Compared to males, females were resistant to arsenic induced changes in GR, 11β-Hsd-1 and 11β-Hsd-2 protein levels despite observed elevations in Nr3c1 and Hsd11b2 mRNA	[4]

methylation, and histone modifications [26, 38, 64, 88]. These mechanisms cooperatively decide when and where the gene expression is to be silenced or activated. Thus, instead of primary nucleotide sequence of a gene, the regulation of gene expression by epigenetics has greatly expanded our understanding the context of toxicities induced by the environmental factors i.e. arsenic associated toxicities.

Role of DNA methylation in arsenic associated early onset of disease

Altered expression of genes after prenatal arsenic exposure can be regulated by epigenetic mechanisms. Time and again, epigenetic dysfunction particularly differential DNA methylation and its role in arsenic induced toxicity and carcinogenesis has been reviewed [8, 109]. A review on the comparison of genes associated in prenatal arsenic induced toxicity in human population cohort studies, suggested a conserved biological response for arsenic induced toxicity [74]. However, till today, researchers are trying to decipher the sequence of events involved in the prenatal arsenic induced early onset of disease. Prenatal arsenic exposure in human and epigenetic alteration i.e. DNA methylation have been examined for arsenic endemic populations (Table 4). Developmental arsenic exposure affects almost all the organs and is associated with several diseases starting from reduced birth weight to early onset of cardiovascular disease, diabetes and cancer (Table 4). The complex interplay between DNA methylation and functional changes in gene expression in newborn cord blood leucocytes had shown in BEAR Pregnancy Cohort of Mexico [111]. The associations between early exposure of arsenic and DNA methylation suggest interference of arsenic with de novo DNA methylation in Matlab population in Bangladesh [17]. Low dose of Arsenic can also alter the DNA methylation globally [71]. Higher levels of arsenic in mother's urine are correlated with the increase Global DNA hypomethylation in infants cord blood. [100]. In Taiwan cohort, altered DNA methylation at various CpGs associated with low density lipoproteins (LDL) have been identified (cg25189764, cg04986899, cg04903360, cg08198265 and cg10473311) that may help to determine pathological epigenetic mechanisms linked to LDL later in life [67]. In cord blood lymphocytes of gestationally arsenic-exposed newborns had promoter hypomethylation of inflammatory genes [69]. Further, DNA methylation has been altered with exposure dependent manner in cord blood [70]. Newborn proteome analysis after prenatal Arsenic exposure suggested the role of TNF signalling pathway for inter-individual differences [8]. Comparative analysis of Infectious Disease Genes (IDGs) and Exposure Responsive Genes (ERGs), identified genes including TNF and IFNγ (GR-associated genes) which is link to cause infectious disease after gestational As in humans [104]. Further, altered DNA methylation pattern ofplacental tissues suggested placental subpopulations changes is associated with As exposure in the New Hampshire birth cohort [53]. Cardenas et al., 2015 evidenced that in utero exposure to arsenic can alter DNA methylation of artery and placenta tissues [19]. In addition, DNA methylation at promoter region of tumor suppressor gene p16, were positively associated with higher level exposure of arsenic in both maternal and fetal leukocytes [68]. Hypermethylation in the promoter region of p53 increases in infants exposed in utero to arsenic [63]. DNA methylation of extracellular matrix remodeling genes was positively associated with arsenic levels, which in turn might be the cause of predisposing of lung diseases in children [51].

In animal model, in utero exposure to arsenic induces epigenetic change i.e. alteration in DNA methylation [85, 86, 92, 144]. Further, genes involved in neuronal plasticity showed hypomethylation in hippocampus and frontal cortex region of Wistar rats and suggested that memory deficit behaviour is associated with arsenic exposure [85, 86]. Thus, these results suggest that there are tissue-specific effects of As exposure on the fetal epigenome (Table 4). Moreover, the effects of iAs exposure vary across individuals and populations, may be as a result of genotype and/or hormonal factors.

Role of histone modifications and micro RNA in arsenic associated early onset of disease

Studies on mice suggested a link between DNA methylation and impaired effects on several tissues following prenatal arsenic exposure [87, 127]. Gestational arsenic exposure and their association with post translational histone modifications for adverse health effects have shown in Table 5. Embryonic arsenic exposure caused global hypoacetylation at H3K9 and overexpression of Krüppel associated box (KRAB) transcription factors in altered genes in brain [29]. Sex specific alteration in H3K4me3 levels, however, there is no change in the level of H3K9me3 in the brain tissue [129]. Further, enrichment of H3K4me3 levels for genes associated with neuropathy and cancer in brain has been observed in C57BL/6 J after prenatal arsenic exposure [131]. Further, developmental arsenic exposure altered histone deacetyltransferase levels in brain and lead to aberrant cognitive capabilities in a sex dependent manner [132].

In cord blood of an arsenic endemic Mexican population, alterations in the miRNAs expression were found in response to prenatal arsenic exposure [103] (Table 5). Exposure of in utero arsenic changes the developmental trajectory of microRNAs in mouse liver and might cause to early onset of atherosclerosis due to persistent pro-inflammatory state in the liver

Table 4 Studies on alteration in DNA methylation and its association with the onset disorders after prenatal arsenic exposure at different doses in both human population cohort and animal model

S. no.	Model/samples	Arsenic dose	Alteration in DNA methylation	Associations with onset disorders	References
1	C3H mice (liver tissue)	85 ppm	Reduction in methylation occurred globally in GC-rich regions	Liver carcinogenesis	[144]
2	Wistar rats	3 and 36 ppm	Alterations of the methylation pattern of genes involved in neuronal plasticity	Memory deficit	[85]
3	ApoE Knockout Mice	49 ppm	Differential methylation in CpG sites of Hsp70	Impaired liver development, atherosclerosis	[92]
4	New Hampshire Cohort USA (cord-blood)	0.03–100 µg/L	Hypermethylation of CpG islands and Increased proportions of cord-blood CD8+ T lymphocytes	Immune response	[71]
5	Matlab population Cohort Cord blood mononuclear cells	< 1–3640 µg/l	Altered developmental-related pathways;Hypomethylation at CpG sites (PLIN5, LRRC26, RPS6KA) in boys	Cancer	[17]
6	Bangladesh Cohort Leukocyte in cord blood	< 1–510 µg/L	Altered production of leukocyte subpopulation and Increased LINE 1 Methylation	Immune response	[69]
7	Bangladesh populations Maternal and Umbilical Cord Blood Leukocytes	< 1–230 µg/L	Hypermethylation at CpG sites in the promoter region of p16 and LINE-1 in umbilical cord and maternal leukocytes	Cardiovascular diseases, and Cancer	[68]
8	Mexico Populations Cord Blood	< 1–230 µg/l	Higer protein level of genes regulated by TNF	Immune/inflammatory response	[67]
9	Bangladesh Cohort Umbilical artery and Placenta	< 1–510 µg/L	Hypomethylated CpG islands at artery hypermethylation of CpG in placenta	Adverse health effects	[19]
10	Pregnancy Cohort Mexico Newborn cord blood leukocyte	0.456–236 mg/L	CpG methylation within CpG islands within first exon, the 5′ untranslated region	Metabolic disorders	[111]
11	Prenatally exposed children (6–12 years)	104–360 ppb	DNA methylation of extracellular matrix remodeling genes(MMP9, TIMP1 and RAGE genes)	Lung diseases	[51]
12	Maternal infant and Birth cohort (cord blood)	< 1–230 µg/L	DNA methylation at various CpGs associated with LDL	Cardiovascular diseases and diabetes mellitus	[67]
13	South of Thailand (cord blood lymphocytes)	8.38 ± 2.49 µg/L	Hypomethylation of inflammatory genes (COX2, EGR1, and SOCS3)	Inflammation and cancer	[99]
14	Mother-child Bangladesh cohort (peripheral blood mononuclear cells)	< 1–230 µg/L	Methylation of the IGFBP3 promoter	Type2 diabetes, cancer	[46]

[119]. Aberrant programming of neural stem cells (NSCs) function is associated with arsenic-induced deregulation of REST/NRSF and its target microRNAs which might induce glitches in neurogenesis [130]. Thus, iAs-associated miRNA deregulation may cause disease by alter the functional consequences for downstream gene expression.

Table 5 Effect of prenatal Arsenic Exposure on the histone modificationand micro RNA and its association with the onset disorders

S. no.	Model/sample	Arsenic dose	Alteration in Histone modifications and miRNA	Associations with onset disorders	References
1	C57BL/6 mice (brain)	50 ppb	Sex specific alteration in H3K4me3 levels. No Change in H3K9me3	Psychiatric disease	[129]
2	C57Bl6/J mice	100 mg/L	Global Hypo-acetylation at H3K9	Memory and cognitive impairments	[29]
3	C57BL/6J mice(frontal cortex)	50 ppb sodium arsenate	Sex dependent alteration in HDAC levels and Bdnf expression	Cognitive function	[132]
4	C57BL/6 male mice (brain)	50 ppb	Enrichment of H3K4me3 levels for genes associated with neuropathy and cancer in brain	Cancer and neuropathy of brain	[131]
5	Mexico population (human cord blood)	0.456 mg/L	12 miRNAs with increased expression associated with U-tAs	Cancer and diabetes mellitus	[103]

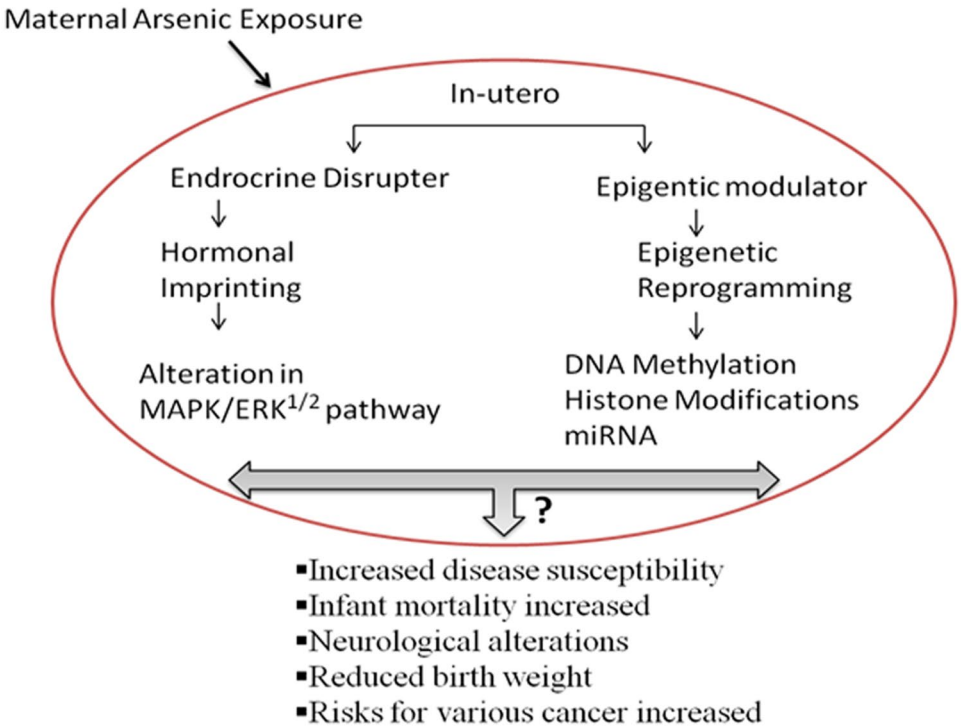

Fig. 1 Hypothesis of occurence of adverse health outcome after prenatal arsenic exposures due to hormonal imprinting or/and epigenetic reprogramming

Looking forward: link between endocrine disruption and epigenetics

Arsenic can induce alteration in epigenome of the foetus which may result into various disease outcomes later in life. Arsenic associated changes in DNA methylation, histone modifications, miRNA has been studied well in both human populations cohort and in animal model as shown in Tables 4 and 5. Majority of human cohort studies are on cord blood cells or leukocytes populations, while majority of animal studies are on brain and liver tissue (Tables 4, 5). However, these changes are not in developmental stage specific manner. Development timings are crucial for the imprinting of epigenetic marks and associated with the hormonal imbalance in the maternal or foetal microenvironment during pregnancy. Adverse effects of prenatal arsenic exposure suggested that maternal/fetal environment is involved in the regulation of some transgenerational effects that are translated into disease phenotypes later in life of the offspring [93]. Arsenic as an endocrine disruptor may modulate the microenvironment of the foetus by alteration in various cell signalling pathways regulated by hormones (estrogens

and glucocorticoids; Tables 2, 3). However, the downstream targets analysis and their regulatory mechanisms are still awaited. Apart from DNA methylation, histone modifications and miRNA (Tables 4, 5), cellular memory modules (PcG and TrxG proteins) could be the master regulators as these proteins are known to memorize the genomic imprints during development [44]. So far, we can suggest that low level arsenic exposure during development leads to change in the microenvironment of the developing foetus (hormonal imbalance), imprinting of the differential marks (hormonal imprinting/genetic imprinting), maintenance of the imprint marks by PcG/TrxG proteins and as a result that maternal the hormonal imbalance may maintain in the offspring, alteration in the cell signalling, alteration in gene/protein expression, their regulation by epigenome which leads to disease in the later life (Fig. 1). In addition, arsenic induced lifelong diseased state may persist because of the predisposition of the hormonal or genetic or epigenetic imprinting which can be identified by development stage specific experiments. Thus, the association of epigenetic changes and endocrine disruption by prenatal arsenic exposure may represent a critical mechanism for the development of disease later in life and need more attention in future.

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