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Use of amniotic fluid for determining pregnancies at risk of preterm birth and for studying diseases of potential environmental etiology

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ABSTRACT

Amniotic fluid (AF) is a biological medium uniquely suited for the study of early exposure of the human fetus to environmental contaminants acquired by the mother before and during pregnancy. Traditional diagnostic applications of AF have focused almost exclusively on the diagnosis of genetic aberrations such as Trisomy-21 and on heritable diseases in high-risk pregnancies. Since more than 50 anthropogenic compounds have been detected in AF, there is considerable potential in utilizing fetal protein biomarkers as indicators of health effects related to prenatal toxic exposure. Here, we focus on preterm birth (PTB) to illustrate opportunities and limitations of using AF as a diagnostic matrix. Representing a pervasive public health challenge worldwide, PTB cannot be managed simply by improving hygiene and broadening access to healthcare. This is illustrated by 15-year increases of PTB in the U.S. from 1989 to 2004. AF is uniquely suited as a matrix for early detection of the association between fetal exposures and PTB due to its fetal origin and the fact that it is sampled from women who are at higher risk of PTB. This critical review shows the occurrence in AF of a number of xenobiotics, including endocrine-disrupting compounds (EDCs), which are known or may reasonably be expected to shorten fetal gestation. It is not yet known whether EDCs, including bisphenol A, phytoestrogens, and polychlorinated biphenyls (PCBs), can affect the expression of proteins considered viable or potential biomarkers for the onset of PTB. As such, the diagnostic value of AF is broad and has not yet been fully explored for prenatal diagnosis of pregnancies at risk from toxic, environmental exposures and for the elucidation of mechanisms underlying important public health challenges including PTB.

1. Introduction

Identifying adverse human health outcomes from exposures to mixtures of anthropogenic chemicals is a recognized challenge deserving more scrutiny (Carlin et al., 2013). Environmental exposures are inherently complex and of great plasticity, varying by individual, life phase, geography, and behavior. Numerous individual and nationwide surveys, including the National Health and Nutrition Examination Survey (NHANES) and the National Children's Study, confirm that women and children in the U.S. are ubiquitously exposed to complex mixtures of persistent and non-persistent environmental contaminants (CDC, 2013), with the relevant exposures occurring prenatally (Barr et al., 2007). Fetal serum, cord blood, and meconium are all appropriate matrices for monitoring fetal environmental exposures (Barr et al., 2007). However, only amniotic fluid (AF) and certain surrogate matrices (*i.e.*, maternal serum, plasma, urine, or placental tissue) can provide information prior to delivery to inform intervention strategies directed at improving perinatal outcomes.

Due to its fetal origin, AF is the matrix of choice for prenatal screening of risk factors of adverse health outcomes and associated molecular predictors. Formation during embryogenesis occurs by way of diffusion of maternal plasma through the fetal membranes and includes transudate through the unkeratinized fetal skin.

Following keratinization of the fetal skin (mid-trimester), AF is a product of fetal urination, tracheal secretions, and intramembranous and transmembranous pathways (Sherer and Langer, 2001). Thus, AF is a principal fetal repository of metabolized environmental toxicants that can be accessed for prenatal assessments throughout gestation (Lozano et al., 2007).

Here, we review the state of science in the evolution of AF diagnosis from monitoring of genetic abnormalities, to elucidating

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Table 1
Natural and xenobiotic contaminants detected in amniotic fluid.

Xenobiotic (summedanalytes)	AF range [ng/mL]	AF median [ng/mL]	Det. freq. (Subjects)	Gestation [weeks]	Collection date	Other matrices	Reference
Inorganic contaminants							
Iodide	1.7–170	8.1	100% (48)	15–20	–	–	Blount et al. (2009)
Nitrate	288–8940	1500	100% (48)	15–20	–	–	Blount et al. (2009)
Perchlorate	0.057–0.71	0.18	100% (48)	15–20	–	–	Blount et al. (2009)
Organic contaminants							
Benzoylecgonine (Cocaine metabolite and topical analgesic)	143–925	909	30% (20)	Birth	–	MU, IU, Me	Casanova et al. (1994)
	ND–152,288	–	9% (32)	–	–	UC	Winecker et al. (1997)
	51–836	277	1% (450)	13–39	1991	MS	Ripple et al. (1992)
Bisphenol A (BPA)	ND–0.75	0.47	80% (20)	T2	–	–	Chen et al. (2011)
	0.36–0.66	0.45	80% (20)	14–21	2010	–	Edlow et al. (2012)
	0.1–0.46	–	10% (20)	33–38	2006	–	Edlow et al. (2012)
	0.5–1.96	0.5	10% (21)	<20	2004	–	Engel (2006)
	ND–5.62	0.26	−(200)	16.3 ± 1.0	1989–1998	MS	Yamada et al. (2002)
	–	0	−(48)	16.2 ± 1.0	1989–1998	MS	Yamada et al. (2002)
Caffeine	–	–	– (–)	16–17	–	–	Graca et al. (2008)
Carbofuranphenol	0.12–0.12	0.12	5% (20)	18 ± 2.6	–	–	Bradman et al. (2003)
Cocaine	–	–	56% (16)[a]	–	–	CB, IU, Mec, MH	Eyler et al. (2005)
	11–24	18	1% (450)	13–39	1991	MS	Ripple et al. (1992)
Cotinine	ND–531	2.2	98% (300)	10–30	1980–1996	–	Jensen et al. (2012)
∑ Cyclodienes (9)	–	0.038	17% (100)	15–20	2006–2007	MS	Luzardo et al. (2009)
Daidzein	0.5–5.52	1.08	68.4% (57)	15–23	1999–2000	–	Foster (2002)
	3.84–17.4	9.52	100% (21)	<20	2004	–	Engel (2006)
p,p'-DDE	0.10–0.63	0.211	28.3% (41)	15–23	–	–	Foster (2000)
	ND–1.67	0.21	25% (70)	14–21	1999–2000	–	Foster (2002)
	ND–0.63	0.24	20.8% (48)	15–23	1999–2000	–	Foster (2002)
2,5-Dichlorophenol	0.37–0.43	0.39	55% (20)	18 ± 2.6	–	–	Bradman et al. (2003)
Diethylphosphate	0.26–0.36	0.31	10% (20)	18 ± 2.6	–	–	Bradman et al. (2003)
Dimethylphosphate	0.30–0.34	0.32	10% (20)	18 ± 2.6	–	–	Bradman et al. (2003)
Dimethylthiophosphate	0.43–0.43	0.43	5% (20)	18 ± 2.6	–	–	Bradman et al. (2003)
D-Xylitol	–	–	– (–)	16–17	–	–	Graca et al. (2008)
Ecgonine methyl ester	40–115	–	30% (20)	Birth	–	MU, IU, Me	Casanova et al. (1994)
	ND–11,879	–	16% (32)	–	–	UC	Winecker et al. (1997)
	11–34	17	1% (450)	13–39	1991	MS	Ripple et al. (1992)
Enterolactone	11.8–112	95.9	100% (21)	<20	2004	–	Engel (2006)
Genistein	0.20–7.88	1.38	100% (21)	<20	2004	–	Engel (2006)
	0.5–4.86	0.94	89.5% (57)	15–23	1999–2000	–	Foster (2002)
α-HCH	0.10–0.26	0.147	14.6% (41)	15–23	–	–	Foster (2000)
	ND–0.26	0.15	8.3% (48)	15–23	1999–2000	–	Foster (2002)
γ-HCH (Lindane)	–	0.003	28% (100)	15–20	2006–2007	MS	Luzardo et al. (2009)
∑ HCH	–	0.017	30% (100)	15–20	2006–2007	MS	Luzardo et al. (2009)
Hexachlorobenzene	–	0.023	66% (100)	15–20	2006–2007	MS	Luzardo et al. (2009)
Monobutyl phthalate (MBP)[b]	ND–263.9	5.8	92.6% (54)	–	–	–	Silva et al. (2004)
	28.4–192.0	85.2	100% (64)	27.9 ± 2.3	2005–2006	MU	Huang et al. (2009)
Mono-*n*-butyl phthalate (MnBP)	NR–18.7	7.8	100% (11)	Birth	–	MU	Wittassek et al. (2009)
Monoisobutyl phthalate (MiBP)	NR–35.7	4.2	100% (11)	Birth	–	MU	