FAMILIES, MATERNAL DRUG USE, PRENATAL DRUG EXPOSURE AND LATER DRUG USE: A REVIEW OF THE EVIDENCE

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Nature of the review

Drug dependence is the result of a complex interaction between genetic and environmental factors that can occur during development. Prenatal drug exposure is among the environmental factors that have been examined for its possible impact on child development. This review summarises available evidence for the impact of prenatal drug exposure, including alcohol and tobacco, on the long-term neuro-developmental outcomes of infants and, in particular, the extent to which this exposure may increase the vulnerability to later drug use. It then summarises the evidence for genetic predisposition to addiction and its implications for understanding the role of maternal drug use and its effect on offspring.

Identifying the evidence

The main general electronic databases MEDLINE, PsycINFO and Web of Science, and the specialist databases of the DrugScope, US National Institute on Drug Abuse and Substance Abuse and Mental Health Services Administration were searched for relevant references with a range of search terms appropriate to each database. Addiction Abstracts and bibliographies of research papers were also hand searched for relevant references. Key individuals in the specialities of longitudinal studies of prenatal exposure and infant development and genetics have also been consulted for guidance and comment on the literature.

The evidence

While there are a number of on-going US longitudinal studies of prenatal alcohol, tobacco and drug exposure, this is an evolving area of research, perhaps constrained by the costs and complexities of such long-term studies. The research literature on the effects of prenatal exposure to alcohol or tobacco is more developed, and there are no large-scale reports of the longitudinal impact of prenatal cocaine or opiate exposure in mental, motor or behavioural development in infants older than seven years, nor any studies directly addressing their impact on vulnerability to later drug use.

Conducting research on prenatal exposure to alcohol, tobacco and drugs and their impact on later behavioural and cognitive development is made difficult by a number of methodological challenges. Notable among these are the co-occurrence of risk factors such as a range of substances used, poor maternal health and nutrition which could potentially confound the results; the difficulty of identifying valid measures sensitive enough to measure outcomes; differences in the post- natal child-rearing environment (Alessandri et al, 1998). While more recent research has attempted to

construct dynamic models which take into account these methodological difficulties together with the complex interrelated influences of risk factors for the child's cognitive and behavioural development, these methodological advances are still at an early stage (Jacobson and Jacobson, 2001).

This review draws on published meta-analyses where available and longitudinal prospective studies which are likely to provide the most rigorous sources of evidence. In their absence systematic reviews are cited, together with evidence generated by studies using more limited research designs where the literature is notably sparse.

Prenatal exposure and increasing vulnerability

Research on the effects of prenatal alcohol, tobacco and drug use has been underway for three decades. This research has been able to identify associations between foetal exposure to these substances and problems in cognitive and behavioural development such as memory problems, impulsivity and deficits in executive cognitive. These problems have been identified as potential factors for the development of substance misuse disorders. In the absence of a research literature investigating the link between prenatal exposure and later drug use by the infant, the research on the impact of cocaine, opiate and cannabis use on neurocognitive and behavioural development has been summarised here to provide some indication of the magnitude of risk for later drug use.

Short-term physical outcomes

Tobacco

Tobacco has been found to be associated with effects on foetal growth resulting in lower birth weight babies (Abel, 1984). The risk of having small for gestational age has been found to be two to four times higher for smokers than non-smokers (Howell et al, 2004).

Alcohol

A range of early problems in offspring of alcohol abusing mothers have been identified since the late 1960s. The foetal Alcohol Syndrome includes a range of effects including lower birth weight and physical anomalies (Jones and Smith, 1973; Abel and Sokol, 1986). However, a meta-analysis found no evidence that moderate alcohol consumption during the first trimester of pregnancy is associated with increased risk of foetal problems (Polygenis et al, 1998).

Cannabis, cocaine and heroin

Both prenatal opiate and cocaine exposures are associated with premature birth and lower birth weight. A meta-analysis, which included only studies which had controlled for maternal smoking reported that cocaine use causes low birth weight and that this effect is greater with heavier use. However, the authors cautioned that other lifestyle factors that were not controlled may be responsible for the observed effects (Hulse et al, 1997). The authors advanced similar caution in their meta-analysis of the research on heroin and prenatal exposure, where both heroin and, to a lesser extent methadone, were associated with lower birth weights (Hulse et al, 1997). Finally the same research group also conducted a meta-analysis of studies investigating the association between low birth weight and maternal cannabis use. They concluded that there is inadequate evidence to suggest that cannabis use by pregnant women causes low birth weight (English et al, 1997).

Impact on infant development

Measures

Most studies of prenatal drug exposure and infant cognitive and behavioural have used the Bayley Scales of Infant Development. These scales have been taken as being able to detect the effects on development measured by the Scales' Psychomotor Development Index and Mental Development Index, although some concerns have been raised about their sensitivity and specificity (Rose-Jacobs et al, 1996).

Alcohol

Reviews

A recent meta-analysis examined the effects of prenatal exposure to alcohol on subsequent infant mental development. Criteria for inclusion in the analysis were: studies using human subjects who were 2 years or younger; studies using the Mental Development Index (MDI) from the Bayley Scales of Infant Development as the outcome measure; studies using a prospective design, with the alcohol usage of the mothers assessed during pregnancy and the mental development of the resulting offspring also assessed. Nine studies were identified for inclusion. The results for children ages 6-8, 12-13 and 18-26 months were analysed separately. The authors had three main reasons for this. The scales used to assess developmental skills are designed for different ages. It also enabled them to identify whether the effects of prenatal exposure were more likely at certain developmental stages. Lastly it avoided combining observations at different ages which would have compromised the necessity for independence of effects (Testa et al, 2003).

While the analysis found that alcohol usage at the three dosage levels was significantly associated with lower Mental Development Index scores among the 12-

13 month olds, an effect that was not eliminated when effect sizes were adjusted when relevant covariates were added, the same effect was not found for the other age groups. The authors suggest that the inconsistency of findings may be related to the differences in MDI item content at different ages or the decline in MDI scores among children of low socioeconomic status. However, the authors also urge caution in interpreting the results presented because of the small number of studies included in the analysis and the heterogeneity in measurement, analysis and sample sizes

Cocaine

Reviews

In the absence of a meta-analysis, the systematic review conducted by Frank et el provides the most recent critical examination of outcomes in early childhood of physical growth, cognition, language skills, motor skills and behaviour, attention, affect and neurophysiology after prenatal cocaine exposure. Thirty six research papers met the authors' criteria for the review; published in a peer-reviewed English-language journal; had a comparison group; used prospective samples recruited in the perinatal period; used masked assessment and; did not include a substantial proportion of subjects exposed to other drugs or maternal human immunodeficiency virus infection.

After controlling for confounders the review found that there was no consistent negative association between prenatal cocaine exposure and physical growth, developmental test scores or development of language skills. No independent cocaine effects were found on standardised parent and teacher reports of child behaviour. (Frank et al, 2001).

Longitudinal studies

The Frank et al review demonstrated that a wide range of studies using masked examiners and standard intelligence tests had failed to find a negative association between prenatal exposure to cocaine and cognitive development of offspring. Other studies have explored the impact of different levels of cocaine use.

One prospective study was conducted with 236 infants whose mothers were recruited at 2 inner city hospitals in Philadelphia and Trenton. Substance misuse information was obtained prenatally using a semi-structured questionnaire in 65% of the cases. The results of the interviews were confirmed by analysis of the infants' meconium. 37 of the infants were classified as heavily exposed, 30 were lightly exposed, and 169 were not exposed. The Bayley Scales of Infant Development were used to measure cognitive functioning in the infants Infant information processing was also assessed. The results showed that the infants of cocaine-using mothers had higher environmental medical risk scores. At 8 months all exposure groups were the same on

measures of Psychomotor Development and Mental Development Index scores and recovery to a novel stimulus. Although MDI scores for all groups decreased between 8 and 18 months these decreases were more pronounced. Infants who were heavily exposed to cocaine or had high environmental risk had a decrease in MDI scores from 8 to 18 months (Alessandri et al, 1998).

Another major prospective longitudinal study tested 203 infants at 6, 12 and 24 months of age using masked examiners applying Bayley Scales of Infant Development. Three cocaine exposed groups were constructed for the analysis and defined by maternal self-report and meconium assays: unexposed, heavy users and lighter users (all others). There was no significant effect of level of cocaine exposure on Mental Development Index, Psychomotor Development Index or Infant Behaviour Record. However there was an interaction effect, with those who were heavier exposed and born at slightly lower gestational age having higher mean MDI scores compared with other children born at same gestational age. Early intervention attenuated the age decline in PDI scales for all groups (Frank et al, 2002).

The most recent study from this group using the same sample and methodology assessed 91 4-year-old children with prenatal exposure and 709 non-exposed children. In this study masked examiners tested the infants using the Weschler Preschool and Primary Scale of Intelligence. Analysis showed that prenatal cocaine exposure was not associated with deficits in full-scale IQ, verbal IQ or any of the subtests. In some tests children with heavier exposure attained higher scaled scores. Mother's education and child's experience with pre-school something were not associated with higher verbal IQ scales (Frank et al., 2005).

The Maternal Lifestyle Study (MLS) is a large multi-site prospective longitudinal study of cocaine and opiate exposure using matched controls. The study was designed to evaluate the direct impact of prenatal cocaine/opiate exposure using masked assessments and the power to control for a wide range of covariables. As part of this study 1227 infants (572 in the cocaine/opiate–exposed group, 655 exposed to neither substance) were assessed on mental, motor and behavioural outcomes longitudinally between 1 and 3 years of age (Messinger et al, 2004).

Overall retention rate for the study was nearly 90%. While significant differences in Mental Development Index scores were found between the cocaine-exposed infants and the non-exposed infants this effect did not remained significant after controlling for covariates. Low birth weight and disruptions in maternal care, low SES and low vocabulary scores, rather than cocaine exposure were associated with the large deficits in mental development of the cocaine-exposed infants.

Recent results from a prospective study of 499 children of African American mothers found that at age 7, boys with prenatal alcohol exposure together with persistent cocaine exposure throughout pregnancy had significantly higher levels of delinquent behaviour compared to boys without cocaine exposure. No similar associations were found among boys exposed solely to cocaine prenatally. However, girls exposed to cocaine prenatally, but not alcohol, demonstrated significantly higher levels of aggressive behaviours compared to girls without the cocaine exposure. Again in contrast to the results for boys, for girls with prenatal alcohol exposure, no association was found between prenatal cocaine exposure and a range of behavioural scores after

controlling for confounding factors. While suggesting that gender and alcohol may moderate the effects of prenatal cocaine exposure on child behaviour problems, the inclusion of just African American families and the exclusion of children whose mothers did not receive prenatal care from the study group limit the generalisability of the study findings (Bailey et al, 2005).

Opiates

Longitudinal studies

In the absence of meta-analyses or reviews, research evidence is dependent on two longitudinal studies. A small longitudinal study comparing the mental and motor development of 33 infants from innercity, African American families whose mothers used opioids during pregnancy with 45 infants whose mothers did not use opioids found evidence of poorer mental and psychomotor development in the opioid-exposed infants. This poorer performance was related to social- environmental risk factors in the case of mental development and low birth weight in the case of psychomotor development (Hans and Jeremy, 2001).

Similar findings emerged from the larger Maternal Lifestyle Study (MLS) where opiate- exposed infants recorded lower scores on the Psychomotor Development Index than non-exposed infants. However, these differences did not remain significant after controlling for covariates. Low HOME scores, low vocabulary scores and low birth weight, rather than opiate exposure, were associated with substantial deficits in psychomotor performance and behavioural difficulties (Messinger et al, 2004).

Cannabis

Reviews

Reviewing the consequences of prenatal cannabis exposure, Fried and Smith found a limited amount of data to review and drew on the two longitudinal studies discussed below for their salient findings (Fried and Smith, 2001). While prenatal exposure did not have an impact on global IQ, the reviewers suggest that it did appear to have an impact on aspects of Executive Function, and in particular attentional behaviour and visual analysis/hypothesis testing beyond the infant stage. However, the reviewers draw attention to the limited literature, the small sample sizes in the studies reviewed and the quasi-experimental nature of the studies reviewed and urge caution when interpreting the results of their review.

Longitudinal studies

There are two major on-going longitudinal studies examining prenatal cannabis exposure and subsequent effects on growth, cognitive behaviour and behaviour. The first is the Ottawa Prospective Prenatal Study (OPPS) underway since 1978. The

sample in this study consists of low-risk, white and predominantly middle-class families (Fried, 1980). The second study, the Maternal Health Practices and Child Development Study (MHPCD), begun in 1982. The study sample is high-risk, with low socioeconomic status and just over half are African American (Goldschmidt et al, 2000).

The OPPS found that there was a developmental delay after birth in the infant's visual system with an increased rate of tremors and startle among the children of cannabis uses. These effects had disappeared at one month and there were no detectable effects on standardised ability tests at six months and twelve months (Fried and Smith, 2001).

Effects that were attributed to cannabis were identified at 36 and 48 months, but were not detectable at 60 and 72 months. The researchers suggest that this may mark a subtle developmental impairment among children who had experienced a shorter gestation period and prematurity (Fried and Smith, 2001). The cohort has now been followed up to age 13 to 16 years. Effects were found on memory at age 4, attention at age 6 and visual integration and attention and visual-related aspects of executive function in 9 to 12 year olds. There was no difference between children who were and were not prenatally exposed to cannabis on global IQ scores but there were differences in tasks that required visual memory, analysis and integration at ages 13 to 16 (Fried et al, 2003).

A recent study from the Pittsburgh MHPCD, examined the effects of prenatal cannabis and alcohol exposure on academic achievement at age 10. In contrast to the OPPS which found no effects of prenatal exposure to cannabis on school performance, use of cannabis in the first trimester was associated with poorer performance on reading and spelling tests and a lower performance evaluation by the children's' teachers. Analysis suggested these effects were mediated by the effect of first trimester use of cannabis on the children's anxiety and depression symptoms. Cannabis use in the second trimester was significantly associated with underachievement in school performance. While a range of factors, including socioeconomic, home environment and maternal prenatal and current drug, were taken into account in the study, other important factors such as motivation and parent involvement in the child's education did not feature in the statistical analysis (Goldschmidt et al, 2004).

Prenatal exposure and subsequent substance misuse by offspring

Tobacco

There are few studies providing evidence that the children of mothers who smoked during pregnancy may become smokers themselves. A retrospective study reported a four-fold increased risk of tobacco use among adolescent girls who were exposed prenatally (Kandel et al, 1991). The same research group used follow-up interview data on two samples, one sample of 192 mother-first-born child pairs from New York State and 797 pairs from a national sample were used to explore further the role of maternal smoking on offspring. In both samples, maternal smoking during pregnancy after controlling for post natal smoking in the analysis, increased the risk that female children would smoke and persist in smoking, persistent smoking defined as smoking

in the last three months (Kandel et al,1994). A further study from the same group found that maternal smoking was associated with higher levels of problem behaviour and these behaviour problems increased the likelihood of lifetime smoking among daughters between the ages of 9 and 17 years (Griesler et al, 1998).

A cross-sectional study used self-reports to examine the impact of maternal smoking of 298 treatment seeking smokers, examining the role of gender on smoking initiation and progression to cigarette use, and current levels of nicotine dependence. Participants were asked to recall whether or not their mother smoked during the pregnancy and then asked for a range of data about their own smoking history. Females who reported being exposed moved from initiation to daily use more rapidly than those not exposed. Fagerstrom Test, prior quit attempts and prior withdrawal were taken as measures of nicotine dependence and were found to be significant association with prenatal exposure gender and interaction between the two. This study suggested that prenatal drug exposure may accelerate the progression from experimentation to daily use, result in early tobacco experimentation in boys and produce higher levels of nicotine dependence in adults. (Oncken et al, 2004).

Further evidence is provided by a prospective study of the offspring of low SES birth cohort followed since gestation. The mothers provided data on exposure to tobacco, alcohol, and cannabis in prenatal and post natal period.52.6% of the mothers smoked during pregnancy. 589 10-year olds completed a self-report questionnaire. . Six per cent of the children reported ever smoking. Statistical analysis showed that maternal smoking during pregnancy was significantly associated with an increased risk of childhood experimentation. Offspring exposed to more than half a pack a day during gestation had a 5.5 fold increase for early experimentation. Prenatal tobacco exposure had a direct effect on the child's smoking while maternal current smoking was not significant. Prenatal tobacco exposure also predicted child anxiety and depression and externalising behaviours which affected child smoking through the mediating effect of peer tobacco use. The study was marked by low numbers of children experimenting with tobacco, the sample predominantly from low SES background (Cornelius et al, 2000).

A prospective study of a cohort of 1,248 subjects from the National Collaborative Perinatal Project was followed op after 30 years. Data from maternal smoking was obtained from prenatal visits. Information on the offspring was obtained using structured questionnaires. Those offspring whose mothers reported smoking a pack or more during pregnancy were more likely to meet DSM criteria for lifetime nicotine dependence. Odds ratio for progressing to nicotine dependence was twice that for offspring whose mothers smoked heavily against those who didn't. In the study gender, socioeconomic status and age at pregnancy were controlled for. Similar results were found for men and women. While the study drew on self-reports the authors drew attention to the concordance between self-reports and maternal sera stored for 40 years of 448 participants in the NCPP. (Buka et al, 2003).

A recent study from the OPPS also found a positive association between maternal tobacco smoking during pregnancy and the risk of subsequent cigarette initiation by offspring. Following up 152 adolescents aged between 16 and 21, those whose mothers who reported smoking tobacco during pregnancy were more than twice as

likely to have started smoking later in adolescence, compared to the offspring of non-smokers. The association was stronger for male rather than female offspring in this study (Porath and Fried, 2005).

Alcohol

Data from the Seattle Longitudinal Study on Alcohol and Pregnancy directly examined the relationship between prenatal exposure and adolescent and adult drinking (Baer et al, 1998, 2003). Maternal drinking, as well as the use of nicotine, caffeine and other drugs were assessed during pregnancy in 1974-5. Family history of alcohol problems was assessed at ages 14 and 21. Parental use alcohol and other drugs, together with a range of environmental factors were assessed at seven different ages. Young adult offspring provided self-reports of quantity and frequency of alcohol use and completed the Alcohol Dependence Scale. Statistical analysis found that prenatal alcohol exposure was significantly associated with alcohol problems at 14, and the relationship persisted after controlling for the effects of family history, maternal use of other drugs and post birth environmental factors (Baer, 1998). Analysis of the data at age 21 similarly found a relationship between maternal drinking and alcohol problems in young adults.

Cannabis

The recent study from the OPPS reported above also found evidence of a positive association between prenatal cannabis use and subsequent initiation of cannabis use by offspring, again an effect that was found to be stronger for male rather than female offspring. However, no significant association was found between prenatal cannabis exposure and regular cannabis use, despite regular use being defined as just use once a week in this study (Porath and Fried, 2005).

Imprinting

A study using the birth records of 200 opiate addicts born in Stockholm between 1945 and 1966 tested the hypothesis that later dependence may result partly from an imprinting process during birth when mothers were given opiates, barbiturates or nitrous oxide during labour. After controlling for a number of variables including hospital of birth, duration of labour, birthweight and surgical intervention, the estimated relative risk was 4.7 if all three drugs were administered compared with when no drug was given when the addicts were compared to their own siblings (Jacobson et al, 1990).

Genetics

The evidence for a genetic contribution to drug use lies with two major population-based twin studies. The Vietnam Era Twin (VET) registry found heritabilities of between 0.25 and 0.44 for abuse and/or dependence for the drugs studied, including stimulants and opioids (Tsuang et al, 2001). The Virginia twin studies found

heritabilities of roughly twice that of the VET study (Kendler et al, 2000). Taken together these studies suggest that genetic factors have a large effect on vulnerabilities to drug use and that heavy use and dependence have a stronger genetic effect than occasional use.

Conclusions

There is an extensive research literature exploring maternal drug use and its impact on infant development and the risk for later drug use. While this literature has explored the association between drug use and a range of infant cognitive and behavioural abilities, there is little strong evidence that prenatal drug exposure is an independent risk factor for later infant development. Research evidence examining prenatal drug exposure and vulnerability to later drug use for infants is almost completely absent, although there is an emerging evidence base for a link between maternal alcohol or tobacco use and later alcohol and tobacco use by their offspring. While there are a number of ongoing US longitudinal studies which are likely to generate useful evidence in the future, there still remains a number of methodological issues such as measures, analysis and sampling that need to be addressed before results can be treated with some confidence.

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