41

Alcohol, caffeine and nicotine: as factors in pregnancy

Paul S. Weathersbee, M.S.
J. Robert Lodge, Ph.D.

University of Illinois
Urbana-Champaign

Address reprint requests to:

Paul S. Weathersbee; 315 Animal Science Laboratory; Urbana, IL 61801

Memo from Leonard S. Zahn

March 14, 1979

Attached is a copy of a manuscript which, I am told, is in press in Postgraduate Medicine. It should not be cited until it is published.

LSZ

38309

This work was supported in part by the Illinois Agricultural Experiment Station

TI05192631

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

Placental membranes function not only as a bi-directional route of exchange for needed nutrients and metabolic waste products, but allow for the often unempeded transferance of a wide variety of drugs and other exogenous substances, some of which are or may be injurious to fetal development. Historically, clinical experience with thalidomide and diethylstibestrol (DES) should provide adequate reminders that any prescribed drug use during the course of pregnancy be undertaken in a careful and deliberate fashion. Such forms of restraint in drug use are equally applicable to the self-administered category of alcohol, caffeine and nicotine, which are often perceived by the user as being habits, rather than biologically active substances. Of these, alcohol probably provides the clearest example of a compound whose pharmacological properties makes its use incompatable with pregnancy. Epidemiologic studies [1] have documented a characteristic pattern of altered morphogenesis in children born to alcoholic mothers, which has been termed fetal alcohol syndrome (FAS). Similarly, smoking has been associated with lowered birthweights, varying degrees of embryonic and fetal mortality [2], and increased incidence of congenital anomalies [3]. High levels of caffeine intake, on the order of 600 mg/day, can also be related with a higher than expected incidence of pregnancy loss [4]. The association between caffeine intake and a history of reproductive loss is statistically significant even when alcohol and smoking are controlled for in analysis, as the latter two variables were not significantly related to the finding [5].

We have summarized previously the known and potential mechanisms by which alcohol, caffeine and nicotine influence the reproductive process [6,7]. Broadly, these drug mediated effects can be assigned to either of two categories, a direct effect on the embryo or fetus or indirect through an induced imbalance in maternal and/or fetal homeostasis. A clearer understanding of these processes

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

should provide the clinician with useful information both for prenatal counseling and identifying a potential cause for the subfertile couple where there is no apparent etiology.

Despite a plethora of research efforts, a full understanding of the physiological mechanisms by which drugs influence pregnancy is still not readily available. In Figure 1, some of the more general means by which alcohol, caffeine and nicotine could effectively alter the course of human pregnancy are depicted. While the model system begins during post-implantation stages of development, it should be appreciated that these drugs could be influential during the earlier stages, by either altering the ovulatory process or by exerting a more direct effect through their transfer into seminal and/or uterine contents [6,7].

Model for Drug Action

In humans, drug ingestion is followed by a fairly orderly process of absorption and distribution, after which the compounds are most often removed from circulation and rendered inactive through one of the available metabolic routes. In the non-pregnant female, this process generally proceeds in a fairly uneventful manner, as any changes in blood chemistry would not hold the risk of affecting fetal development. However, in the pregnant female, the use of either alcohol [8] or nicotine [9] leads to increased circulating levels of lactate, a change which is readily reflected in both maternal and fetal blood supplies [8]. Lactate accumulation, with its accompanying acidosis, can be related to alterations in both uterine perfusion [10] and fetal nervous system function [11]. The use of alcohol leads also to hypoglycemia, while smoking can be related with increased circulating levels of carbon monoxide [12].

Alcohol [13], caffeine [7], and nicotine [9] share a common property in that their use dramatically increases circulating levels of the catecholamines. While contradictory findings are present in the literature regarding the placental transfer of catecholamines, the hormones, through their vasoactive prop-

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

erties, can effectively alter both uterine and placental blood flow patterns. These latter effects have been studied in detail, in both the pregnant rhesus monkey [14] and the ewe [15], where exogeneous catecholamines were injected and decreased blood perfusion monitored. It seems that the vascular beds associated with both the pregnant uterus and the placenta are extremely sensitive to this form of hormone treatment, even when administered doses are physiologic rather than pharmacologic.

We have previously summarized the evidence that catecholamine turnover patterns occurring at either the maternal or fetal level operate under a fairly narrow and predictable range, which presumeably reflects the normal endocrinology of pregnancy and the developmental process [7]. When these data are combined with results from animal studies [6,7,14,15], it may be interpreted that the release of catecholamines by these drugs might be one of the most significant consequences of their utilization. That such a change can occur at the fetal level is suggested by work completed in rats, showing a reversible retardation of some 20 to 30 percent in the maturation of fetal adrenal catecholamine storage vesicles when pregnant females were treated with alcohol (6% w/v) from day 13 of pregnancy to term [16].

Placental membranes do afford the developing fetus protection from certain classes of drugs and metabolites by blocking or severely retarding their transport. Acetaldehyde which is the first metabolic by-product from alcohol's breakdown can apparently not cross the placenta. This would seem to be a highly beneficial function of the membranes, as many of the physiological effects attributed to alcohol are believed to be mediated through acetaldehyde. Similarly, nicotine crosses the placenta in only the most negligable of quantities. This lack of bioavailability displayed by nicotine does not necessarily circumvent smoking from exerting an effect, since the accompanying increases in carbon monoxide can be readily reflected across the placental membranes [12]. Recent

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

evidence has shown that fetal hemoglobin and hematocrit values are significantly elevated in the twenty-four hour old infant when the mother smoked during pregnancy [17]. This relationship is dose-dependent, up to two packs of cigarettes per day, and may well reflect the fetuses attempts to compensate to the adverse changes in its' microenvironment brought about by either maternal smoking or more generally speaking, coming as a result of exposure to high levels of air borne environmental pollutants.

The use of the electron microscope has allowed for the study of more discrete changes in tissues brought about by drugs. When segments of the umbilical cord from smoking and non-smoking mothers are studied in this manner, the tissue from the former had present large areas of swollen and distinctively irregular endothelial cells, which take on a cobblestone-like appearance. Transmission electron microscopy of these same tissues showed extensive areas of subendothelial edema and markedly thickened basement membranes [18]. Caffeine may also serve to disrupt the normal functionality of the feto-placental unit, as experiments conducted in rats have noted decreased placental weights in treated animals [19]. These latter two effects of nicotine and caffeine should bear further experimental consideration, as it represents another potential overlap of effect exerted by these related habits.

When the placenta does not block the transfer of a drug, as is the case with alcohol [6,8] and caffeine [7], the fetus is placed in the position of metabolizing or otherwise eliminating the compound through its movement back into either maternal circulation or the amniotic fluid compartment. Where it has been studied, fetal drug metabolizing ability is extremely limited in comparison to that of the adult, and should it occur, proceeds at a noticeably diminished rate [20]. As a drug, caffeine is apparently not metabolized by the fetus

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

in utero, with the ability to do so gained only after the first several days of life [20]. On the other hand, alcohol can be metabolized by the near term fetal liver, with it taking approximately 12 hours to clear the drug, in those cases where maternal blood levels reached 100 mg/dl [21].

We have suggested recently [6] that drugs capable of crossing the placenta may mediate a portion of their effect by altering the function of the fetal endocrine system. Presumedly, this system operates under a defined pattern, which is so designed as to be compatible with the endocrine directed aspects of development. There is also the possibility that such an endocrine imbalance would be additive, in that many of the changes in maternal hormonal balance brought about by a drug, would be reflected across the placental membranes.

A model system for this type of drug mediated change in endocrine function can be seen in the ability of alcohol [22] and smoking [9] to increase circulating levels of the corticosteroids. Physiologically, the exogeneous application of corticosteroids to pregnant test animals has shown the potential of this class of hormones to affect cellular division and in doing so alter the development of a diverse number of bodily systems [6]. Should alcohol increase the rate of synthesis and release of fetally derived corticosteroids, one is left to speculate whether premature shifts in endogeneous hormone concentrations would not exert the same form of negative effect as those seen where the hormone was exogeneously applied. That alcohol may mediate such a hormonal event can be partially supported by the observation that in those cases where premature labor was blocked by maternal alcohol infusion adjunct administration of lung maturing corticoids is not necessary, presumeably because of drug induced fetal corticoid secretion [23].

Experimental evidence in animal models and clinical observations in humans have shown that pregnancy is accompanied by characteristic changes in the cyclic nucleotide balance. This pattern is evident whether monitored at the

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

fetal tissue level, amniotic fluid, maternal plasma or urine [6,7]. While the cyclic AMP concentrations vary with the compartment analyzed, the basic trend is most generally one of low values during the earliest stages of pregnancy but increasing as development progresses. That cyclic AMP plays a role in the reproductive process can be seen by the fact that pregnancy in mice can be blocked by the administration of the nucleotide [24]. When early mouse embryos are cultured in the presence of phosphodiesterrase inhibitors, the treated embryos die in a dose-response manner, presumeably as a result of accumulating intracellular levels of the nucleotide [25]. Alcohol and caffeine both possess the biochemical ability to affect these levels of cyclic AMP in the fetus, and, in doing so, potentially alter the course of development. It has been suggested that alterations in cyclic AMP levels may explain a portion of the dose-response increase in reabsorptions been in laboratory animals treated with caffeine during pregnancy [7]. The diverse number of cellular processes which are apparently mediated through the cyclic nucleotides makes this a particularly vulnerable locus for drug action. This is especially true in the developing fetus, where cellular division and differentiation represent such key elements of the process.

The extent to which a drug exerts a negative influence on the reproductive process may never be known conclusively, as a firm judgement of effect can only be made after a careful assessment of the compounds biological and chemical properties, properly designed animal experimentation, and appropriate epidemiologic observations. Even in those cases where all of these criteria have been adequately satisfied, there may still exist certain extricable doubt as to the conclusions drawn. This type of contradiction can best be illustrated with epidemiologic studies of smoking and pregnancy. Even though similar methodologies have been employed in all of these studies, the final conclusions rendered range from increased incidence of reproductive loss [2] and congenital malformations [3], to observations which do not allow for a clear case of cause and

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

effect [26], to even questioning the role of smoking [27]. To a lesser extent animal studies display this same basic pattern of variability of noted response. The natural association and overlap of physiologic effects exerted by alcohol, caffeine and nicotine necessitates their being tentatively thought of as a group until claritative data can be derived. This reservation seems especially pertinent in the epidemiologic investigations of the area which in the past have not always considered the possibility of overlapping and additive effects of drug useage.

Summary

While it is often convenient to visualize drug mediated effects as being a direct consequence of the drugs' presence or action, in the course of pregnancy, the indirect alterations may be of more importance. Clearly, metabolic and endocrine imbalances, whether occurring at the maternal and/or fetal level, represents drug effects which may seriously jeopardize the normal completion of the delicate developmental process. It may well be that these indirect effects are the primary mode by which the associated habits of alcohol, caffeine and nicotine affect the course of pregnancy.

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

REFERENCES

1. Streissguth AP: Fetal alcohol syndrome: An epidemiologic perspective. Am J Epidemiol (in press)
2. Meyer MB, Tonascia JA: Maternal smoking, pregnancy complications, and perinatal mortality. Am J Obstet Gynecol 128:494-502, 1977
3. Naeye RL: Relationship of cigarette smoking to congenital anomalies and perinatal death. Am J Pathology 90:289-294, 1978
4. Weathersbee PS, Olsen LK, Lodge JR: Caffeine and pregnancy: A retrospective survey. Postgrad Med 62:64-69, 1977
5. Streissguth AP, Martin DC, Barr HM: Caffeine effects on the outcome of pregnancy: A preliminary report. Proceedings National Drug Abuse Conference, Seattle, April 3-8, 1977 (Abstract)
6. Weathersbee PS, Lodge JR: A review of ethanol's effects on the reproductive process. J Reprod Med 21:63-78, 1978
7. Weathersbee PS, Lodge JR: Caffeine: Its direct and indirect influence on reproduction. J Reprod Med 19:55-63, 1977
8. Mann LI, Bhaktavathsalan A, Liu M, et al: Placental transport of alcohol and its effect on maternal and fetal acid-base balance. Am J Obstet Gynecol 122:837-844, 1975
9. Cryer PE, Haymond MW, Santiago JV, et al: Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Eng J Med 295:573-577, 1976
10. Blechner JN, Stenger VG, Prystowsky H: Blood flow to the human uterus during maternal metabolic acidosis. Am J Obstet Gynecol 121:789-794, 1975
11. Mann LI, Bhakthavathsalan A, Liu M, et al: Effect of alcohol on fetal cerebral function and metabolism. Am J Obstet Gynecol 122:845-851, 1975

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

12. Longo LK: The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol 129:69-103, 1977

13. Perman ES: The effect of ethyl alcohol on the secretion from the adrenal medulla in man. Acta Physiol Scand 44:241-247, 1948

14. Adamsons K, Mueller-Heubach E, Meyers RE: Production of fetal asphyxia in the rhesus monkey by administration of catecholamines to the mother. Am J Obstet Gynecol 109:248-267, 1971

15. Rosenfeld CR, Barton MD, Meschia G: Effects of epinephrine on distribution of blood flow in the pregnant ewe. Am J Obstet Gynecol 124:156-163, 1976

16. Lau C, Thadanai PV, Schanberg SM, et al: Effects of maternal ethanol ingestion on development of adrenal catecholamine and dopamine-β-hydroxylase in the offspring. Neuropharmacology 15:505-507, 1976

17. Garn SM, Shaw HA, McCabe KD: Effect of maternal smoking on hemoglobins and hematocrits of the newborn. Am J Clinical Nutr 31:557-558, 1978 (Letter to the Editor)

18. Asmussen I, Kjeldsen K: Intimal ultrastructure of human umbilical arteries: Observations on arteries from newborn children of smoking and non-smoking mothers. Circulation Res 36:579-589, 1975

19. Gilbert EF, Pistley WR: Effect on the offspring of repeated caffeine administration to pregnant rats. J Reprod Fertil 34:495-499, 1973

20. Horning MG, Butler CM, Nowlin J, et al: Drug metabolism in the human neonate. Life Sci 16:651-672, 1975

21. Wagner L, Wagner G. Guerrero J: Effect of alcohol on premature newborn infants. Am J Obstet Gynecol 108:308-315, 1970

22. Jenskins JS, Connolly J: Adrenocortical response to ethanol in man. Br Med J 2:804-805, 1968

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

Figure 1 - Model for describing direct and indirect effects of drugs on the developing fetus.

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

23. Barrada MI, Virnig NL, Edwards LE, et al: Maternal intravenous ethanol in the prevention of respiratory distress syndrome. Am J Obstet Gynecol 129:25-30, 1977

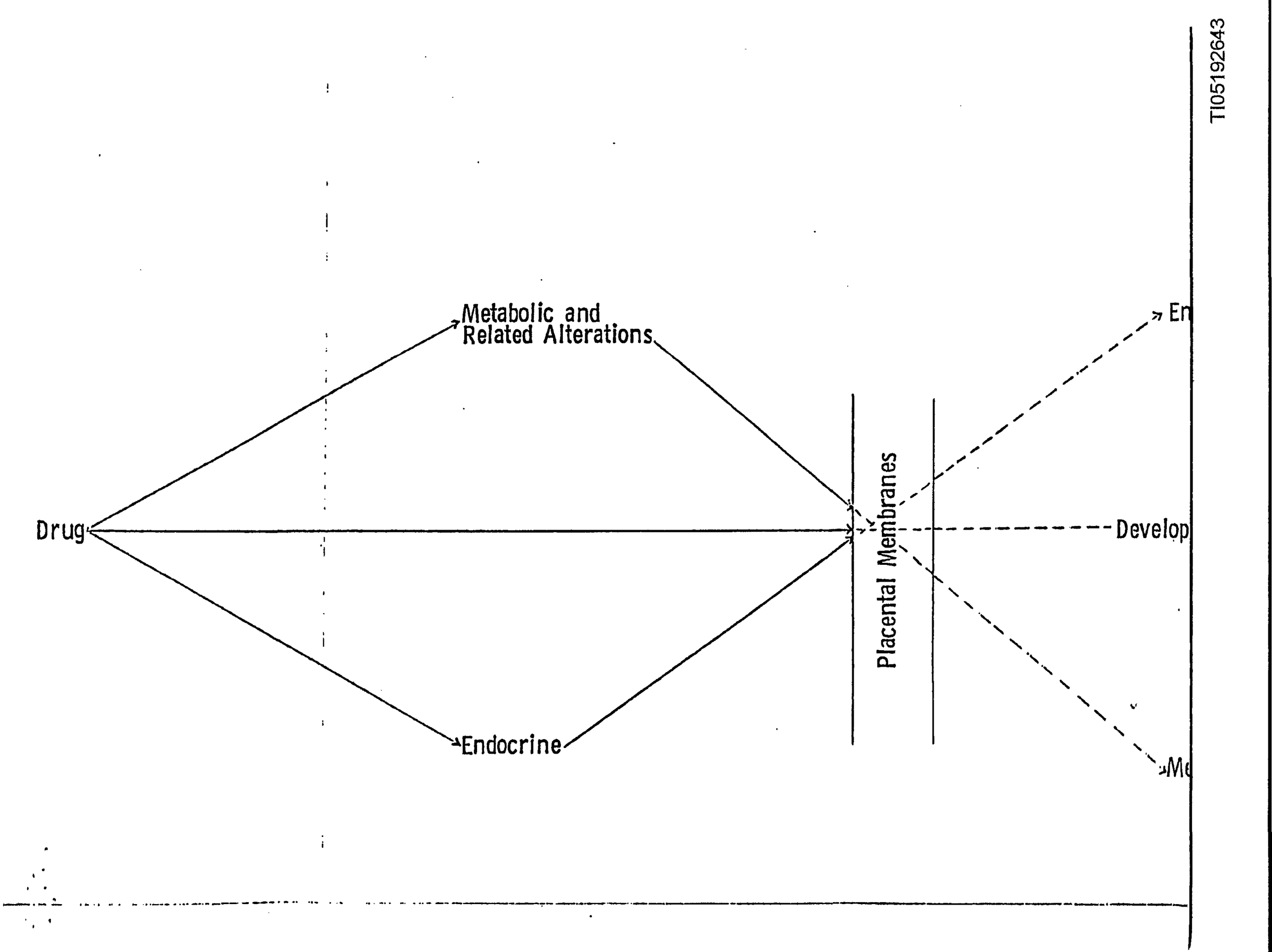
24. Ryan WL, Coronel DM: Adenosine 3',5', monophosphate as an inhibitor of ovulation and reproduction. Am J Obstet Gynecol 105:121-123, 1969

25. Fisher DL, Gunaga KP: Theophylline induced variations in cyclic AMP content of superovulated preimplantation mouse embryos. Biol Reprod 12:471-476, 1975

26. Silverman DT: Maternal smoking and birth weight. Am J Epidemiol 105:513-521, 1977

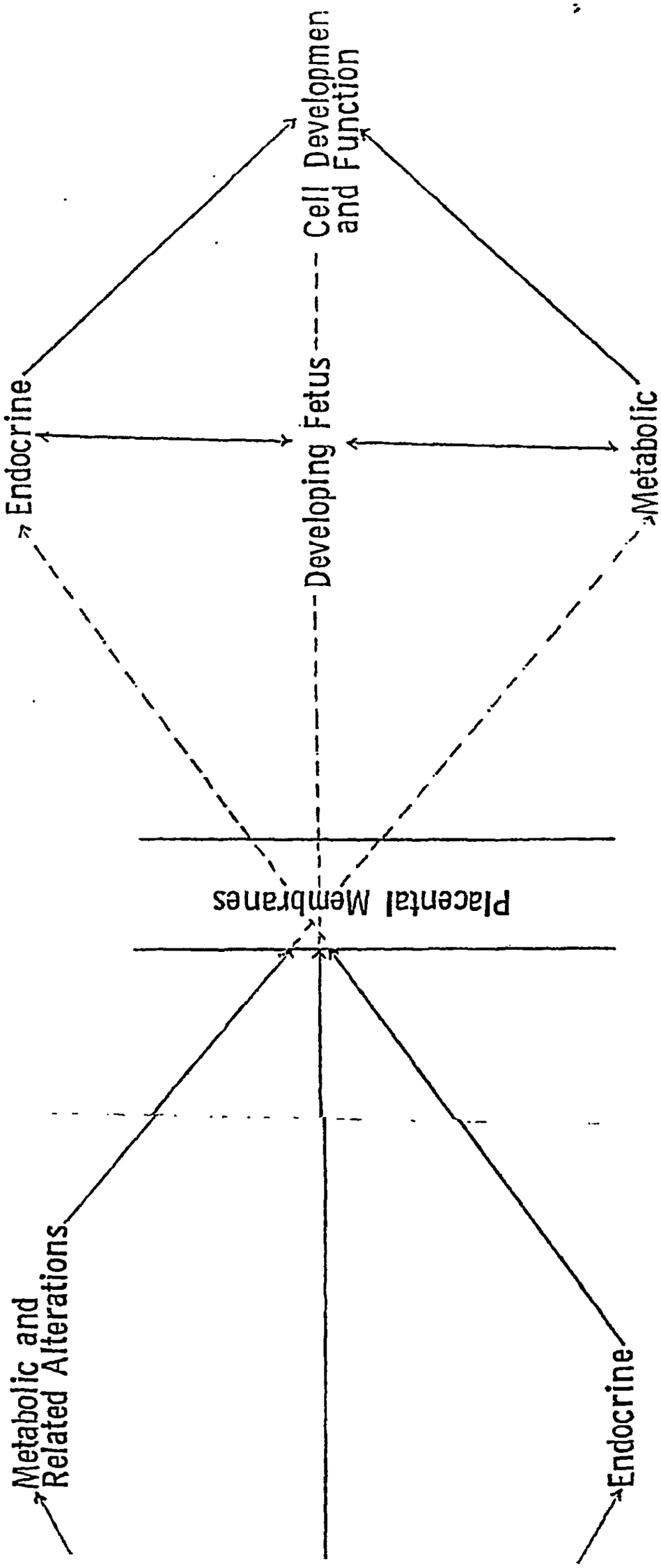
26. Yerushalmy J: The relationship of parents' cigarette smoking to the outcome of pregnancy: Implications as to the problem of inferring causation from observed associations. Am J Epidemiol 94:443-456, 1971

Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029



Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029

TI0519264



Source: https://www.industrydocuments.ucsf.edu/docs/fldg0029