Surveillance of Adverse Pregnancy Outcomes and their Causes: Theoretical Considerations

Mark Lubinsky*

6003 W. Washington Blvd, Wauwatosa, WI 53213, USA

*Corresponding author: Mark Lubinsky, 6003 W. Washington Blvd, Wauwatosa, WI 53213, USA

ABSTRACT

Causes of common Adverse Pregnancy Outcomes (APOs), such as prematurity, fetal demise, and growth restriction, are worth addressing collectively as often non-specific apogens (from the Greek apó [ἀπό] = away from, and génos [γένος] = giving birth to). A rationale is presented for using population distributions of maternal serum markers, such as alpha-fetoprotein from neural tube defect detection programs, for apogen screening. Abnormal distributions can indicate APO risks prior to clinical findings, with skewed distributions with adverse exposures. Temporal or spatial controls are available for widespread effects, and unexposed controls for limited exposures. Alternatively, with apogen related marker skewing, pregnancies with abnormal marker level should be "enriched" for exposures to both known and otherwise unsuspected factors.

Abbreviations: APOs: Adverse Pregnancy Outcomes; MS: Maternal Serum; AFP: Alpha-Fetoprotein

Introduction

Causes of common Adverse Pregnancy Outcomes (APOs), such as prematurity, fetal demise, and growth restriction, are difficult to monitor, with often inter-related multifactorial components and confounders (below) that make them worth addressing collectively, with a suggested designation here as apogens (also, from the Greek apó [ἀπό] = away from, and génos [γένος] = giving birth to). With this, a rationale is presented for using Maternal Serum (MS) markers such as Alpha-Fetoprotein (AFP) from neural tube defect detection programs as apogen screens. Marker levels can indicate risks prior to clinical findings [1], with skewed distributions with adverse exposures, as with smoking [2]. Temporal or spatial controls are available for widespread exposures, and unexposed controls for specific limited effects. Alternatively, with apogen related marker skewing, pregnancies with abnormal marker levels should be "enriched" for exposures to both known and otherwise unsuspected factors.

Justifying Apogens

APOs are more than just random pregnancy-related issues. First, the most common disorders- growth delays, losses, and prematurity- associate with each other, and with perinatal difficulties, fertility issues in the parents, life-long fetal origin hypothesis-related risks and occasional imprinting disorders, all consistent with a common epigenetic pathogenesis [3]. Second, the same APOs all have multifactorial etiologies, with considerable causal overlap, so that a single factor can affect them all non-specifically. Third, they have generally similar monitoring issues, with high background frequencies and low signal to noise ratios, uncertain cut-offs, definitional issues, differences between and within populations, and variations over time. More specifically:

a) Rates of preterm birth before 37 weeks of gestation vary geographically and over time, with maternal age and obesity, and other factors [4], and time of delivery can be altered by

medical inductions [5]. Early term births (37–38 weeks) show greater infant mortality compared to 39–40 weeks [6], so a 37 week cutoff includes minor gestational reductions that may still have medical implications.

b) Fetal growth restriction affects 5-10% of pregnancies [7] and is highly heterogeneous [7]. Nomenclature is inconsistent [8], with "a lack of consensus regarding terminology, etiology, and diagnostic criteria… [and] difficulty in differentiating between the fetus that is constitutionally small and fulfilling its growth potential and the small fetus… [with] an underlying pathologic condition [9].

c) For losses, about half of all biochemically verified implantations, mostly aneuploid and clinically unrecognized, fail to reach term [10,11]. With a high mortality, aneuploidy rates progressively decrease, so that of 544 second trimester miscarriages, only 1.3% were affected [12]. For stillbirths after 20 weeks, the best ascertained group, world rates range from under 5 to roughly 32 per 1000 births. "Disparities also apply within countries, since economically deprived communities have higher stillbirth rates than wealthier populations due to disparities in risk factors and inequalities in access to and quality of health care" [13], while losses have declined with medical advances [14].

In short, common APOs often overlap, share surveillance issues, and can have non-specific origins, making it useful to study causal factors as a group with shared characteristics. Non-specificity also differentiates apogens from teratogens, which are typically monofactorial causes of distinct physical birth defects. However, there is some overlap, since apogens can cause structural anomalies in addition to functional pregnancy issues- fetal alcohol [15] and maternal diabetes [16] are classic examples. The cited APOs also associate with the physical anomalies found in the VACTERL association of vertebral, ano-rectal, cardiac, tracheo-esophageal, renal, and limb defects, connections typically absent when the same anomalies occur in genetic disorders [17,18]. This suggests that apogens can sometimes cause isolated birth defects as part of a broader spectrum of effects.

Maternal Serum Markers as Apogen Screens

Maternal marker data from existing neural tube defect surveillance programs may provide inexpensive screens for apogens while minimizing confounders. These programs were established for neural tube defect detection using early second trimester MSAFP. AFP produced by the fetus is secreted into the amniotic fluid, and then diffuses into the maternal circulation. With open neural tube defects, higher levels in the amniotic fluid can be detected in the maternal serum. It was soon recognized that factors that impaired maternal-fetal integrity and led to outcomes such as

stillbirths, prematurity, and small for gestational age, could affect MSAFP levels [19], and even influence levels at the opposite ends of distribution curves, as with prematurity [20]. Unexpectedly, fetuses with trisomy 18 and 21 had reduced levels, and other maternal serum markers such as human chorionic gonadotropin, pregnancy-associated plasma protein A, unconjugated estriol, and inhibin were found to assist in assessing risks here [21]. Such markers can also supplement AFP assessments for APOS [2,22,23], with risks that can be independent of each other, or more than just additive [24,25].

Since only a minority of marker abnormalities ultimately involve clinical disorders, this is a classic iceberg model, with mostly hidden effects as MSAFP levels indicate problems with maternal-fetal integrity or with fetal viability. With this, apogens should detectably alter APO related marker distributions with even small increases in abnormal outcomes, opening options for apogen screening. While it is possible to use various combinations of markers, AFP alone is emphasized here for simplicity: First, population wide apogen exposures should affect statistical parameters such as standard deviations, means, modes, etc. Appropriate controls are vital and should be generally available. They can be temporal, as for agricultural chemicals, with comparison during different seasons, geographical, as with power line emissions, using similar demographics in adjacent areas, or even historical, e.g., the same area before and after fracking. High and low marker levels could also be compared to each other and to the median for signs of shifts.

Second for agents with limited distributions, such as medications, exposed and non-exposed cohorts could be compared.

Third, if an apogen affects marker levels, women with abnormal values would be more likely to show exposures compared to controls at around the median. So, for maternal smoking, which is related to a variety of APOs, women who smoked had 3% higher MSAFP medians than those who did not [2], "enriching" a smoking history at higher marker levels.

Fourth, women with high risks for APOs can be identified through factors such as specific polymorphisms [26], previous marker elevations, or a history of losses [22], raising possibilities for prospectively monitoring a "sentinel cohort" with increased sensitivities.

Statistical analysis should be inexpensive using already obtained data. Some studies would entail interview expenses, but, since follow-up is already in place for women with abnormal levels, this would largely apply to control groups.

Early second trimester timing is also helpful. Studies can be initiated close to possible causative events, recall biases are reduced, late pregnancy confounders eliminated, and aneuploid

confounders unrelated to apogens are greatly decreased by this time [12].

Finally, for growth restriction, markers should be unaffected with a fetus "constitutionally small and fulfilling its growth potential" [9].

Conclusion

Common APOs associate with each other, and toxicities during pregnancy can non-specifically increase vulnerabilities to causative factors, with risks for losses, preterm delivery, and growth restriction, as well as certain structural defects. With these considerations, APOs can be considered as a group, with apogens that can affect risks in general. Overall, surveillance is difficult with common, continuous, and multifactorial APOs. However, marker data from existing neural tube defect detection programs should facilitate screening based on statistical distortions with altered risks, addressing issues otherwise generally refractory to analysis.

References

1. Gagnon A, Wilson RD, Audibert F (2008) Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can 30(10): 918-932.

2. Spencer K (1998) The influence of smoking on maternal serum AFP and free beta hCG levels and the impact on screening for Down syndrome. Prenat Diagn 18(3): 225–234.

3. Lubinsky M (2018) An epigenetic association of malformations, adverse reproductive outcomes, and fetal origins hypothesis related effects. J Assist Reprod Genet 35(6): 953-964.

4. Goldenberg RL, Culhane JF, Iams JD, Roberto Romero (2008) Epidemiology and causes of preterm birth. Lancet 371(9606): 75-84.

5. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F (2018) Effect of maternal age on the risk of preterm birth: A large cohort study. PloS one 13(1): e0191002.

6. Mathews TJ, MacDorman MF (2012) Infant mortality statistics from the 2008 period linked birth/infant death data set. Natl Vital Stat Rep 60(5):1-27.

7. Nardozza LM, Caetano AC, Zamarian AC, Jaqueline Brandão Mazzola, Carolina Pacheco Silva, et al. (2017) Fetal growth restriction: current knowledge. Arch Gynecol Obstet 295(5): 1061-1077.

8. Easter SR, Eckert LO, Boghossian N, Rebecca Spencer, Eugene Oteng Ntim, et al. (2017) Fetal growth restriction: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 35(48): 6546-6554.

9. (2013) American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 134: Fetal Growth Restriction. Obstet Gynecol 121(5): 1122-1133.

10. Jarvis GE (2016) Estimating limits for natural human embryo mortality. F1000Research 5: 2083.

11. Van den Berg MM, Van Maarle MC, Van Wely M, Mariëtte Goddijn (2012) Genetics of early miscarriage. Biochim Biophys Acta 1822(12): 1951-1959.

12. Joó JG, Beke A, Berkes E, János Rigó Jr, Csaba Papp (2009) Fetal pathology in second-trimester miscarriages. Fetal Diagn Ther 25: 186-191.

13. Lawn JE, Yakoob MY, Haws RA, Tanya Soomro, Gary L Darmstadt, et al. (2009) 3.2 million stillbirths: epidemiology and overview of the evidence review. BMC Pregnancy Childbirth 9(Suppl 1): S2.

14. Wou K, Ouellet MP, Che MF, Richard N Brown (2014) Comparison of the aetiology of stillbirth over five decades in a single centre: a retrospective study. BMJ Open 4(6): e004635.

15. Bailey BA, Sokol RJ (2011) Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. Alcohol Research & Health 34(1): 86.

16. Loffredo CA, Wilson PD, Ferencz C (2001) Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants. Teratology 64(2):98-106.

17. Milunsky A (1992) Maternal serum screening for neural tube and other defects. In Milunsky A (edt.)., Genetic disorders and the fetus. Diagnosis, prevention, and treatment (3rd edn.)., The Johns Hopkins University Press, Baltimore 1992: 507–656.

18. Soni S, Krantz DA, Greenberg M, Nidhi Vohra, Burton Rochelson (2017) Recurrence of extreme serum analytes in consecutive pregnancies and association with obstetrical outcomes. J Maternal-Fetal Neonatal Med 32(1): 85-91.

19. Lubinsky M (2019) The VACTERL association: mosaic mitotic aneuploidy as a cause and a model. Journal of Assisted Reproduction and Genetics 36(8): 1549-1554.

20. Waller DK, Lustig LS, Cunningham GC, LB Feuchtbaum, EB Hook (1996) The association between maternal serum alpha-fetoprotein and preterm birth, small for gestational age infants, preeclampsia, and placental complications. Obstet Gynecol 88(5): 816-822.

21. Spencer K (2002) Point-of-care screening for chromosomal anomalies in the first trimester of pregnancy. Clin Chem 48(3): 403-404.

22. Gunnarsdottir J, Stephansson O, Cnattingius S, Helena Akerud, Anna Karin Wikström (2014) Risk of placental dysfunction disorders after prior miscarriages: a population-based study. Am J Obstet Gynecol 211(1): 34-e1-e8.

23. Malhotra A, Allison BJ, Jenkin G, Polglase GR, Miller SL, et al. (2019) Neonatal morbidities of fetal growth restriction: pathophysiology and impact. Frontiers Endocrinol 10: 55.

24. Yefet E, Kuzmin O, Schwartz N, Flora Basson, Zohar Nachum (2017) Predictive value of second-trimester biomarkers and maternal features for adverse pregnancy outcomes. Fetal Diagn Ther 42(4): 285-293.

25. Malhotra A, Allison BJ, Jenkin G, Polglase GR, Miller SL, et al. (2019) Neonatal morbidities of fetal growth restriction: pathophysiology and impact. Frontiers Endocrinol 10: 55.

26. Borelli M, Baer RJ, Chambers CD, Tyler C Smith, Laura L Jelliffe Pawlowski (2017) Critical congenital heart defects and abnormal levels of routinely collected first-and second-trimester biomarkers. Am J Med Genet A 173(2): 368-374.

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