TECHNICAL COMMENTARY

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Obstetric complications

Introduction

Obstetric complications are a broad class of deviations from a normal course of events experienced during pregnancy, labour, delivery and the early neonatal period. Studies have attempted to investigate whether any deviation or combination of deviations are related to the subsequent development of schizophrenia. Teasing out possible effects of obstetric complications is not simple because many other, and often unknown, contributing factors are most probably involved. This table summarizes the available evidence to date from systematic reviews on the topic.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data were given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found five systematic reviews that met our inclusion criteria[3-7].

- Moderate to high quality evidence finds a large effect of increased odds of schizophrenia with exposure to maternal diabetes in utero. There were medium-sized effects of birth weight <2,000g, congenital malformations, uterine atony, Rhesus variables (comprising rhesus incompatibility, rhesus-negative mother and rhesus antibodies), and a small effect of bleeding in pregnancy. Moderate quality evidence also found a small effect of preeclampsia, and moderate to low quality evidence found

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small effects of asphyxia and birth weight <2,500g. Review authors state that uncontrolled confounding variables may account for some of the associations observed.

- For obstetric complications in general, moderate quality evidence finds a medium-sized increased risk of ultra high-risk mental states and a small effect of increased risk of schizophrenia compared to bipolar disorder.

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Cannon M, Jones PB, Murray RM

Obstetric complications and schizophrenia: historical and meta-analytic review

American Journal of Psychiatry 2002; 159(7): 1080-1092

View review abstract online

Comparison	**Exposure to obstetric complications and schizophrenia in adulthood.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) finds a large effect of increased odds of schizophrenia with exposure to maternal diabetes in utero. There were medium-sized effects of birth weight <2,000g, emergency caesarean section, congenital malformations, uterine atony, Rhesus variables (comprising rhesus incompatibility, rhesus-negative mother and rhesus antibodies), and a small effect of bleeding in pregnancy. Moderate to low quality evidence (inconsistent, imprecise) also found small effects of asphyxia and birth weight <2,500g.** **Authors state that uncontrolled confounding variables may account for some, if not all associations observed.**
Maternal diabetes during pregnancy	
Significant, large increase in odds of development of schizophrenia; 2 studies, N = 2,146, OR = 7.76, 95%CI 1.37 to 43.90, $p < 0.03$	
Birth weight <2,000g	
Significant, medium increase in odds of later development of schizophrenia; 2 studies, N = 11,430, OR = 3.89, 95%CI 1.40 to 10.84, $p = 0.009$	
Caesarean section	

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Significant, medium increase in odds of later development of schizophrenia with emergency caesarean; 3 studies, N = 508,681, OR = 3.24, 95%CI 1.40 to 7.50, *p* = 0.006 *No significant increase in odds of later development of schizophrenia with caesarean section;* 5 studies, N = 527,259, OR = 0.99, 95%CI 0.70 to 1.41, *p* = 0.98
Congenital malformations
Significant, medium increase in odds of later development of schizophrenia; 3 studies, N = 509,518, OR = 2.35, 95%CI 1.21 to 4.57, *p* < 0.02
Uterine atony
Significant, medium increase in odds of later development of schizophrenia; 2 studies, N = 508,362, OR = 2.29, 95%CI 1.51 to 3.50, *p* < 0.001
Rhesus variables comprising rhesus incompatibility, rhesus-negative mother and rhesus antibodies
Significant, medium increase in odds of later development of schizophrenia; 3 studies, N = 18,296, OR = 2.00, 95%CI 1.01 to 3.96, *p* < 0.05
Asphyxia
Significant, small increase in odds of later development of schizophrenia; 3 studies, N = 3,406, OR = 1.74, 95%CI 1.15 to 2.62, *p* = 0.008, Q = 10.41, *p* = 0.005
Bleeding in pregnancy
Significant, small increase in odds of later development of schizophrenia; 6 studies, N = 526,195, OR = 1.69, 95%CI 1.14 to 2.52, *p* = 0.009
Birth weight <2,500g

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Significant, small increase in odds of later development of schizophrenia; 5 studies, N = 537,339, OR = 1.67, 95%CI 1.22 to 2.29, *p* = 0.002, Q = 12.56, *p* = 0.02
Head circumference <32cm
No significant increase in odds of later development of schizophrenia; 2 studies, N = 509,073, OR = 1.38, 95%CI 0.97 to 1.91 *p* = 0.08 No Q, *p* value reported, authors state data homogeneous
Threatened premature delivery
No significant increase in odds of later development of schizophrenia; 2 studies, N = 508,660, OR = 1.98, 95%CI 0.79 to 4.90, *p* = 0.14
Placental abruption
No significant increase in odds of later development of schizophrenia; 2 studies, N = 508,660, OR = 4.02, 95%CI 0.89 to 18.12, *p* = 0.07
Smoking in pregnancy
No significant increase in odds of later development of schizophrenia; 2 studies, N = 17,991, OR = 1.38, 95%CI 0.88 to 2.14, *p* = 0.16
Preeclampsia
No significant increase in odds of later development of schizophrenia; 6 studies, N = 511,987, OR = 1.36, 95%CI 0.99 to 1.85, *p* = 0.05
Anemia in pregnancy
No significant increase in odds of later development of schizophrenia; 3 studies, N = 2,048, OR = 1.26, 95%CI 0.69 to 2.28, *p* = 0.45

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Gestational age <37 weeks
No significant increase in odds of later development of schizophrenia; 5 studies, N = 537,341, OR = 1.22, 95%CI 0.90 to 1.65, *p* = 0.20
Small for gestational age
No significant increase in odds of later development of schizophrenia; 5 studies, N = 520,501, OR = 1.21, 95%CI 0.91 to 1.61, *p* = 0.19
Induction of labour
No significant increase in odds of later development of schizophrenia; 4 studies, N = 3,050, OR = 1.18, 95%CI 0.89 to 1.56, *p* = 0.25
Apgar score <7 at 1 min after birth
No significant increase in odds of later development of schizophrenia; 2 studies, N = 507,824, OR = 1.09, 95%CI 0.62 to 1.92, *p* = 0.76
Gestational age >42 weeks
No significant increase in odds of later development of schizophrenia; 3 studies, N = 509,934, OR = 1.08, 95%CI 0.69 to 1.68, *p* = 0.72
Child stayed in hospital after mother discharged
No significant increase in odds of later development of schizophrenia; 3 studies, N = 2,461, OR = 1.07, 95%CI 0.79 to 1.44, *p* = 0.65
Forceps delivery or vacuum extraction

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No significant increase in odds of later development of schizophrenia; 7 studies, N = 528,782, OR = 1.07, 95%CI 0.85 to 1.35, *p* = 0.48
Birth length <49cm
No significant increase in odds of later development of schizophrenia; 3 studies, N = 52,081, OR = 1.06, 95%CI 0.86 to 1.31, *p* = 0.59
Cephalopelvic disproportion
No significant increase in odds of later development of schizophrenia; 2 studies, N = 3,000, OR = 1.04, 95%CI 0.28 to 3.82, *p* = 0.95
Cord around neck
No significant increase in odds of later development of schizophrenia; 2 studies, N = 2,238, OR = 1.03, 95%CI 0.81 to 1.31, *p* = 0.83
Birth weight <2500g and premature
No significant increase in odds of later development of schizophrenia; 4 studies, N = 12,360, OR = 0.96, 95%CI 0.62 to 1.46, *p* = 0.84
Non-vertex presentation
No significant increase in odds of later development of schizophrenia; 6 studies, N = 511,875, OR = 0.89, 95%CI 0.67 to 1.20, *p* = 0.45
Breech delivery
No significant increase in odds of later development of schizophrenia; 3 studies, N = 508,972, OR = 0.87, 95%CI 0.38 to 1.97, *p* = 0.74

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Urinary tract infection in pregnancy	
No significant increase in odds of later development of schizophrenia; 3 studies, N = 508,420, OR = 0.86, 95%CI 0.48 to 1.55, $p = 0.63$	
Non-spontaneous delivery	
No significant increase in odds of later development of schizophrenia; 2 studies, N = 17,435, OR = 0.63, 95%CI 0.39 to 1.01, $p < 0.06$	
Consistency in results‡	Mostly consistent; authors report most data are homogenous.
Precision in results§	Imprecise
Directness of results‖	Direct

Dachew BA, Mamun A, Maravilla JC, Alati R

Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: A systematic review and meta-analysis

Psychiatry Research 2018; 260: 458-67

View review abstract online

Comparison	**Exposure to preeclampsia in utero and schizophrenia in adulthood.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests a small effect of increased risk of schizophrenia in offspring exposed to preeclampsia in utero.**
Prevalence of adverse life events	
Small, significant increased risk of schizophrenia in offspring exposed to preeclampsia; 11 studies, N = 1,462,823, RR = 1.37, 95%CI, 1.08 to 1.72, $I^2 = 64\%$, $p < 0.001$ Subgroup analyses revealed the effect size was larger in cohort vs. case-control studies, studies with large vs. small samples, and in good vs. poor quality studies.	

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Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J, Kotlicka-Antczak M, Valmaggia L, Lee J, Millan MJ, Galderisi S, Balottin U, Ricca V, McGuire P

Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk

European Psychiatry 2017; 40: 65-75

View review abstract online

Comparison	**Obstetric complications in people with ultra high-risk (UHR) mental states, which are determined as; attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, and genetic risk and functional deterioration.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) suggests a medium-sized relationship between obstetric complications in general and ultra high-risk mental states.**

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A significant medium-sized association between unspecified obstetric complications and the UHR state;

2 studies, N = 211, OR = 3.06, 95%CI 1.813 to 5.171, $p < 0.001$, $I^2 = 0\%$, $p = 0.585$

There were no significant associations between UHR and caesarean delivery.

There was no evidence of publication bias

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Scott J, McNeill Y, Cavanagh J, Cannon M, Murray R

Exposure to obstetric complications and subsequent development of bipolar disorder: Systematic review

British Journal of Psychiatry 2006; 189: 3-11

View review abstract online

Comparison	**Obstetric complications and schizophrenia vs. bipolar disorder in adulthood.**
Summary of evidence	**Moderate quality evidence (large sample, imprecise, unable to assess consistency, direct) suggests a small increased risk of schizophrenia compared to bipolar disorder with exposure to obstetric complications in general.**
Obstetric complications	
Small, significant effect of an increased risk of schizophrenia with exposure to obstetric complications; 5 studies, N = 640, OR = 0.61, 95%CI 0.39 to 0.95, *p* = 0.035, Q,*p* value not reported Similar results were found in analyses of studies controlling possible confounders; sex, maternal age, or socioeconomic status and another assessing study quality.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Zhang T, Sidorchuk A, Sevilla-Cermeno L, Vilaplana-Perez A, Chang Z, Larsson H, Mataix-Cols D, Fernandez De La Cruz L

Association of Cesarean Delivery with Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis

JAMA Network Open 2019; 2(8): e1910236

View review abstract online

Comparison	**Association between caesarean delivery and the development of schizophrenia by 29 years.** **Note: the sample included people with schizophrenia and other**

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	non-affective psychoses.
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds no association between caesarean section and schizophrenia.**
Elective and emergency caesarean section	
No significant association; 5 studies, N >1.5M, OR = 0.97, 95%CI 0.78 to 1.21, $p > 0.05$, $I^2 = 83\%$ The results were similar in the subgroup analysis of elective and emergency caesarean.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, RR = risk ratio, vs. versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[8].

† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[8].

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[10].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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