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Biochemical tests of placental function for assessment in pregnancy (Review)

Neilson JP

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TABLE OF CONTENTS

[Intervention Review]

Biochemical tests of placental function for assessment in pregnancy

James P Neilson[1]

[1]Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK

Contact: James P Neilson, Department of Women's and Children's Health, The University of Liverpool, First Floor, Liverpool Women's NHS Foundation Trust, Crown Street, Liverpool, L8 7SS, UK. jneilson@liverpool.ac.uk.

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ABSTRACT

Background

Biochemical tests of placental or feto-placental function were widely used in the 1960s and 1970s in high-risk pregnancies to try to predict, and thus try to avoid, adverse fetal outcome.

Objectives

To assess the effects of performing biochemical tests of placental function in high-risk, low-risk, or unselected pregnancies.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (10 May 2012).

Selection criteria

Controlled trials (randomized or 'quasi-randomized') that compare the use of biochemical tests of placental function in pregnancy with non-use.

Data collection and analysis

Trial quality was assessed and data were extracted by the review author.

Main results

A single eligible trial of poor quality was identified. It involved 622 women with high-risk pregnancies who had had plasma (o)estriol estimations. Women were allocated to have their (o)estriol results revealed or concealed on the basis of hospital record number (with attendant risk of selection bias). There were no obvious differences in perinatal mortality (relative risk (RR) 0.88, 95% confidence interval (CI) 0.36 to 2.13) or planned delivery (RR 0.97, 95% CI 0.81 to 1.15) between the two groups.

Authors' conclusions

The available trial data do not support the use of (o)estriol estimation in high-risk pregnancies. The single small trial available does not have the power to exclude a beneficial effect but this is probably of historical interest since biochemical testing has been superseded by biophysical testing in antepartum fetal assessment.

PLAIN LANGUAGE SUMMARY

Biochemical tests of placental function for assessment in pregnancy

Testing women's hormone levels during high-risk pregnancy has not been shown to benefit women or their babies.

The placenta provides nourishment for the baby in the womb (uterus) during pregnancy. It has been thought that testing women's hormone levels during pregnancy, might show how well the placenta is functioning and whether the baby is growing as would be expected. (Hormones are natural chemicals produced in the body.) The review of one trial (622 women) found some evidence that measuring (o)estriol levels in high-risk pregnancies did not affect the outcome of the pregnancy.

BACKGROUND

A wide range of biochemical tests of fetal well-being were introduced during the 1950s and 1960s, but there was little agreement on their usefulness (Alexander 1989). Greene 1965 listed more than 20 biochemical tests of placental function, but only two found an established role in antepartum assessment: urinary or plasma (o)estriols, and human placental lactogen (Chard 1982). Human placental lactogen is produced by the placenta while oestriol is produced by a biochemical pathway that involves both the placenta and the endocrine system of the fetus. Both hormones tend to demonstrate low (and sometime falling) levels in association with utero-placental dysfunction manifesting as fetal growth restriction. Although there was little strong evidence to either commend or reject the use of these tests, they fell rapidly out of favour during the 1970s and became superceded by biophysical fetal testing, notably by antepartum cardiotocography and the ultrasound-based fetal biophysical profile. Ironically, the evidence base for the use of these tests is similarly thin (Alfirevic 2002; Pattison 2002). It was not until 1995 that a systematic review of randomized controlled trials of use of any method of antepartum fetal assessment demonstrated any tangible evidence of benefit - in this case, Doppler assessment of umbilical artery waveforms in high-risk pregnancies (Alfirevic 1995; Neilson 2002).

It is possible that trials of the effects of using other biochemical tests may take place in the future. Both alpha-fetoprotein (a fetal product) and human chorionic gonadotropin (a placental hormone) are biochemical tests used to screen for fetal chromosomal disorders in early to mid pregnancy. Both tests have a loose capability of predicting subsequent pregnancy complications including fetal growth restriction and pre-eclampsia (e.g. Luckas 1998) and could, theoretically, provide the basis for future screening trials.

OBJECTIVES

To determine if knowledge of the results of placental or feto-placental hormone levels are of benefit in improving fetal outcome or obstetric care in high-risk, low-risk, or unselected pregnancies.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomized or 'quasi-randomized' controlled trial that assesses the effects of biochemical testing of placental or feto-placental function in pregnancy and reports clinically meaningful results on an intention to treat basis.

Types of participants

Pregnant women with high-risk, low-risk, or unselected pregnancies.

Types of interventions

Biochemical tests that predict adverse pregnancy outcome.

Types of outcome measures

Adverse fetal outcomes, pregnancy complications, obstetric intervention.

Search methods for identification of studies

The Cochrane Pregnancy and Childbirth Group's Trials Register (10 May 2012).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group. Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

No language restrictions were applied.

Data collection and analysis

Reports of identified trials that appeared relevant to the objectives of the review were evaluated for inclusion. Both published and unpublished reports could be included. Attempts would be made to translate identified, non-English language reports. Primary authors would be contacted for additional details when necessary. Reasons for excluding apparently relevant trials are made explicit.

Included trials were assessed according to the following criteria:
(1) adequate concealment of treatment allocation (e.g. sealed, opaque, numbered envelopes);
(2) method of allocation to treatment (e.g. by computer randomisation, random number tables);
(3) adequate documentation of how exclusions were handled after treatment allocation - to facilitate 'intention to treat' analyses;
(4) adequate blinding of outcome assessment, where appropriate;
(5) losses to follow up (trials with losses of greater than 25% will be excluded).

Data were entered directly from reports into Review Manager software (RevMan 2000) and statistical analysis performed. For dichotomous data, relative risks (RRs) and 95% confidence intervals (CIs) were calculated. Weighted mean differences (WMDs) and 95% CIs were calculated for continuous data (Clarke 2001).

Heterogeneity between trials is tested using a standard chi squared test. In the presence of significant heterogeneity, a sensitivity analysis is used to explore the influence of high quality trials (fulfilling the criteria above) compared with those of lesser quality.

RESULTS

Description of studies

A single trial of 622 women that met the criteria for this review was found (Duenhoelter 1976) (*see* table of Characteristics of included studies). Three potentially eligible trials were excluded - *see* Characteristics of excluded studies for details.

Risk of bias in included studies

In the included study participants were allocated into groups by hospital number, with the attendant risk of selection bias.

Effects of interventions

In the Duenhoelter 1976 trial, there were similar rates of perinatal death (relative risk (RR) 0.88, 95% confidence interval (CI) 0.36 to 2.13) and planned delivery (RR 0.97, 95% CI 0.81 to 1.15) in the two groups (oestriol results reported or concealed).

DISCUSSION

Available data from the single, identified trial provide no encouragement for the use of biochemical testing of feto-placental wellbeing during pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

There is no support from the single available randomized trial for the use of oestriol estimation in high-risk pregnancies.

Implications for research

It seems unlikely at the moment that this area will be a major focus for research effort in the future, but innovations in laboratory techniques could change that.

ACKNOWLEDGEMENTS

None.

REFERENCES

References to studies included in this review

Duenhoelter 1976 *{published data only}*

Duenhoelter JH, Whalley PJ, MacDonald PC. An analysis of the utility of plasma immunoreactive estrogen measurements in determining delivery time of gravidas with a fetus considered at high risk. *American Journal of Obstetrics and Gynecology* 1976;**125**:889-98.

References to studies excluded from this review

Grudzinskas 1990 *{unpublished data only}*

Grudzinskas JG. To assess the effects of biochemical placental function testing. Personal Communication 1990.

Sharf 1984 *{published data only}*

Sharf M, Eibschitz I, Hakim M, Degani S, Rosner B. Is serum free estriol measurement essential in the management of hypertensive disorders during pregnancy?. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1984;**17**:365-75.

Spellacy 1975 *{published data only}*

Spellacy WN, Buhi WC, Birk SA. The effectiveness of human placental lactogen measurements as an adjunct in decreasing perinatal deaths. Results of a retrospective and randomized controlled prospective study. *American Journal of Obstetrics and Gynecology* 1975;**121**:835-44.

Additional references

Alexander 1989

Alexander S, Stanwell-Smith R, Buekens P, Keirse MJNC. Biochemical assessment of fetal well-being. In: Chalmers I, Enkin MW, Keirse MJNC editor(s). Effective care in pregnancy and childbirth. Vol. **1**, Oxford: Oxford University Press, 1989:455-76.

Alfirevic 1995

Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: systematic review with meta-analysis. *American Journal of Obstetrics and Gynecology* 1995;**172**:1379-87.

Alfirevic 2002

Alfirevic Z, Neilson JP. Biophysical profile for fetal assessment in high risk pregnancies. *Cochrane Database of Systematic Reviews* 2002, Issue 2.

Chard 1982

Chard T, Klopper A. Placental function tests. Berlin: Springer-Verlag, 1982.

Clarke 2001

Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook 4.1 [updated June 2000]. In: Review Manager (RevMan) [Computer program]. Version 4.1. Oxford, England: The Cochrane Collaboration, 2000.

Greene 1965

Greene JW Jr, Duhring JL, Smith K. Placental function test. A review of methods available for assessment of the fetoplacental complex. *American Journal of Obstetrics and Gynecology* 1965;**92**:1030-58.

Luckas 1998

Luckas MJ, Sandland R, Hawe J, Neilson JP, McFadyen IR, Meekins JW. Fetal growth retardation and second trimester maternal serum human chorionic gonadotrophin levels. *Placenta* 1998;**19**:143-7.

Neilson 2002

Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. *Cochrane Database of Systematic Reviews* 2002, Issue 2.

Pattison 2002

Pattison N, McCowan L. Cardiotocography for antepartum fetal assessment. *Cochrane Database of Systematic Reviews* 2002, Issue 2.

RevMan 2000 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan). Version 4.1 for Windows. Oxford, England: The Cochrane Collaboration, 2000.

References to other published versions of this review

Neilson 1995

Neilson JP. Hormonal Placental Function Tests [revised 12 May 1994]. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds) Pregnancy and Childbirth Database [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Neilson 1997

Neilson JP, Cloherty LJ. Hormonal placental function tests for fetal assessment in high risk pregnancies. *Cochrane Database of Systematic Reviews* 1997, Issue 2.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Duenhoelter 1976

Methods	'Quasi-randomization' by hospital record number.

Duenhoelter 1976 *(Continued)*

	Group A (reported group), plasma oestrogen levels measured and reported promptly. Group B (concealed group), plasma oestrogen levels measured but values were neither computed nor reported; they were computed and evaluated retrospectively. A total of 4,678 plasma samples were assayed in the 622 women, an average of 7.5 samples per woman.
Participants	622 women with high risk pregnancies, including fetal growth restriction, hypertension, adverse obstetric history. There were 315 in Group A (reported group) and 307 in Group B (concealed group).
Interventions	Oestriol results revealed or concealed.
Outcomes	Perinatal deaths (stillbirths and neonatal deaths), planned delivery (induction of labour and elective caesarean section).
Notes	The study was conducted at two different sites which dealt with high risk obstetric problems.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Grudzinskas 1990	Trial abandoned - no data available.
Sharf 1984	'Patients were divided into two ... groups according to the diagnoses, ages, parity and weeks of gestation' - so unlikely to have been allocated randomly.
Spellacy 1975	Data only available for the 8% of participants who had abnormally low human placental lactogen results.

DATA AND ANALYSES

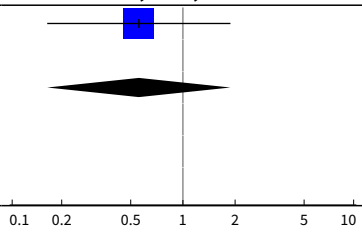
Comparison 1. Oestriol levels reported versus not reported

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fetal death	1	622	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.16, 1.88]
2 Neonatal death	1	622	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.39, 6.74]
3 Perinatal death	1	622	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.36, 2.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Induction of labour	1	622	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.64, 1.06]
5 Elective caesarean section	1	622	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.89, 1.79]
6 Planned delivery	1	622	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.15]

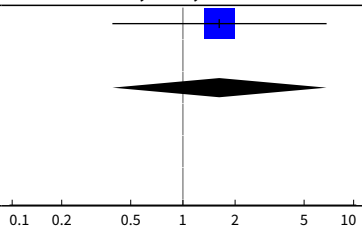
Analysis 1.1. Comparison 1 Oestriol levels reported versus not reported, Outcome 1 Fetal death.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Duenhoelter 1976	4/315	7/307		100%	0.56[0.16,1.88]
Total (95% CI)	**315**	**307**		**100%**	**0.56[0.16,1.88]**
Total events: 4 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					



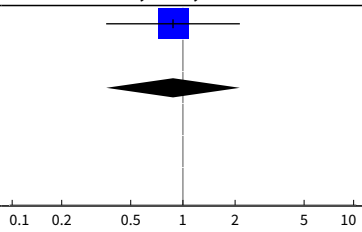
Analysis 1.2. Comparison 1 Oestriol levels reported versus not reported, Outcome 2 Neonatal death.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Duenhoelter 1976	5/315	3/307		100%	1.62[0.39,6.74]
Total (95% CI)	**315**	**307**		**100%**	**1.62[0.39,6.74]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					

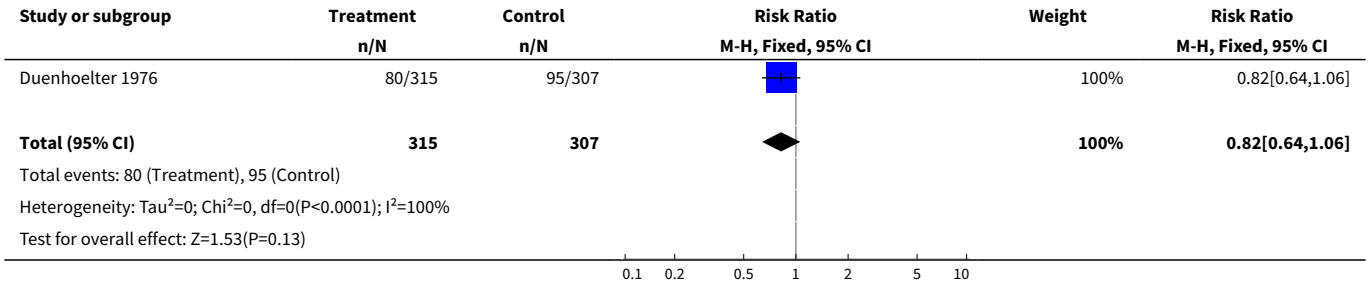


Analysis 1.3. Comparison 1 Oestriol levels reported versus not reported, Outcome 3 Perinatal death.

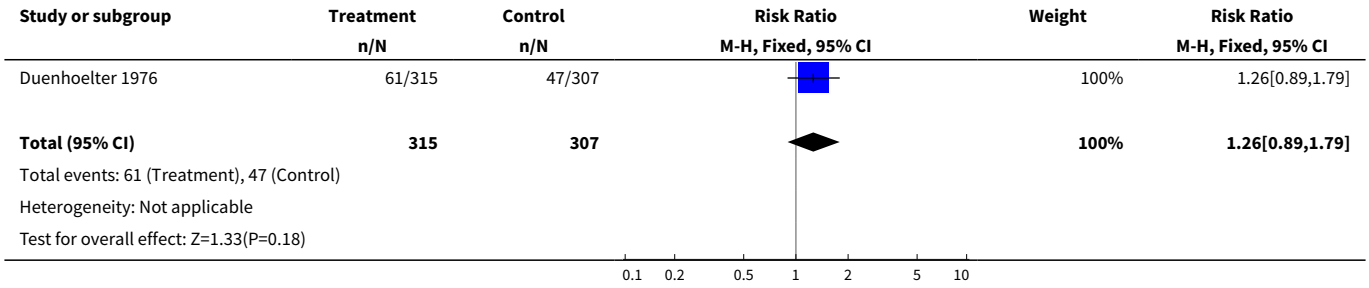
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Duenhoelter 1976	9/315	10/307		100%	0.88[0.36,2.13]
Total (95% CI)	**315**	**307**		**100%**	**0.88[0.36,2.13]**
Total events: 9 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.29(P=0.77)					



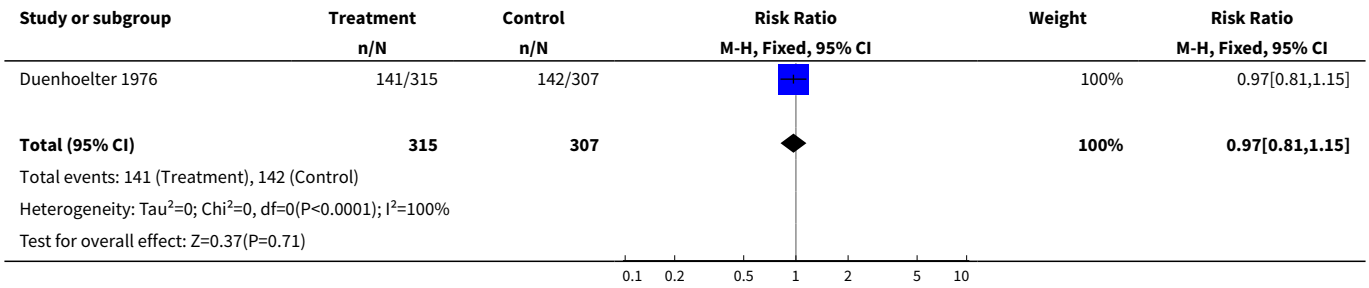
Analysis 1.4. Comparison 1 Oestriol levels reported versus not reported, Outcome 4 Induction of labour.



Analysis 1.5. Comparison 1 Oestriol levels reported versus not reported, Outcome 5 Elective caesarean section.



Analysis 1.6. Comparison 1 Oestriol levels reported versus not reported, Outcome 6 Planned delivery.



WHAT'S NEW

Date	Event	Description
27 June 2012	New citation required but conclusions have not changed	Review updated with results of new search.
10 May 2012	New search has been performed	Search updated. No new trials identified

HISTORY

Protocol first published: Issue 2, 1997
Review first published: Issue 2, 1997

Date	Event	Description
1 October 2009	New search has been performed	Search updated. One new study identified and excluded (Sharf 1984).
31 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JP Neilson prepared and maintains the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Liverpool, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Biomarkers [blood]; Estriol [*blood]; Fetal Diseases [*diagnosis]; Placental Function Tests [methods]; Pregnancy, High-Risk [*blood]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy