Prenatal diagnosis and outcome of fetuses with isolated agenesis of septum pellucidum: cohort study and meta-analysis

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Long-term outcome of fetuses with prenatal diagnosis of isolated Agenesis of Septum Pellucidum

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CONTRIBUTION

What are the novel findings of this work?

This study has evaluated the pediatric outcome of more than 70 children with prenatal diagnosis of agenesis of the Septum Pellucidum (ASP) and demonstrated that in the vast majority of cases the prognosis is favorable. However, additional anomalies are detected after birth in about 10% of these cases and have a negative impact on the clinical outcome.

What are the clinical implications of this work?

This study provides evidence that in fetuses with apparently isolated ASP a detailed antenatal assessment of the brain and the optic nerves is strongly recommended in order to identify the presence of associated anomalies.

Keywords: Septum pellucidum, Septo-Optic Dysplasia, optic nerves, neurological disability

ABSTRACT

OBJECTIVE

To evaluate the postnatal outcome of children with prenatal diagnosis of apparently isolated agenesis of the septum pellucidum agenesis (ASP).

METHODS

A retrospective cohort study of cases of prenatally diagnosed ASP followed in 2 tertiary centers and a systematic review were carried out. Only cases with apparently isolated ASP at antenatal ultrasound and/or MRI and available postnatal follow-up were considered eligible for this study. The following outcomes were analyzed: incidence of chromosomal anomalies, the agreement between antenatal and postnatal findings, the overall incidence of SOD (septo-optic dysplasia) and the incidence of major neurological disability (motor, language of behavioral disease) in non-SOD children. The incidence of SOD in those cases with apparently normal visual pathways at antenatal imaging was also evaluated.

RESULTS

Fifteen cases of isolated ASP with a median postnatal follow up of 36 months (12-60) were selected from the two Centres. Six studies met the inclusion criteria for the systematic review and a total of 79 cases were eligible for the analysis, including our series. Genetic tests were antenatally carried out in 30 fetuses and turned out to be abnormal in 2 of them (pooled proportion 9.0%; 95% CI 1.8-20.7; I^2 0%). Additional or discordant imaging findings were postnatally noted in 9/70 patients (Pooled proportion 13.7%; 95%CI 3.5-29.0; I^2 63.9%); Among the 79 neonates with available follow-up, SOD was postnatally diagnosed in 14 cases (Pooled proportion 19.0%; 95% CI 8.6-32.2; I^2 48.0%). In 60 cases Optic nerves or optic tracts were considered to be normal at antenatal imaging; among them, a diagnosis of SOD was carried out in 6 cases (Pooled proportion 9.1%; 95%CI 1.1-24.0; I^2 62.0%). Among the 57 infants with available neurological follow-up that were not affected by SOD,

a major neurological disability was diagnosed in 5 (pooled proportion 8.3%; 95% CI 1.4-20.2; I^2 45.9%)

CONCLUSION

In the vast majority of cases with apparently isolated ASP the prognosis is favorable. However, additional anomalies are detected after birth in about 10% of these cases and have a negative impact on the clinical outcome. The antenatal visualisation of optic tract does not rule out SOD.

INTRODUCTION

The agenesis of the septum pellucidum (ASP) is a rare cerebral malformation characterized by the partial or the complete absence of the leaflets of the septum pellucidum; its prevalence in the general population is about 2-3/100.000[1]. Although it may be incidentally detected in normal individuals, this finding is often part of complex cerebral anomalies such as holoprosencephaly (HPE), schizencephaly, corpus callosum agenesis or severe ventriculomegaly that are mostly detectable at prenatal imaging[2,3] and for which prenatal counselling is fairly clear and straightforward.

ASP may be also the clue of a rare midline anomaly (1:10000 live births) known as Septo-Optic Dysplasia (SOD) or DeMorsier Syndrome which is characterized by a variable association of septal agenesis, hypoplasia of one or both optic nerves, pituitary anomalies or endocrine impairment and whose antenatal diagnosis is extremely challenging [4,5]. Therefore, in absence of major brain malformations, ASP should be always considered as highly suggestive of SOD and therefore the assessment of the optic chiasm (OC), optic tracts (OTs) or Optic Nerves (ONs) by means of 2D/3D ultrasound or antenatal Magnetic Resonance Imaging (MRI) is warranted [6-9]. In addition, a wide spectrum of neurological manifestations (developmental delay, seizures and cerebral palsy) has been also described in patients with ASP without SOD [2,10]. For these reasons, although the recent advances in prenatal imaging have made possible the visualization and the measurement of the OTs, the antenatal counselling of the prospective parents still represents a challenge for clinicians[8,9,11].

The purpose of this study was to investigate the ultrasound characteristics and outcome of fetuses with apparently isolated ASP followed at two tertiary university hospitals, to provide a meta-analysis of the studies on the long-term outcome of fetuses with prenatal diagnosis of apparently isolated ASP.

MATERIALS AND METHODS

Cohort study

A retrospective cohort study of cases with apparently isolated fetal ASP was carried out at two tertiary university hospitals (Necker Enfants Malades Hospital in Paris and Maggiore Hospital in Parma). Cases followed between January 2010 and December 2020 were retrieved from the ultrasound (US) database and medical records were collected including demographic data, gestational age at diagnosis, pre- and post-natal ultrasound and MRI findings. Pregnancy outcome, gestational age at- and mode of delivery, birthweight, obstetric and fetal complications were also registered. Stillbirths or cases of ASP associated with others major fetal anomalies or severe ventriculomegaly (VM) (≥15 mm) were excluded.

Postnatal follow-up data was searched through the medical notes of the infant or by a telephonic questionnaire addressed to the parents and/or to the family paediatrician. The following information were collected: age at the evaluation, neurological assessment (motor deficit, epilepsy, mental retardation, language delays, learning difficulties and behavioural disorders), ophthalmological assessment (presence of myopia, amblyopia, hyperopia, astigmatism, nystagmus, strabismus or blindness) and presence of endocrine dysfunction.

Systematic review

Search strategy and study selection

This review was performed according to the PRISMA guidelines[12]. Medline and Embase, databases were searched electronically on April 2020 and updated on the 16th of February 2021 using combinations of the relevant medical subject heading terms (MeSH) and keywords variants for "agenesis of the septum pellucidum", "septo-optic dysplasia", "outcome", "MRI" and "ultrasound". Two independent investigators (EDP, MK) conducted the literature search, reviewed all the abstracts and independently extracted relevant data regarding study characteristics and neonatal outcome. Inconsistencies were discussed by the reviewers and consensus reached. Studies published before

2010 were not included because advances in prenatal imaging techniques has led to an improvement in the definition of prenatal structural anomalies. Only full text articles were considered eligible for the inclusion and the search was restricted to English-language articles. The reference list of any included article was crosschecked for additional reports. Cohort studies were included. Editorials, conference abstracts, case reports and case series of fewer than 3 patients were excluded. Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies[13].

Data extraction and definitions

ASP was defined isolated in absence of additional cerebral or extra-cerebral major anomalies and with an atrial width of the lateral ventricle ≤15mm.

The Agenesis of the Septum Pellucidum was defined partial if only one of the two leaflets was absent and complete if both the leaflets were absent (Figure 1, Video).

The incidence of the following outcomes was investigated as available:

- Incidence of discordant or additional findings at post-natal imaging
- Incidence of chromosomal anomalies
- Overall incidence of SOD
- Incidence of SOD in those cases with normal ONs, OTs and/or OC at antenatal imaging
- Incidence of a major neurological disability in non-SOD children, defined by the presence of at least one of the following: motor, language, coordination or behavioural disease, epilepsy

Only cases with isolated ASP at antenatal imaging (US and/or MRI) and available postnatal follow-up were considered suitable for the inclusion in the current systematic review.

Fetuses with apparently isolated ASP at ultrasound but additional findings at MRI were excluded from the final analysis

Moreover, for cases in which termination of pregnancy (TOP) was elected, only the results of genetic testing when available were considered for the study purposes

Statistic analysis

Meta-analyses of proportions were used to combine data[14]. Between-study heterogeneity was explored using I^2 statistic which indicates the percentage of between-study variation that is due to heterogeneity rather than chance. A value of I^2 of 0% indicates no observed heterogeneity, whereas values $\geq$ 50% indicate a substantial level of heterogeneity. Given the retrospective design and the small sample size of the included studies, a random effect model was preferred, regardless of I^2 [15]. Tests for funnel plot asymmetry were carried out in order to display the outcome rate from individual studies versus their precision (1/standard error). Potential publication bias was assessed by using Begg's and Egger's regression asymmetry test. StatsDirect 3.4.4 (StatsDirect Ltd, Altrincham) statistical software was used for all data analyses.

RESULTS

Our series

Over the study period, 20 fetuses with isolated ASP were antenatally diagnosed at the two participating Centres. Three of them were lost at follow-up and 2 cases were excluded due to the association with arhinencephaly and with periventricular heterotopia respectively. Pregnancy and fetal characteristics of the 15 cases included in the final analysis are reported in Table 1.

Septum pellucidum agenesis was complete in 4 fetuses (26.7%) while in a case a mild VM was also associated. Optic tracts and chiasma were visualized in all fetuses with the exception of one whose chiasma was not clearly discernible at antenatal imaging (both US and MRI). In this child SOD with visual impairment was postnatally diagnosed. In the other 14 cases, a normal neurological, endocrinological and ophthalmological development at a median follow-up of 36 (12-60) months was reported with no children presenting major neurological disability.

Review of literature

Five hundred forty-five records were identified through the database searching and were screened by the abstract assessment while for 21 studies the full text was evaluated (Table 6 Supplem). Fifteen studies were excluded due to a specific reason (Table 7 Supplem) while 6 studies with a sample size ranging between 5 and 17 cases met the inclusion criteria (Figure 2) [9,11,16-20]. The quality assessment of the included studies is illustrated in Table 2. Overall, 79 cases with available post-natal follow-up including our own series were considered for the present review. A summary of the main characteristics of the included studies is illustrated in Table 3.

Genetic tests were antenatally carried out in 30 fetuses and turned out to be abnormal in 2 of them (pooled proportion 9.0%; 95% CI 1.8-20.7; I^2 0%) (Figure 5 Supplem.); in one case a microdeletion of 30 kb of the region 1p14 was found at the chromosomal microarray and the woman underwent a TOP; in the latter case a variant of unknown significance (VOUS) was demonstrated on the chromosome 10p13; this latter patient was postnatally diagnosed with SOD.

At comparison with prenatal imaging (US and/or MRI), additional or discordant findings were postnatally noted in 9/70 patients (Pooled proportion 13.7%; 95%CI 3.5-29.0; I^2 63.9%); in 4/9 of them (44.4%) the additional findings were represented by anomalies interesting the visual pathways (Table 4 and Table 8 Supplem, Figure 6 Supplem.).

Among the 79 neonates with available follow-up, SOD was postnatally diagnosed in 14 cases (Pooled proportion 19.0%; 95% CI 8.6-32.2; I^2 48.0%), with 9 of them (64.3%) having an ophthalmologic impairment (Figure 7 Supplem).

In 60 cases ONs/OTs were evaluated at the antenatal imaging (US and/or MRI) and considered to be normal; among them, a diagnosis of SOD was carried out in 6 cases (Pooled proportion 9.1%; 95%CI 1.1-24.0; I^2 62.0%) (Figure 3, Figure 8 Supplem). In two of these the optic tracts turned out to be normal at antenatal imaging but were found to be hypoplastic at post-natal follow-up while in 4 cases (66.7%) only the endocrinological criteria of SOD were present (Table 4 and 5).

Eventually, among the 57 infants with available neurological follow-up that were not affected by SOD, a major neurological disability was diagnosed in 5 (pooled proportion 8.3%; 95%CI 1.4-20.2; I^2 45.9%) (Table 4 and 5, Figure 4, Figure 9 Supplem).

DISCUSSION

Summary of Evidence

This study has evaluated the paediatric outcome of more than 70 children with prenatal diagnosis of apparently isolated ASP. The findings from this review have showed that the diagnosis of isolated ASP at antenatal imaging may be considered definitive in about 90% of cases while additional or discordant findings can be detected at the post-natal imaging in a small proportion of cases. We also found that children with antenatal diagnosis of apparently isolated ASP have an overall risk of about 19% of SOD and a risk of about 8% of having a major neurological disability. In those fetuses whose OTs/OC/ONs have been visualized at antenatal imaging the residual risk of SOD is halved (about 9%) and is mainly related to the endocrine spectrum disorders.

Implication for Clinical Practice and Future Perspectives

Data from our meta-analysis confirmed that when OTs/OC appear normal at antenatal MRI or US the likelihood of SOD is almost halved.

A detailed antenatal study of ONs/OTs/OC in fetuses with SA is clinically mandatory in order to anticipate the presence of SOD as the diagnosis of this condition is based on the variable association of two out of three features (SA, hypoplasia of one or both optic nerves and pituitary anomalies or endocrine impairment) with only the 30% of patients presenting the complete clinical triad. The optic nerve hypoplasia can be uni- or bilateral (57% and 32% of cases, respectively) and significant visual impairment may occur in 23% of patients [5,21]. Other anomalies such as nystagmus or strabism may also be present. Hypopituitarism is usually present in 62-80% of patients and although growth hormone (GH) deficiency (leading to short stature in childhood) is the most frequent endocrine anomaly, additional hormone insufficiencies may develop (thyroid-stimulating, adrenocorticotropic and gonadotropin-releasing hormone deficiencies)[22,23]. While endocrinological assessment can only be investigated postnatally, the antenatal evaluation of the optic pathways may be extremely helpful as usually, the involvement of the visual pathways in SOD carries a much poorer prognosis than the endocrine dysfunction[24].

On note that, although the I^2 for the pooled proportion of SOD among those infants with normal OTs/ONs assessment at antenatal imaging was >50% thus indicating a good degree of heterogeneity among the included studies, the only two cases with normal OTs/ONs assessment at antenatal imaging that were postnatally diagnosed with SOD with visual impairment were from a series published in 2010 and including cases evaluated between 1992-2007. This data may be explained by the fact that advances in prenatal imaging techniques has recently led to an improvement in the evaluation of the visual pathways. While there are few studies on the antenatal evaluation of the OTs by means of MRI, the OT evaluation by means of the 2D and 3D ultrasound technique have only recently been described [25,9,11]. Two studies gave evidence that the optic tracts diameter increases linearly throughout gestation and provided reference ranges; in these two studies a total of 14 fetuses were diagnosed as having isolated ASP based on the ultrasound examination of the optic pathways. Among them, nine children from the series by Bault et al. had a good ophtalmological outcome with a normal vision while 5 children from the series by Viñals et al. had a normal vision and a normal pituitary function at a follow up[9,11]. Although both methods seem to have a good reproducibility, the measurement of the OTs remains technically challenging thus requiring a top level of competence in the ultrasound examination of the fetal central nervous system.

Recent guidelines recommend performing a prenatal brain MRI when the SP is not visualized at ultrasound [26]. However, even in cases of an apparently isolated anomaly at expert antenatal imaging, the risk of ASP being not truly isolated is relatively high, with additional cerebral or also only optic anomalies detected only at postnatal imaging and/or clinical examination in a tangible proportion of cases. Actually, more than 40% of the additional findings detected postnatally were anomalies of the optic nerves thus underlining that the antenatal assessment of this structure is extremely challenging. Several factors such as operator's experience, type of antenatal assessment, clinical protocol and technological facilities used for fetal imaging, may explain the wide discrepancy between antenatal and postnatal findings reported in the included studies.

We also reported a risk of about 8% of major neurological disorders in non-SOD infants. To date, current imaging techniques do not permit to estimate this risk prenatally. The spectrum of neuro-developmental disorders reported in our current review was rather heterogeneous thus a pathological link between them and the absence of septum pellucidum is to be confirmed. Earlier animal studies suggested that spatial skills are dependent on an intact septum pellucidum. In addition, septum pellucidum takes part of limbic system playing a role in emotional response, attention and activity[27]. For this reason, it could be involved in neurological, behavioural, learning and psychiatric disorders that sometimes may appear later in life especially at school age [28]. The relatively short follow-up reported in the present review and lacking information regarding family environment do not allow to confirm this hypothesis.

Regarding the association with chromosomal anomalies, although only 4 included studies investigated this outcome, our meta-analysis found a higher incidence of chromosomal anomalies than previously reported. More specifically, we have reported two chromosomal anomalies found by using chromosomal microarray analysis (CMA); to date, we are not able to associate the reported anomalies with the clinical phenotype. Previous studies have described a pattern of SOD-associated mutations in genes that encode transcription factors that are essential for normal forebrain/pituitary development such as HESX1, SOX2, OTX2, TCF7L1[5,29,30]. More recently, a novel splice site mutation of the X-linked FLNA gene encoding for the filamin-A has also been reported as associated with a case of SOD; this protein is implicated in the neuronal migration to the cortex[31]. Nonetheless, the aetiology remains unclear in the majority of the cases. The development and the growing widespread of the Exome sequencing may better clarify the genetic mechanism underlying this spectrum of condition and improve our knowledge about the prognosis of SOD.

Strengths and limitations

The major strength of this study is in the methodology used to identify all the published studies and to assess the quality of data. The small number of the included studies and their retrospective design have to be acknowledged among the main limitations of our meta-analysis leading to a high risk of

selection bias. Due to the relatively short and heterogeneous post-natal follow-up period, the overall rate of additional disabilities may have been underestimated. Furthermore, it was not possible to stratify the analysis including only fetuses with normal standard full karyotype and no pathogenic CNVs as karyotype analysis was not carried out for all the included fetuses, thus biasing the results.

Conclusion

This study provides evidence that in fetuses with ASP a detailed antenatal assessment of the brain and the optic nerves is strongly recommended in order to identify the presence of associated anomalies. The option of invasive testing with chromosomal microarray analysis (CMA) should be also considered. In the vast majority of cases with apparently isolated ASP the prognosis is favorable. However, additional anomalies are detected after birth in about 10% of these cases and have a negative impact on the clinical outcome.

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30. Hagstrom SA, Pauer GJT, Reid J et al: SOX2 mutation causes anophthalmia, hearing loss, and brain anomalies. Am J Med Genet A 2005; 138A: 95–98

31. Fontalba A, Marco de Lucas E, Martínez MT, Cabero Pérez MJ, Couce ML. Septo-optic dysplasia caused by a novel FLNA splice site mutation: a case report. BMC Med Genet. 2019 Jun 24;20(1):112. doi: 10.1186/s12881-019-0844-5. PMID: 31234783; PMCID: PMC6591933

Table 1. Main characteristics of the fetuses included in the cohort study

	Gestational age at diagnosis	Type of agenesis of the septum pellucidum	Ventricular dilatation (<15 mm)	Optic tracts, chiasma and optic nerves	Karyotype	Term at birth	Child's sex	Age at follow-up (months)	Outcome (SOD or major neurological disability in non-SOD cases)
Case 1	28	Complete	Mild	Normal	NA	39	F	48	Normal
Case 2	27	Partial	No	Normal	Normal (aCGH)	38	M	60	Normal
Case 3	27	Partial	No	Normal	Normal (aCGH)	40	M	24	Normal
Case 4	30	Partial	No	Normal	Normal	40	F	60	Normal
Case 5	25	Partial	No	Normal	Normal	39	F	60	Normal
Case 6	28	Partial	No	Normal	Normal (aCGH)	35	M	12	Normal
Case 7	26	Partial	No	Normal	Normal	40	M	24	Normal
Case 8	30	Partial	No	Normal	Normal	40	M	60	Normal
Case 9	30	Complete	No	Normal	NA	37	F	36	Normal
Case 10	21	Complete	No	OC and OTs hypopla	NA	39	F	36	SOD

				sia					
Case 11	29	Complete	No	Normal	NA	37	F	24	Normal
Case 12	22	Partial	No	Present	Normal (aCGH)	37	F	36	Normal
Case 13	24	Partial	No	Present	Normal (aCGH)	38	M	36	Normal
Case 14	25	Partial	No	Present	Normal (aCGH)	40	M	12	Normal
Case 15	33	Partial	No	Present	Normal (aCGH)	37	M	12	Normal

NA=Not Assessed, aCGH=array-Comparative Genomic Hybridization; F=Female; M=Male; SOD=Septo-Optic Dysplasia

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies

Author	Year	Selection	Comparability	Outcome
Damaj[16]	2010	★★	★★	★★★
Bault [9]	2011	★★	★	★★
Pilliod [17]	2018	★★★	★★	★★★
Vawter-Lee[18]	2018	★★★	★★	★★
Shinar[19]	2020	★★★	★★	★★★
Borkowski-Tillman [20]	2020	★★	★	★★★

Study, Years	Country	Study type	Study years	Cases with suspected isolated ASP at prenatal US or MRI	Cases with antenatal OTs/ONs evaluation	GA at diagnosis Median (range)	Follow-up available	Median age at follow-up (months)	Outcome
Damaj et al. 2010 [16]	France	Multicenter retrospective	1992-2007	17	16	31 (28-34)	17	36.0 (2.0-72.0)	Discordant pre- and post-natal imaging, overall incidence of SOD, SOD in cases with normal ONs/OTs, major neurological disability in non-SOD neonates
Bault et al. 2011[9]	France	Prospective cross-sectional	2007-2009	10	8	28 (22-34)	10	NS	Overall incidence of SOD, SOD in cases with normal ONs/OTs
Pilliod et al. 2018 [17]	USA	Monocentric, retrospective	2011-2016	15	NS	27.1 (20.3-40.4)	8	13 (3-36)	Chromosomal anomalies, discordant pre- and post-natal imaging, overall incidence of SOD, major neurological disability in non-SOD neonates
Vawter-Lee et al. 2018 [18]	USA	Monocentric, retrospective	2008-2016	6	NS	28.6 (23.6-31.2)	6	21.0 (8.0-72.0)	Discordant pre- and post-natal imaging, overall incidence of SOD, major neurological disability in non-SOD neonates
Shinar et al. 2020 [19]	Canada	Monocentric, retrospective	2008-2019	9	8	24.5+/- 4.7	8	4.7 anni 15 mesi-10 anni	Chromosomal anomalies, discordant pre- and post-natal imaging, overall incidence of SOD, SOD in cases with normal ONs/OTs, major neurological disability in non-SOD neonates

Table 3. Main characteristics of included studies

Borkowski-Tillman et al. 2020 [20]	Israel, Spain, Portugal, Chile	Multicentric, retrospective	2008-2017	14	14	24.9 (22.6-33.0)	14	45 (3-84)	Chromosomal anomalies, discordant pre- and post-natal imaging, overall incidence of SOD, SOD in cases with normal ONs/OTs, major neurological disability in non-SOD neonates
Present study, 2021	France, Italy	Multicentric, retrospective	2010-2020	14	10/11	27.0 (21.0-33.0)	15	36 (12-60)	Chromosomal anomalies, discordant pre- and post-natal imaging, overall incidence of SOD, SOD in cases with normal ONs/OTs, major neurological disability in non-SOD neonates

OTs= Optic Tracts, ONs=Optic Nerves; SOD=Septo-Optic Dysplasia, NS=Not Stated

Table 4. Pooled proportions for the investigated outcome

	Nr of studies	Cases	Raw proportion (%)	Pooled proportion % (95%CI)	I^2
Discordant pre- and post-natal imaging	6	9/70	12.9	13.7% 3.5-29.0	63.9 %
Chromosomal anomalies	4	2/30	6.7	9.0 1.8-20.7	0 %
Overall incidence of SOD	7	14/79	17.7	19.0 8.6-32.2	48.0%
Major neurological disability in non-SOD infants	6	5/57*	8.8	8.3 1.4-20.2	45.9%
SOD in cases with normal antenatal ONs/OTs	5	6/60	10.0	9.1 1.1-24.0	62.0%

**Study by Bault et al.[9] excluded as neurological follow-up was not available*

Case	Term at birth	Type of SA	Ventriculomegaly	Optic pathways at antenatal imaging	Postnatal Imaging	Pediatric outcome
Case 1	38	Partial	No	Normal optic tracts and chiasma	Normal	Oculo-céphalic incoordination; Astigmatism/hypermétropia
Case 2	39	Partial	No	Normal optic tracts and chiasma	Normal	Language delay; under left cristalinian opacity
Case 3	38	Partial	No	Normal optic tracts and chiasma	Normal	Visuo-spatial dyspraxia; isolated strabism
Case 4	39	Partial	Mild VMG	Normal optic tracts and chiasma	Normal	Severe language delay
Case 5	31	Complete	No	Normal optic tracts and chiasma	Chiasma and right ON hypoplasia	SOD (right optic atrophia, normal endocrine assessment)
Case 6	40	Complete	No	Normal optic tracts and chiasma	Bilateral optic nerve hypoplasia	SOD (bilateral optic nerve hypoplasia, normal endocrine assessment)
Case 7	37	Complete	Mild VMG	Normal optic tracts and chiasma	Pituitary anomalies	SOD (GH deficiency, normal aspect of optic nerves)
Case 8	28.9	Complete	Moderate VMG	NS	NS	Mild gross motor delay (normal ophthalmologic and endocrine assessment)
Case 9	39.9	Complete	No	NS	NS	SOD (bilateral optic nerve hypoplasia, normal endocrine assessment)
Case 10	40.6	Complete	Moderate VMG	NS	NS	SOD (bilateral optic nerve hypoplasia, abnormal endocrine assessment, borderline personal

Table 5. Main characteristics of the children with an adverse pediatric outcome (SOD or major neurological disability in non-SOD infants)

						development)
Case 11	37.5	Complete	No	NS	Isolated ASP	SOD (adrenal insufficiency)
Case 12	39.1	Complete	Moderate VMG	NS	Severe Hypoplasia of ONs, OTs, OC	SOD (bilateral optic nerve hypoplasia)
Case 13	NS	complete	Mild VMG	Bilateral ON and OC hypoplasia	Bilateral ON and OC hypoplasia	SOD (bilateral optic nerve hypoplasia and bilateral nystagmus)
Cases 14 to 16	NS	Complete	NS	Normal	Isolated ASP	SOD (endocrinological anomalies)
Case 17	NS	NS	NS	Bilateral hypoplasia	NS	SOD (blindness)
Case 18	NS	NS	NS	Unilateral hypoplasia	NS	SOD (abnormal movements of the eyes)
Case 19	39	Complete	No	OC and OTs hypoplasia	OC and OTs hypoplasia	SOD (visual impairment)

NS=not stated; OTs= Optic Tracts, ONs=Optic Nerves; SOD=Septo-Optic Dysplasia, VMG=ventriculomegaly

Figure 1. Complete agenesis of septum pellucidum (ASP) at antenatal Magnetic Resonance Imaging (a) and Ultrasound (b)

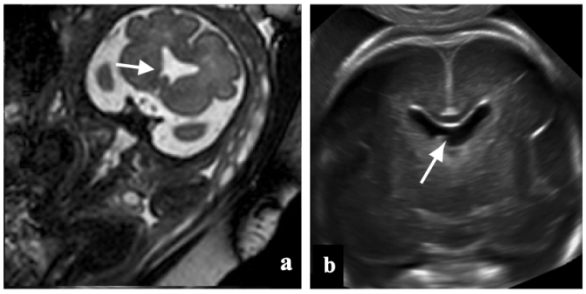


Figure 1. Complete agenesis of septum pellucidum (ASP) at antenatal Magnetic Resonance Imaging (a) and Ultrasound (b)

419x594mm (72 x 72 DPI)

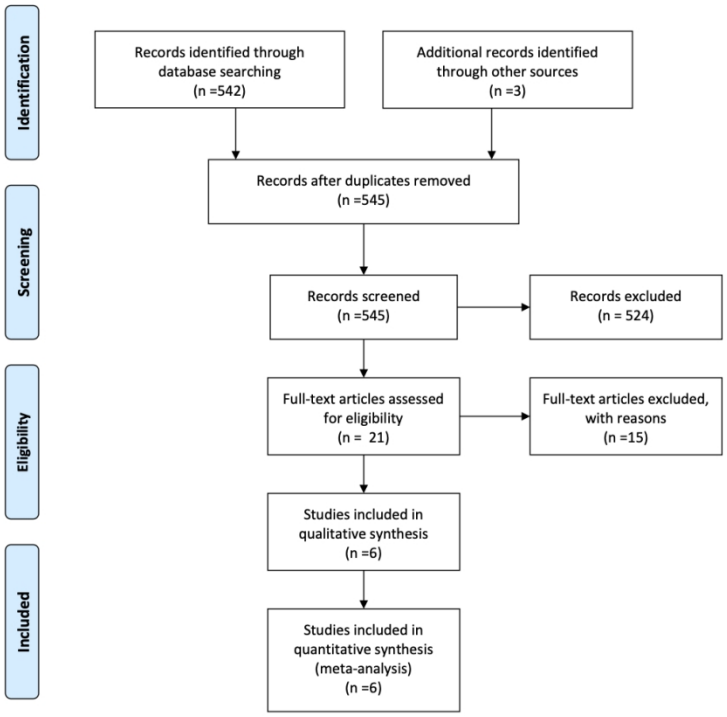


Figure 2. Flow-chart of the included studies

Figure 2. Flow-chart of the included studies

419x594mm (72 x 72 DPI)

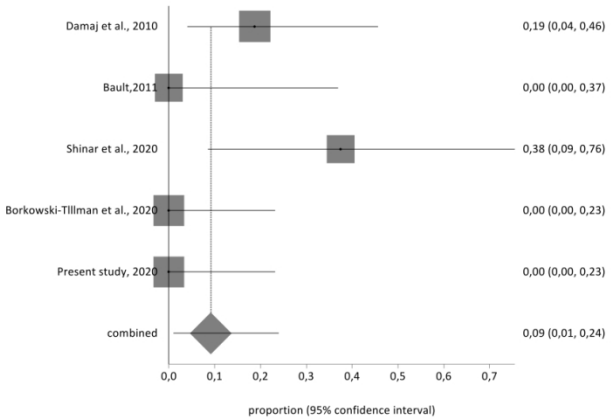


Figure 3. Pooled proportion of cases of SOD in fetuses with normal Optic nerves, chiasma or tracts at antenatal assessment

Figure 3. Pooled proportion of cases of SOD in fetuses with normal Optic nerves, chiasma or tracts at antenatal assessment

419x594mm (72 x 72 DPI)

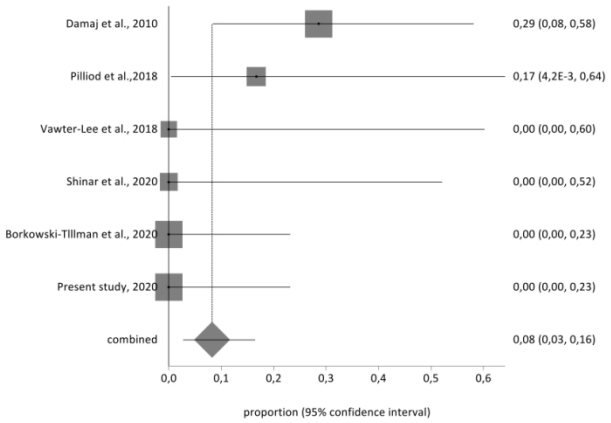


Figure 4. Pooled proportion of cases with major neurological disability in non-SOD infants

Figure 4. Pooled proportion of cases with major neurological disability in non-SOD infants

419x594mm (72 x 72 DPI)

SUPPLEMENTAL MATERIAL

Table 6: Search Strategy

MEDLINE

1 ((agenesis or absence or malform*) adj5 septum pellucid*).mp (194)

2 septum pellucid* abnormalities.mp. (2)

3 Septum Pellucidum/ or Septo-Optic Dysplasia/ (2786)

4 (fetus or fetal or antenatal or prenatal or ante natal or prepregnant).mp (466826)

5 exp fetus/ (133614)

6 exp congenital anomalies/ (62439)

7 exp congenital abnormalities/ (468936)

8 exp prenatal diagnosis/ (63690)

9 exp ultrasonography, prenatal/ (29848)

10 exp magnetic resonance imaging/ (426610)

11 (outcome or result or prognosis or diagnosis).mp (5442414)

12 exp disease/ (119838)

13 exp pregnancy outcome/ (65105)

14 Prognosis/ (428797)

15 Pregnancy Outcome/ or Fatal Outcome/ or Patient Outcome Assessment/ or Adverse Outcome Pathways/ or Outcome Assessment, Health Care/ or "Outcome and Process Assessment, Health Care"/ (204322)

16 1 or 2 or 3 (2871)

17 4 or 5 or 6 or 7 or 8 or 9 or 10 (1303786)

18 11 or 12 or 13 or 14 or 15 (5533012)

19 31 and 32 and 33 (388)

20 limit 19 to yr=”2000 – 2021” (275)

EMBASE

1 agenesis:ti,ab,kw OR absence:ti,ab,kw OR 'malform* adj5 septum pellucidum':ti,ab,kw (871663)

2 fetus OR fetal OR antenatal OR prenatal OR ante) AND natal OR prepregnan* (14968)

3 outcome OR result OR diagnosis OR prognosis (9673027)

4 1 AND 2 AND 3 (234)

5 septooptic dysplasia (712)

6 agenesis AND septum AND pellucidum (503)

7 5 OR 6 (1100)

8 fetus disease (16920)

9 fetus (3980879)

10 prenatal diagnosis (72302)

11 prenatal care (47638)

12 prenatal disorder (853)

13 fetus echography (24588)

14 nuclear magnetic resonance (1241327)

15 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 (1698502)

16 prognosis(1035254)

17 outcome assessment (1035254)

18 pregnancy outcome (585122)

19 outcome assessment (70511)

20 diagnosis (5950469)

21 adverse outcome (60468)

22 follow up (2113906)

23 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 (8341418)

24 7 AND 15 AND 23 (429)

25 4 OR 24 (660)

26 limit 25 to yr="2000 – 2021" (267)

Table 7: List of excluded studies with reason

CASE REPORT WITH<= 3 CASES OF ISOLATED ASP

1. Ben M'Barek I, Tassin M, Guët A, Simon I, Mairovitz V, Mandelbrot L, Picone O. Antenatal diagnosis of absence of septum pellucidum. Clin Case Rep. 2020 Feb 5;8(3):498-503
2. García-Arreza A, García-Díaz L, Fajardo M, Carreto P, Antiñolo G. Isolated absence of septum pellucidum: prenatal diagnosis and outcome. Fetal Diagn Ther. 2013;33(2):130-2: <3 cases with isolated ASP
3. Celentano C, Prefumo F, Liberati M, Tartaro A, Gallo G, Lattanzio G, Rotmensch S. Prenatal diagnosis of septal agenesis with normal pituitary function. Prenat Diagn. 2006 Nov;26(11):1075-7. doi: 10.1002/pd.1559. PMID: 16952197: case report
4. Lepinard C, Coutant R, Boussion F, Loisel D, Delorme B, Biquard F, Bonneau D, Guichet A, Descamps P. Prenatal diagnosis of absence of the septum pellucidum associated with septo-optic dysplasia. Ultrasound Obstet Gynecol. 2005 Jan;25(1):73-5. doi: 10.1002/uog.1807. PMID: 15593257
5. Pilu G, Tani G, Carletti A, Malaigia S, Ghi T, Rizzo N. Difficult early sonographic diagnosis of absence of the fetal septum pellucidum. Ultrasound Obstet Gynecol. 2005 Jan;25(1):70-2. doi: 10.1002/uog.1786. PMID: 15619322
6. Potsi S, Chourmouzi D, Moumtzouoglou A, Drevelegas A. Isolated absence of the cavum septum pellucidum. Acta Neurol Belg. 2011 Mar;111(1):83

LACK OF DATA ON PRENATAL FINDINGS

7. Alt C, Shevell MI, Poulin C, Rosenblatt B, Saint-Martin C, Srour M. Clinical and Radiologic Spectrum of Septo-optic Dysplasia: Review of 17 Cases. J Child Neurol. 2017 Aug;32(9):797-803
8. Cemeroglu AP, Coulas T, Kleis L. Spectrum of clinical presentations and endocrinological findings of patients with septo-optic dysplasia: a retrospective study. J Pediatr Endocrinol Metab. 2015 Sep;28(9-10):1057-63. doi: 10.1515/jpem-2015-0008. PMID: 25879316

FETUSES REFERRED FOR VENTRICULOMEGALY

9. Li Y, Sansgiri RK, Estroff JA, Mehta TS, Poussaint TY, Robertson RL, Robson CD, Feldman HA, Barnewolt C, Levine D. Outcome of fetuses with cerebral ventriculomegaly and septum pellucidum leaflet abnormalities. AJR Am J Roentgenol. 2011 Jan;196(1):W83-92. doi: 10.2214/AJR.10.4434. PMID: 21178039; PMCID: PMC3755483: fetuses referred for ventriculomegaly
10. Malinger G, Lev D, Kidron D, Heredia F, Hershkovitz R, Lerman-Sagie T. Differential diagnosis in fetuses with absent septum pellucidum. Ultrasound Obstet Gynecol. 2005 Jan;25(1):42-9. doi: 10.1002/uog.1787. PMID: 15593321: fetuses referred for ventriculomegaly

CONGRESS ABSTRACT

11. Verma A., Pinto S., Robati S. Prenatal diagnosis of absent cavum septum pellucidum associated with septo optic dysplasia: Case report and literature review. *BJOG: An International Journal of Obstetrics and Gynaecology (2013) 120 SUPPL. 1 (133)*. Date of Publication: June 2013: congress abstract

12. LaBreck K. Absence of cavum septum pellucidum related with optic nerve hypoplasia *Journal of Diagnostic Medical Sonography (2007) 23:6 (336-338)*. Date of Publication: November 2007: congress abstract

OTHER REASONS

13. Belhocine O, André C, Kalifa G, Adamsbaum C. Does asymptomatic septal agenesis exist? A review of 34 cases. Pediatr Radiol. 2005 Apr;35(4):410-8. doi: 10.1007/s00247-004-1378-2. Epub 2005 Feb 15. PMID: 15711998: study on adult population

14. Maduram A, Farid N, Rakow-Penner R, Ghassemi N, Khanna PC, Robbins SL, Hull A, Gold J, Pretorius DH. Fetal Ultrasound and Magnetic Resonance Imaging Findings in Suspected Septo-Optic Dysplasia: A Diagnostic Dilemma. J Ultrasound Med. 2020 Aug;39(8):1601-1614. doi: 10.1002/jum.15252. Epub 2020 Mar 2. PMID: 32118312: series of children with post-natal diagnosis of SOD

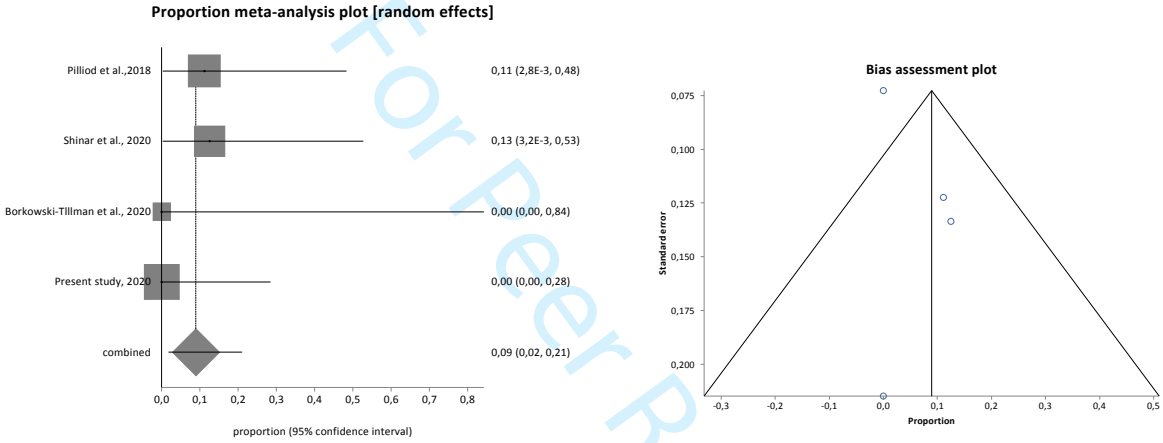
15. Viñals F, Ruiz P, Correa F, Gonçalves Pereira P. Two-dimensional visualization and measurement of the fetal optic chiasm: improving counseling for antenatal diagnosis of agenesis of the septum pellucidum. Ultrasound Obstet Gynecol. 2016 Dec;48(6):733-738. doi: 10.1002/uog.15862. PMID: 26776289: cases included in the series by Borkowski-Tillman et al (ref 20) (corresponding author contacted)

Table 8. Additional or discordant findings at post-natal imaging

	Additional or discordant findings at post-natal imaging
Case 1	Chiasma and right Optic Nerve Hypoplasia
Case 2	Bilateral Optic Nerve Hypoplasia
Case 3	Cavum et vergae, bilateral germinal matrix hemorrhages and ventriculomegaly on postnatal US
Case 4	Severe Hypoplasia Optic Nerve, Optic Tracts, Optic Chasma; incomplete separation of forniceal columns
Case 5	Multifocal cerebellar hemorrhages
Case 6	Hypoplastic splenium of the corpus callosum
Case 7	Thinned corpus callosum
Case 8	Unilateral Optic Nervehypoplasia
Case 9	Normal Corpus Callosum (previously described as thin)

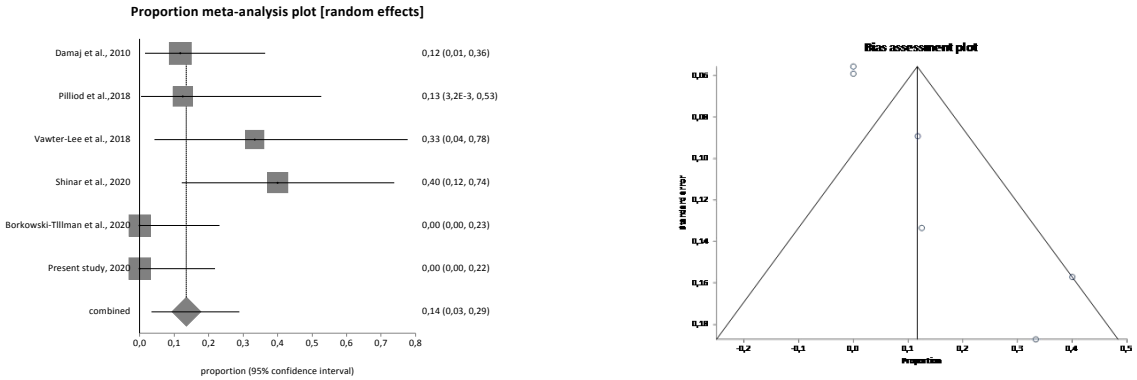
FUNNEL PLOTS AND PUBLICATION BIAS

FIGURE 5. Funnel plot and publication bias for chromosomal anomalies



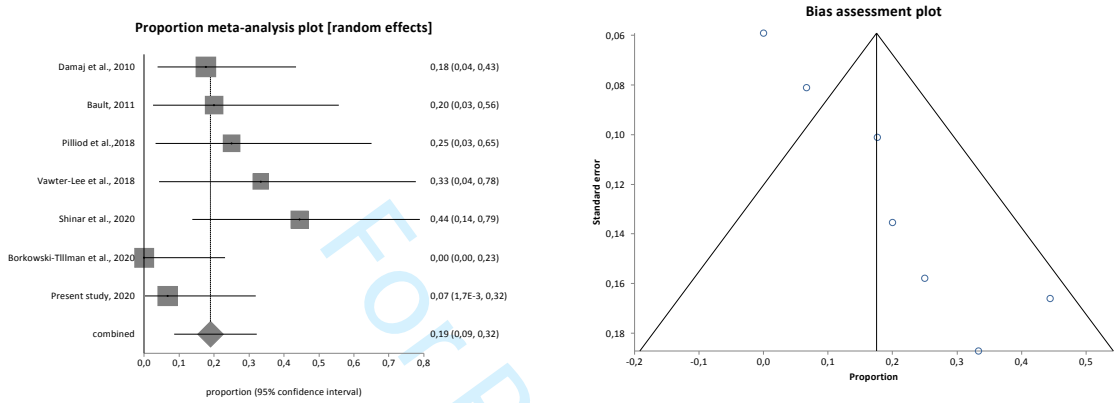
Begg-Mazumdar: Kendall's 0,333333 P = 0,75
Egger: bias = 0,711189 (95% CI = -3,08682 to 4,509199) P = 0,505
Harbord: bias = -0,211079 (92,5% CI = -5,324579 to 4,90242) P = 0,9

FIGURE 6. Funnel plot and publication bias for additional of discordant pre- and post-natal findings



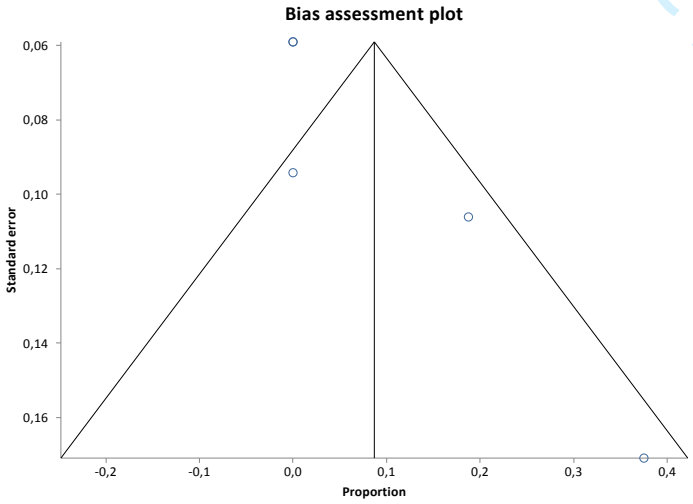
Begg-Mazumdar: Kendall's 0,733333 P = 0,0556
Egger: bias = 2,851836 (95% CI = 1,391456 to 4,312215) P = 0,0056
Harbord: bias = 5,522629 (92,5% CI = -2,682874 to 13,728133) P = 0,1827

FIGURE 7. Funnel plot and publication bias for overall incidence of SOD in apparently isolated ASP



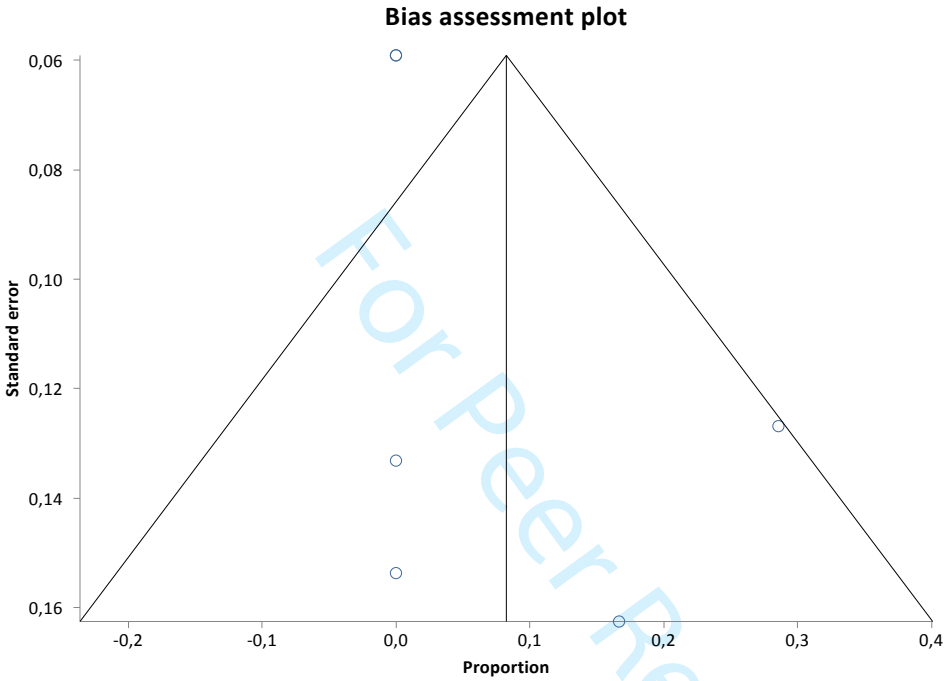
Begg-Mazumdar: Kendall's 0,809524 P = 0,0107
Egger: bias = 3,040732 (95% CI = 1,943144 to 4,13832) P = 0,0008
Harbord: bias = 4,838496 (92,5% CI = -0,379299 to 10,056291) P = 0,0921

FIGURE 8. Publication bias for SOD in cases with normal Optic Tracts/Optic Nerve



Begg-Mazumdar: Kendall's 1 P = 0,0374
Egger: bias = 3,038692 (95% CI = 0,154248 to 5,923136) P = 0,044
Harbord: bias = 3,31223 (92,5% CI = -13,736696 to 20,361156) P = 0,6385

FIGURE 9. Publication bias for neurological disability in non-SOD infants



Begg-Mazumdar: Kendall's 0,571429 P = 0,1731
Egger: bias = 1,303291 (95% CI = -1,29498 to 3,901563) P = 0,2361
Harbord: bias = -0,916379 (92,5% CI = -7,477282 to 5,644525) P = 0,7551

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6-8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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