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

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Manuscripts

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

Short Title: Absent septum pellucidum

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For Peer Review

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

3 **Short Title:** Absent septum pellucidum

4

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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

55 **ABSTRACT**

56 **OBJECTIVE**

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

59

60 **METHODS**

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

69

70 **RESULTS**

71 Fifteen cases of isolated ASP with a median postnatal follow up of 36 months (12-60) were selected
72 from the two Centres. Six studies met the inclusion criteria for the systematic review and a total of
73 79 cases were eligible for the analysis, including our series. Genetic tests were antenatally carried out
74 in 30 fetuses and turned out to be abnormal in 2 of them (pooled proportion 9.0%; 95% CI 1.8-20.7;
75 I^2 0%). Additional or discordant imaging findings were postnatally noted in 9/70 patients (Pooled
76 proportion 13.7%; 95%CI 3.5-29.0; I^2 63.9%); Among the 79 neonates with available follow-up,
77 SOD was postnatally diagnosed in 14 cases (Pooled proportion 19.0%; 95% CI 8.6-32.2; I^2 48.0%).
78 In 60 cases Optic nerves or optic tracts were considered to be normal at antenatal imaging; among
79 them, a diagnosis of SOD was carried out in 6 cases (Pooled proportion 9.1%; 95%CI 1.1-24.0; I^2
80 62.0%). Among the 57 infants with available neurological follow-up that were not affected by SOD,

81 a major neurological disability was diagnosed in 5 (pooled proportion 8.3%; 95% CI 1.4-20.2; I²
82 45.9%)

83

84 **CONCLUSION**

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

88

For Peer Review

89 INTRODUCTION

90 The agenesis of the septum pellucidum (ASP) is a rare cerebral malformation characterized by the
91 partial or the complete absence of the leaflets of the septum pellucidum; its prevalence in the general
92 population is about 2-3/100.000¹. Although it may be incidentally detected in normal individuals, this
93 finding is often part of complex cerebral anomalies such as holoprosencephaly (HPE),
94 schizencephaly, corpus callosum agenesis or severe ventriculomegaly that are mostly detectable at
95 prenatal imaging^{2,3} and for which prenatal counselling is fairly clear and straightforward.

96 ASP may be also the clue of a rare midline anomaly (1:10000 live births) known as Septo-Optic
97 Dysplasia (SOD) or DeMorsier Syndrome which is characterized by a variable association of septal
98 agenesis, hypoplasia of one or both optic nerves, pituitary anomalies or endocrine impairment and
99 whose antenatal diagnosis is extremely challenging^{4,5}. Therefore, in absence of major brain
100 malformations, ASP should be always considered as highly suggestive of SOD and therefore the
101 assessment of the optic chiasm (OC), optic tracts (OTs) or Optic Nerves (ONs) by means of 2D/3D
102 ultrasound or antenatal Magnetic Resonance Imaging (MRI) is warranted⁶⁻⁹. In addition, a wide
103 spectrum of neurological manifestations (developmental delay, seizures and cerebral palsy) has been
104 also described in patients with ASP without SOD^{2,10}. For these reasons, although the recent advances
105 in prenatal imaging have made possible the visualization and the measurement of the OTs, the
106 antenatal counselling of the prospective parents still represents a challenge for clinicians^{8,9,11}.

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

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115 MATERIALS AND METHODS

116 Cohort study

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

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

132 Systematic review

133 *Search strategy and study selection*

134 This review was performed according to the PRISMA guidelines¹². Medline and Embase, databases
 135 were searched electronically on April 2020 and updated on the 16th of February 2021 using
 136 combinations of the relevant medical subject heading terms (MeSH) and keywords variants for
 137 “agenesis of the septum pellucidum”, “septo-optic dysplasia”, “outcome”, “MRI” and “ultrasound”.
 138 Two independent investigators (EDP, MK) conducted the literature search, reviewed all the abstracts
 139 and independently extracted relevant data regarding study characteristics and neonatal outcome.
 140 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 studies¹³.

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 ≤ 15 mm.

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

167 Meta-analyses of proportions were used to combine data¹⁴. Between-study heterogeneity was
168 explored using I^2 statistic which indicates the percentage of between-study variation that is due to
169 heterogeneity rather than chance. A value of I^2 of 0% indicates no observed heterogeneity, whereas
170 values $\geq 50\%$ indicate a substantial level of heterogeneity. Given the retrospective design and the
171 small sample size of the included studies, a random effect model was preferred, regardless of I^2 ¹⁵.
172 Tests for funnel plot asymmetry were carried out in order to display the outcome rate from individual
173 studies versus their precision (1/standard error). Potential publication bias was assessed by using
174 Begg's and Egger's regression asymmetry test. StatsDirect 3.4.4 (StatsDirect Ltd, Altrincham)
175 statistical software was used for all data analyses.

176

177

178 **RESULTS**

179 *Our series*

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

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

190 **Review of literature**

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

198 Genetic tests were antenatally carried out in 30 fetuses and turned out to be abnormal in 2 of them
199 (pooled proportion 9.0%; 95% CI 1.8-20.7; I²: 0%) (Figure 5 Supplem.); in one case a microdeletion
200 of 30 kb of the region 1p14 was found at the chromosomal microarray and the woman underwent a
201 TOP; in the latter case a variant of unknown significance (VOUS) was demonstrated on the
202 chromosome 10p13; this latter patient was postnatally diagnosed with SOD.

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

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

210 In 60 cases ONs/OTs were evaluated at the antenatal imaging (US and/or MRI) and considered to be
 211 normal; among them, a diagnosis of SOD was carried out in 6 cases (Pooled proportion 9.1%; 95%CI
 212 1.1-24.0; I^2 62.0%) (Figure 3, Figure 8 Supplem). In two of these the optic tracts turned out to be
 213 normal at antenatal imaging but were found to be hypoplastic at post-natal follow-up while in 4 cases
 214 (66.7%) only the endocrinological criteria of SOD were present (Table 4 and 5).

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

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219

220 **DISCUSSION**

221 **Summary of Evidence**

222 This study has evaluated the paediatric outcome of more than 70 children with prenatal diagnosis of
223 apparently isolated ASP. The findings from this review have showed that the diagnosis of isolated
224 ASP at antenatal imaging may be considered definitive in about 90% of cases while additional or
225 discordant findings can be detected at the post-natal imaging in a small proportion of cases. We also
226 found that children with antenatal diagnosis of apparently isolated ASP have an overall risk of about
227 19% of SOD and a risk of about 8% of having a major neurological disability. In those fetuses whose
228 OTs/OC/ONs have been visualized at antenatal imaging the residual risk of SOD is halved (about
229 9%) and is mainly related to the endocrine spectrum disorders.

230 **Implication for Clinical Practice and Future Perspectives**

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

233 A detailed antenatal study of ONs/OTs/OC in fetuses with SA is clinically mandatory in order to
234 anticipate the presence of SOD as the diagnosis of this condition is based on the variable association
235 of two out of three features (SA, hypoplasia of one or both optic nerves and pituitary anomalies or
236 endocrine impairment) with only the 30% of patients presenting the complete clinical triad. The optic
237 nerve hypoplasia can be uni- or bilateral (57% and 32% of cases, respectively) and significant visual
238 impairment may occur in 23% of patients^{5,21}. Other anomalies such as nystagmus or strabismus may
239 also be present. Hypopituitarism is usually present in 62-80% of patients and although growth
240 hormone (GH) deficiency (leading to short stature in childhood) is the most frequent endocrine
241 anomaly, additional hormone insufficiencies may develop (thyroid-stimulating, adrenocorticotrophic
242 and gonadotropin-releasing hormone deficiencies)^{22,23}. While endocrinological assessment can only
243 be investigated postnatally, the antenatal evaluation of the optic pathways may be extremely helpful
244 as usually, the involvement of the visual pathways in SOD carries a much poorer prognosis than the
245 endocrine dysfunction²⁴.

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.

271 We also reported a risk of about 8% of major neurological disorders in non-SOD infants. To date,
272 current imaging techniques do not permit to estimate this risk prenatally. The spectrum of neuro-
273 developmental disorders reported in our current review was rather heterogeneous thus a pathological
274 link between them and the absence of septum pellucidum is to be confirmed. Earlier animal studies
275 suggested that spatial skills are dependent on an intact septum pellucidum. In addition, septum
276 pellucidum takes part of limbic system playing a role in emotional response, attention and activity²⁷.
277 For this reason, it could be involved in neurological, behavioural, learning and psychiatric disorders
278 that sometimes may appear later in life especially at school age ²⁸. The relatively short follow-up
279 reported in the present review and lacking information regarding family environment do not allow to
280 confirm this hypothesis.

281 Regarding the association with chromosomal anomalies, although only 4 included studies
282 investigated this outcome, our meta-analysis found a higher incidence of chromosomal anomalies
283 than previously reported. More specifically, we have reported two chromosomal anomalies found by
284 using chromosomal microarray analysis (CMA); to date, we are not able to associate the reported
285 anomalies with the clinical phenotype. Previous studies have described a pattern of SOD-associated
286 mutations in genes that encode transcription factors that are essential for normal forebrain/pituitary
287 development such as HESX1, SOX2, OTX2, TCF7L1^{5,29,30}. More recently, a novel splice site
288 mutation of the X-linked FLNA gene encoding for the filamin-A has also been reported as associated
289 with a case of SOD; this protein is implicated in the neuronal migration to the cortex³¹. Nonetheless,
290 the aetiology remains unclear in the majority of the cases. The development and the growing
291 widespread of the Exome sequencing may better clarify the genetic mechanism underlying this
292 spectrum of condition and improve our knowledge about the prognosis of SOD.

293 **Strengths and limitations**

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

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

301 **Conclusion**

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

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309 **Acknowledgment:** none

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

For Peer Review

	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 hypoplasia	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
Damaj¹⁶	2010	★ ★	★ ★	★ ★ ★
Bault⁹	2011	★ ★	★	★ ★
Pilliod¹⁷	2018	★ ★ ★	★ ★	★ ★ ★
Vawter-Lee¹⁸	2018	★ ★ ★	★ ★	★ ★
Shinar¹⁹	2020	★ ★ ★	★ ★	★ ★ ★
Borkowski-Tillman²⁰	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 atrophy, 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)

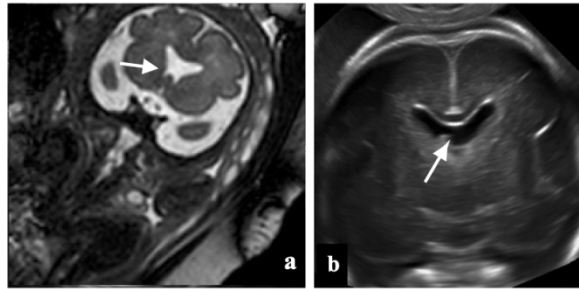


Figure 1. Complete agenesis of septum pellucidum (ASP) at antenatal Magnetic Resonance Imaging (a) and Ultrasound (b)

419x594mm (72 x 72 DPI)

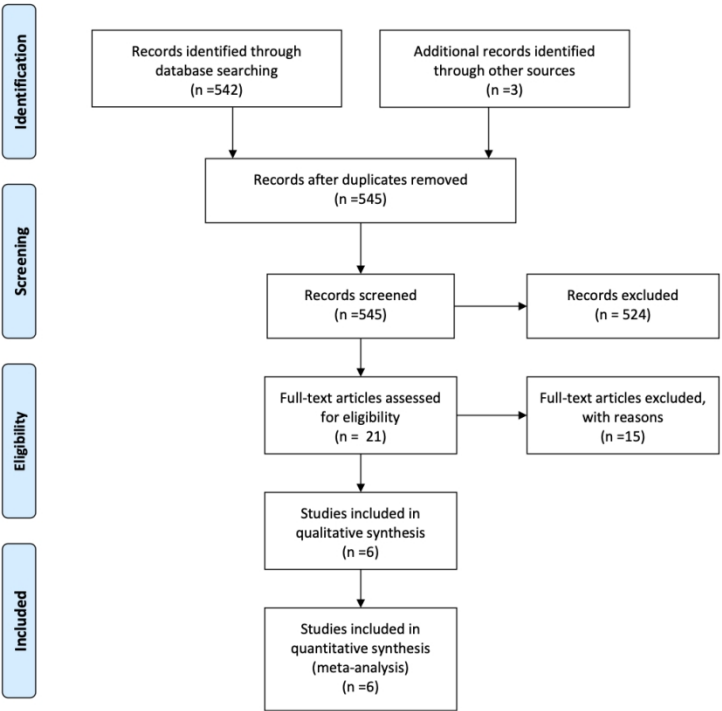


Figure 2. Flow-chart of the included studies

Figure 2. Flow-chart of the included studies

419x594mm (72 x 72 DPI)

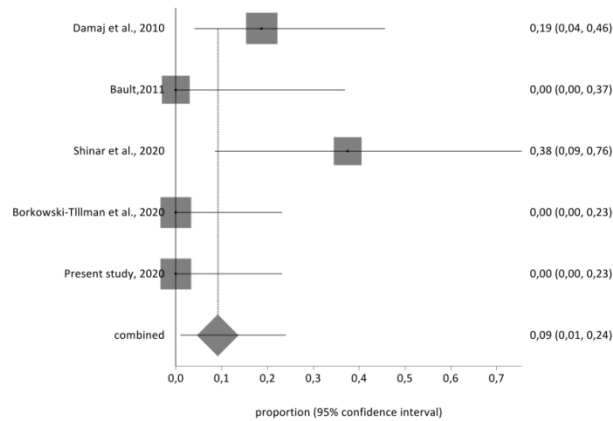


Figure 3. Pooled proportion of cases of SOD in fetuses with normal Optic nerves, chiasma or tracts at antenatal assessment

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)

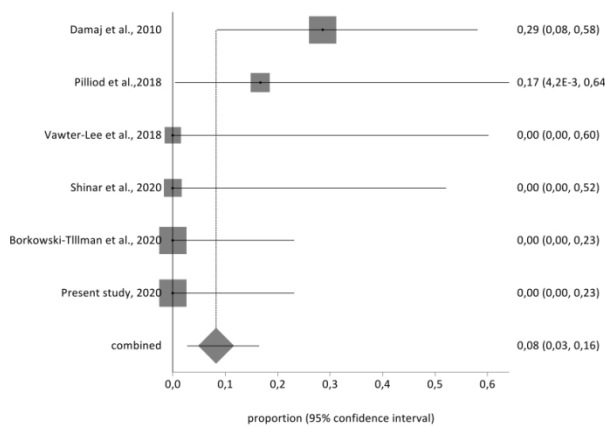


Figure 4. Pooled proportion of cases with major neurological disability in non-SOD infants

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

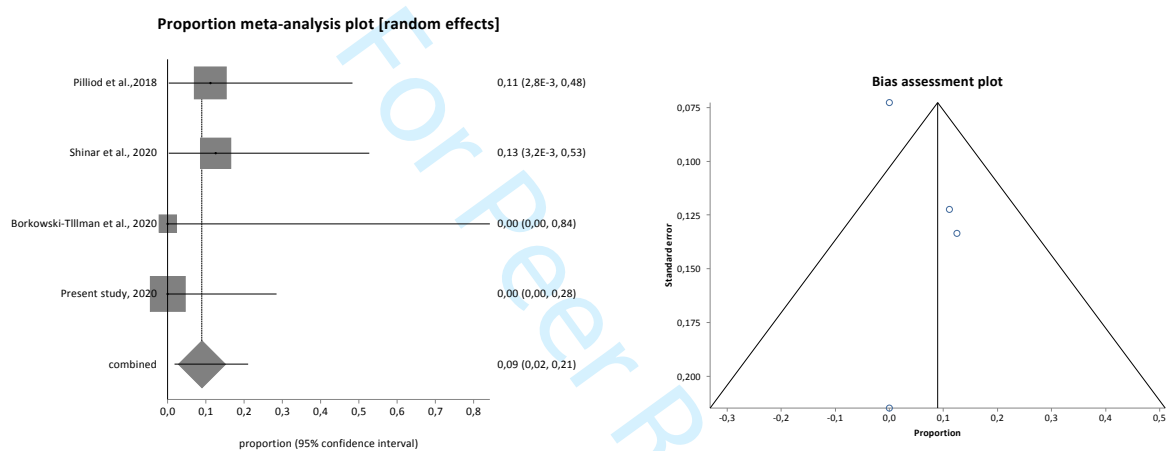
13. Belhocine O, André C, Kalifa G, Adamsbaum C. Does asymptomatic septal agenesis exist?
A review of 34 cases. *Pediatr Radiol*. 2005 Apr;35(4):410-8. doi: 10.1007/s00247-004-1378-2. Epub 2005 Feb 15. PMID: 15711998: study on adult population
14. Maduram A, Farid N, Rakow-Penner R, Ghassemi N, Khanna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

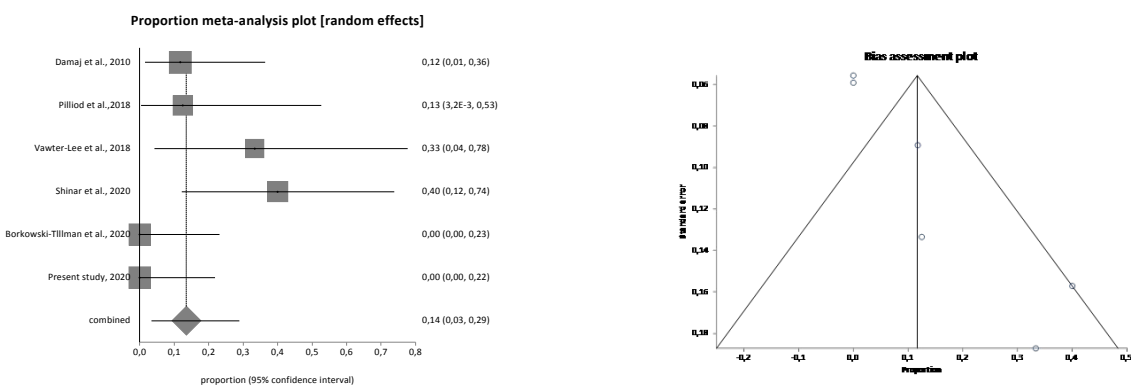


Begg-Mazumdar: Kendall's 0.333333 $P = 0.75$

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

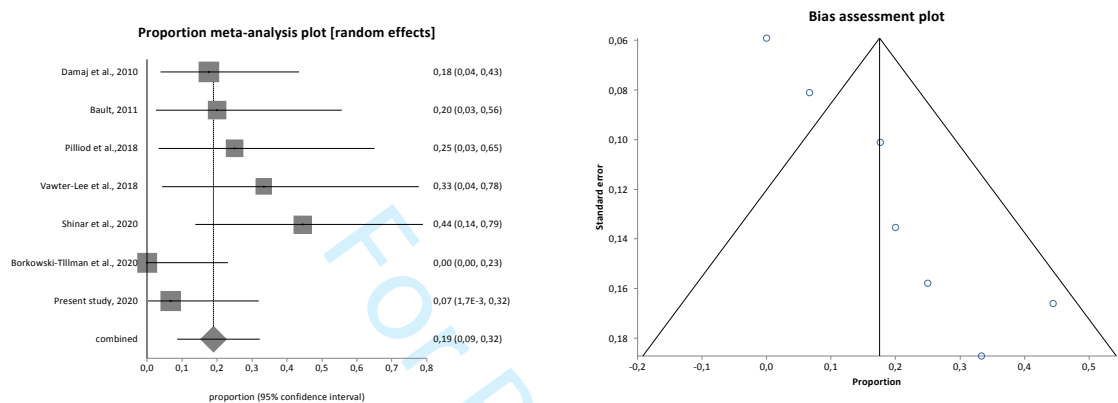


Begg-Mazumdar: Kendall's 0.733333 $P = 0.0556$

Egger: bias = 2.851836 (95% CI = 1.391456 to 4.312215) $P = 0.0056$

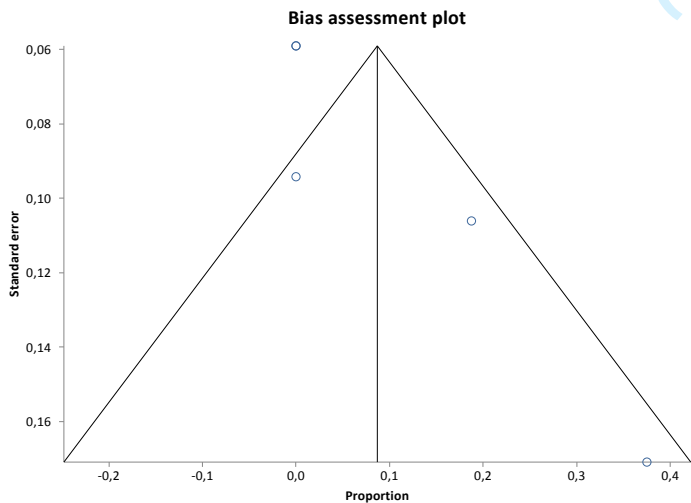
Harbord: bias = 5.522629 (92.5% CI = -2.682874 to 13.728133) $P = 0.1827$

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



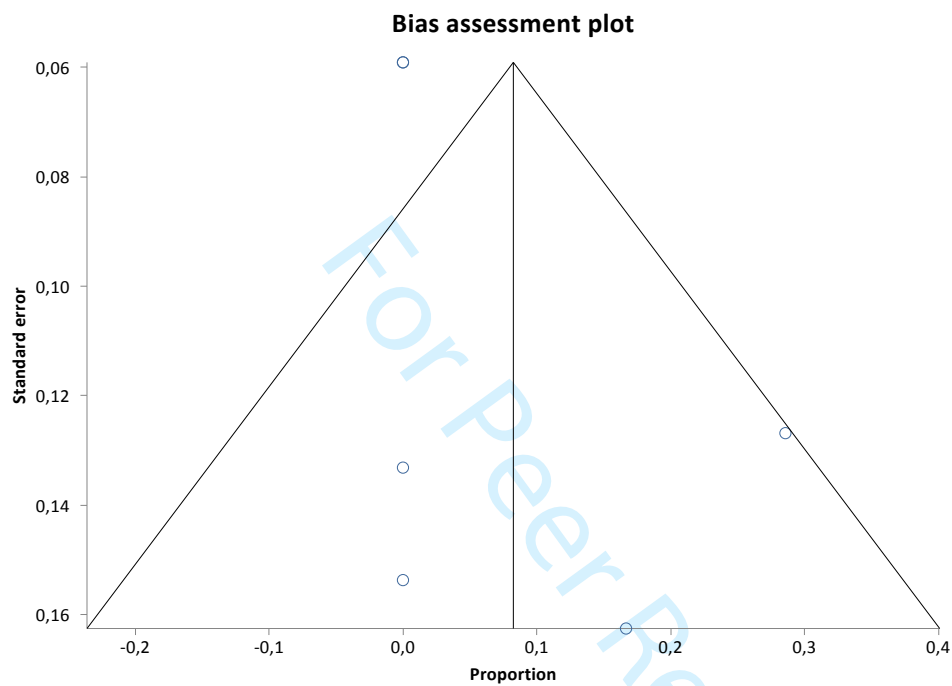
Begg-Mazumdar: Kendall's 0.809524 $P = 0.0107$
Egger: bias = 3.040732 (95% CI = 1.943144 to 4.13832) $P = 0.0008$
Harbord: bias = 4.838496 (92.5% CI = -0.379299 to 10.056291) $P = 0.0921$

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

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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

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