Review article/Pregledni znanstveni članek

Oxytocin for labour induction or augmentation as a risk factor for autism: systematic literature review

Povezava med uporabo oksitocina za sprožitev ali pospeševanje poroda in avtizmom: sistematični pregled literature

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Key words: oxytocin; labour; autism; autism spectrum disorder

Ključne besede: oksitocin; porod; avtizem; spektroavtistične motnje

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ABSTRACT

Introduction: Some studies have shown a potential association between oxytocin use during labour and autism spectrum disorder (ASD) in children. We performed a systematic review of recent studies examining this association.

Methods: Boolean operators (AND/OR) were used to search MEDLINE using the following search criteria: Autistic Disorder or Autism Spectrum Disorder or Autism and Labour Induction or Labour Augmentation. Articles published in English in 2013 or later were considered. Additional studies were identified by reviewing citations. Only studies conducted on people were included. Studies not accounting for potential confounding factors were excluded.

Results: Four retrospective cohort studies met the inclusion criteria. One showed an association between labour induction and augmentation and ASD, one showed a weak association between labour augmentation in boys and ASD, and one showed no association between labour induction or augmentation and ASD. The largest study showed a weak association between labour induction and ASD, which was not significant when siblings were analyzed separately.

Discussion and conclusion: Recently published studies do not support the hypothesis of a causal relationship between oxytocin use during labour and ASD. Benefits of medically indicated induction or augmentation of labour outweigh the theoretical risk of ASD.

IZVLEČEK

Uvod: Raziskave so pokazale morebitno povezavo med uporabo oksitocina med porodom in avtizmom. Skozi sistematični pregled literature so bile preverjene novejše klinične raziskave s področja povezave med sprožitvijo ali pospeševanjem poroda z oksitocinom in avtizmom.

Metode: Z Boolovima operatorjema (AND oz. OR) je bila pregledana bibliografska zbirka MEDLINE s ključnimi besedami avtistična motnja ali spekter avtističnih motenj ali avtizem in sprožitev poroda ali pospeševanje poroda. Vključeni so bili znanstveni članki v angleščini, objavljeni od leta 2013 dalje. Dodatne raziskave so bile identificirane s pregledom citatov. Vključene so bile le raziskave na ljudeh. Izključene so bile raziskave, ki so povezavo med oksitocinom in avtizmom preučevale brez ustreznega upoštevanja morebitnih motečih dejavnikov.

Rezultati: Vključitvenim kriterijem so ustrezale štiri retrospektivne kohortne raziskave. Povezavo med uporabo oksitocina med porodom in avtizmom je ena raziskava pokazala pri sprožitvi ali pospeševanju poroda, ena samo pri pospeševanju poroda pri dečkih, ena povezave ni pokazala niti pri sprožitvi niti pri pospeševanju poroda, četrta, največja raziskava je pokazala morebitno šibko povezavo pri sprožitvi poroda, vendar ob analizi sorojencev le-ta ni bila več statistično pomembna.

Diskusija in zaključek: Do danes objavljene raziskave niso pokazale klinično pomembne vzročne povezave med uporabo oksitocina med porodom in avtizmom. Dokazane koristi medicinsko indicirane uporabe oksitocina odtehtajo teoretično tveganje za nastanek avtizma.

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Introduction

Autism Spectrum Disorder (ASD) refers to a complex developmental disorder that is characterised especially as a qualitative change in behaviour as regards social interaction, verbal and non-verbal communication and imagination, as well as repetitive or unusual behaviours (Macedoni-Lukšič, 2006; Levy, et al., 2009; Macedoni-Lukšič, et al., 2009). Characteristic behaviour includes avoiding eye-contact, challenges in controlling emotions and understanding and recognising emotions of others, as well as a considerably restricted range of activities and interests (Park, et al., 2016). The frequency rate of ASD is supposed to be 1- do 2-% and has considerably risen in the last two decades also as a result of better diagnosis and monitoring of these disorders (Park, et al., 2016). The frequency of ASD in Slovenia is not known, but since epidemiologic research has shown that frequency is not considerably different between different geographical and social environments, the rates for Slovenia should be quite similar (Macedoni-Lukšič, et al., 2009).

The exact cause of ASD is unknown, however, it may be the result of genetic and environmental factors and their interaction. Environmental factors include factors during pregnancy, during labour and immediately after (Hultman, et al., 2002; Glasson, et al., 2004; Larsson, et al., 2005; Durkin, et al., 2008; Williams, et al., 2008; Bilder, et al., 2009; Gardener, et al., 2009; Burstyn, et al., 2010). In recent years a lot of attention has been paid to the potential association between using the synthetic oxytocin during labour and occurrence of ASD.

Oxytocin in obstetrics is used for inducing uterine contractions when the cervix is considered ripe (labour induction) or for augmenting uterine contractions after a spontaneous onset of labour because the contractions are not frequent or strong enough (labour augmentation). Indications for induction of labour can be divided into medical indications where the benefits to either the mother or the foetus have been demonstrated as with hypertensive illnesses during pregnancy, severe intrauterine growth restriction, preterm premature rupture of membranes or with post-term pregnancy. The other type is non-medical indications or those where the benefits of labour induction have not been demonstrated (American College of Obstetricians and Gynecologists, 2009). Between 2002 and 2011 9.8 % of childbirths in Slovenia were induced by artificial rupture of membranes and applying oxytocin, 9.6 % of labour cases were induced by applying prostaglandin E2 used to stimulate cervical ripening, while in 80.6 % of labour cases the onset was spontaneous (Verdenik, et al., 2013). With regard to spontaneous labour, oxytocin was used with primigravidas in 69 % of cases and 43 % with multigravidas (Verdenik, et al., 2013).

The hypothesis of the potential association between using oxytocin used to induce or augment labour and ASD is based on the fact that oxytocin is an important hormone in the development of human behaviour and in social interaction (Ebstein, et al., 2009). Disorder in behaviour and social interactions is one of the criteria of ASD. Additional support of this hypothesis comes from research works that have demonstrated that genetic malfunctions of oxytocin may be associated to ASD (Gregory, et al., 2009). The use of oxytocin during labour could therefore be associated with the development of ASD.

Aims and objectives

Claims of harmful effects of synthetic oxytocin that is used for inducing and augmenting labour may recently be found especially in popular literature; it is, for example mentioned by the following web pages Porodna Hiša (2011), Autism Speaks (2013), Decoded Pregnancy (2013), Disability Scoop (2013). The supposed causal association with ASD is often listed as an adverse reaction of this medicine, so we opted for a systematic review of recent clinical trials that researched the potential association between the use of oxytocin for induction or augmentation of labour and occurrence of ASD.

Methods

A systematic literature review regarding the association of using oxytocin for labour induction or augmentation and ASD was used and designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (PRISMA, 2017).

Review methods

The systematic literature review method was used. The MEDLINE bibliographic database was searched with the PubMed search tool. We searched for clinical trials that studied the connection between using oxytocin for induction and augmentation of labour and ASD. We searched for articles published in the English language from 2013 to 2016. For search with Boolean operators, key words 'Autistic Disorder' OR 'Autism' AND 'Labour Induction' OR 'Labour Augmentation' were used. By reviewing lists of citations in the articles that we found in this way, we then waited for additional studies that could meet our inclusion criteria.

The results of the review

Figure 1 shows the flow of information through the different phases of review. We found 32 articles with our search criteria. One additional article was found by reviewing citations (Clark, et al., 2015). After reviewing abstracts we excluded all review articles, letters to

editors and articles describing research conducted on animals. We reviewed the entire text of the other five articles and assessed the quality of research (Gregory, et al., 2013; Clark, et al., 2015; Weisman, et al., 2015; Oberg, et al. 2016; Smallwood, et al., 2016). Four studies were included in the final review.

The quality assessment of the review and the description of data processing

There were no randomized trials published that met our criteria. All the trials that were suitable for the assessment of suitability or quality were observational studies. Four of the five studies that we evaluated were retrospective cohort studies conducted on the basis of reviewing large epidemiological databases with relevant consideration of confounding factors like sex of the foetus, methods of childbirth (vaginal delivery vs. Caesarean section), mother's age, parity, foetal distress during labour, breech presentation and some complications during pregnancy (preeclampsia, gestational diabetes and growth retardation) (Gregory, et al., 2013; Clark, et al., 2015; Weisman, et al., 2015; Oberg, et al., 2016). All of the above-mentioned factors are well described perinatal risk factors for ASD, therefore they should be considered when studying the

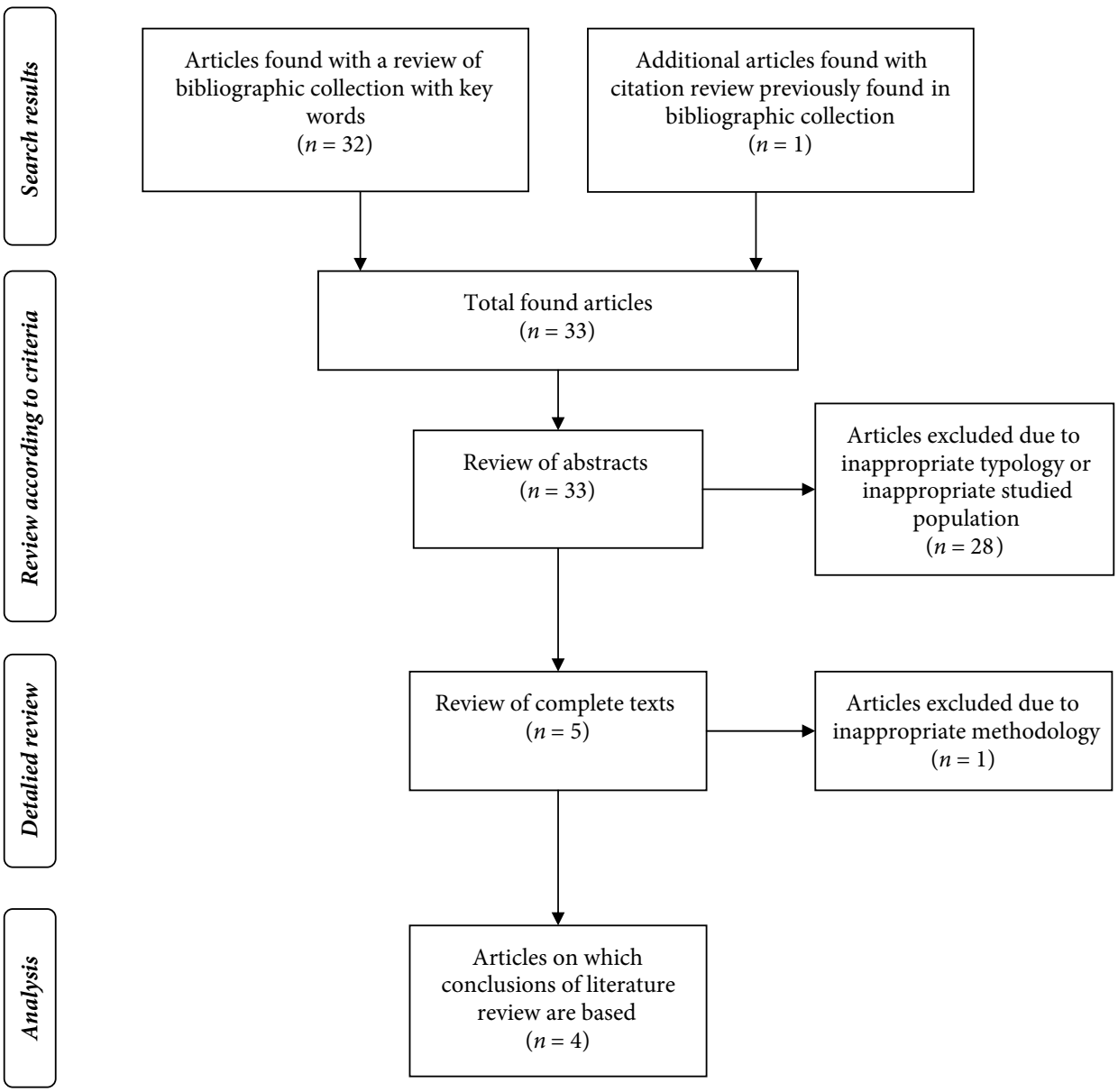


Figure 1: *PRISMA Flow diagram depicting the flow of information through the different phases of systematic review*
Slika 1: *PRISMA diagram poteka raziskave skozi faze sistematičnega pregleda literature (PRISMA diagram)*

potential association between using oxytocin during labour and ASD (Hultman, et al., 2002; Glasson, et al., 2004; Larsson, et al., 2005; Durkin, et al., 2008; Williams, et al., 2008; Bilder, et al., 2009; Gardener, et al., 2009; Burstyn, et al., 2010). The study that was conducted by Smallwood and colleagues (2016) included a sample that was considerably smaller than others (a total of 254 children, 150 with ASD) and was designed as a case-control study. The group of children with ASD and the control group of children without ASD were matched by the children's age, but the above mentioned known perinatal risk factors were not accounted for ASD. Due to disregarding potentially confounding factors we decided not to include this study in the final analysis as we wished to give conclusions on the effect of oxytocin during labour on the risk for ASD.

Results

Table 1 shows characteristics of the four observational studies that met the inclusion criteria of our systematic literature review.

In 2013, Gregory and colleagues (2013) published the largest epidemiological study conducted until then on the potential effect that the use of oxytocin during labour could have on the incidence of ASD. In their perinatal database from North Carolina (United States of America – USA) labour induction and augmentation were independent risk factors for ASD (odds ratio (OR) = 1.27, 95-% confidence interval (95-% CI) = 1.01–1.52). When they analysed only induction and only augmentation of labour, the association was statistically significant (induction: OR = 1.13, 95-% CI = 1.04–1.22; augmentation: OR = 1.16, 95-% CI = 1.07–1.25). After this research was published, the response was quite heated and several claims on the harmful effects of oxytocin followed, especially in popular publications. In scientific circles, the research was met with more scepticism, as there were many potential biases that could have led to the results. Namely, it refers to a database analysis that does not enable precise consideration of all the potentially confounding factors and the actual analysis of oxytocin use. The research only presupposed that the labour cases were induced with oxytocin, while not having any information on the actual methods of induction. Similarly, there were no data on the dose of oxytocin. It can be speculated that a labouring mother who is being induced receives more oxytocin than a labouring mother who is given oxytocin to augment labour. However, there were no differences between the potential risk for ASD in induced and augmented labour (Gregory, et al., 2013).

Clark and colleagues (2015) did not confirm the link between ASD and induction or augmentation of labour with an analysis of the perinatal database

Table 1: *Main characteristics of the effect of the use of oxytocin on induction or augmentation of labour on incidence of ASD*
Tabela 1: *Glavne značilnosti raziskav o vplivu uporabe oksitocina za sprožitev ali pospeševanje poroda na pojavnost SAM*

Author, Year/ Avtor, leto	***Number of all children/ Število vseh otrok (Number of children with ASD/Število otrok s SAM)***	***Key findings/Ključne ugotovitve***	
		Effect on incidence of ASD/ Vpliv na pojavnost SAM	***Odds ratio/ Razmerje obetov (95-% confidence interval/ 95-% interval zaupanja)***
Gregory, 2013	625042 (5500)	Induction or augmentation *all*	1.27 (1.01–1.52)*
		Induction or augmentation *boys*	1.35 (1.01–1.66)*
		Induction or augmentation *girls*	1.01 (0.67–1.53)
		Induction only *all*	1.13 (1.04–1.22)*
		Induction only *boys*	1.18 (1.08–1.30)*
		Induction only *girls*	0.95 (0.80–1.13)
		Augmentation only *all*	1.16 (1.07–1.25)*
		Augmentation only *boys*	1.15 (1.05–1.25)*
		Augmentation only *girls*	1.18 (1.03–1.36)*
Clark, 2015	251404 (2543)	Induction or augmentation *boys*	0.94 (0.77–1.14)
		Induction or augmentation *girls*	0.79 (0.55–1.15)
		Induction only *boys*	1.00 (0.88–1.12)
		Induction only *girls*	0.86 (0.70–1.06)
		Augmentation only *boys*	0.98 (0.85–1.13)
		Augmentation only *girls*	0.98 (0.78–1.24)
Weisman, 2015	557040 (2110)	Augmentation only *boys*	1.13 (1.00–1.26)*
		Augmentation only *girls*	0.99 (0.77–1.27)
Oberg, 2016	1 362 950 (22077)	Induction only *all*	1.19 (1.13–1.24)*
		Induction only *siblings*	0.99 (0.88–1.10)

*Legend/Legenda: n – number/število; * – statistical significance of confidence interval/statistična značilnost intervala zaupanja*

in Utah (USA). A significant association with ASD was also not found when restricted only to labour induction (without augmented labour cases) nor to augmentation of labour (without induced labour cases).

Weisman and colleagues (2015) published the results of a large Danish epidemiological study in which no connection between labour induction and ASD was found. Only a weak association between labour augmentation and ASD and then, only in boys, was found (OR = 1.13, 95-% CI = 1.00–1.26).

The most recent study in the area of the potential association between oxytocin administered during labour and ASD was published in 2016. Swedish researchers confirmed a weak association between labour induction and ASD (OR = 1.19, 95-% CI = 1.13–1.24) on a population of more than 1.3 million mothers by considering the currently known confounding factors. The size of the sample enabled a comparison between siblings whose childbirth differed (induced labour with one and a spontaneous start of labour with the other). Data analysis for siblings, which considers the potentially unconfirmed confounding factors the most, did not show any statistically significant association between labour induction or augmentation with oxytocin and ASD (OR = 0.99, 95-% CI = 0.88–1.10) (Oberg, et al., 2016).

Discussion

Our literature review identified four extensive well-designed retrospective cohort studies regarding the association between labour induction and augmentation with oxytocin and ASD that have been published during the selected period of literature search. The first of these studies showed an association between labour induction/augmentation and ASD, the second only showed an association with ASD in boys, while the third study did not show any connection between labour induction/augmentation and ASD. The final – fourth study was the most extensive in this area and confirmed a potentially weak connection between labour induction and ASD, but data analysis for siblings showed that this connection is probably not causal. Also, from the reviewed research works (retrospective observational cohort studies) we cannot draw reliable conclusions on the causality of the association, not even in cases when the association is statistically significant.

Randomized studies that could answer these questions cannot be expected, for which there are several reasons. The first reason is logistics, as we would need to analyse a very large sample of labouring mothers and their children, whose development we would have to follow for several years to come. Costs of such research would be extremely high. The second reason is the ethical unsoundness of such research. Considering the above-mentioned indications for labour induction or augmentation, the benefits of using oxytocin have been demonstrated; however, when there are no indications present which confirm that the use of oxytocin during labour is not sensible (American College of Obstetricians and Gynecologists, 2009). Therefore, to randomize labouring mothers who would benefit from oxytocin and those who would not need this medicine in two groups, that is, with and without oxytocin, would be unethical.

A positive strenght of the presented literature review is that articles were searched for systematically with search criteria and quality criteria determined in advance. International standards for presenting the results of literature review PRISMA (2017) were considered. Two of the inclusion criteria should be mentioned: 1) the search time frame was restricted to articles that were published in 2013 or later, and 2) only studies that demonstrated an association between the use of oxytocin and ASD by means of a multivariate analysis and appropriate consideration of the known and most relevant perinatal risk factors were included (Gregory, et al., 2013; Clark, et al., 2015; Weisman, et al., 2015; Oberg, et al., 2016).

The decision to only include studies published since 2013 is based on the fact that prior studies that were published were conducted on a considerably smaller sample, so their conclusions are less reliable. However, it should be mentioned that by 2013 nine cohort studies had been published that showed a connection between the use of oxytocin and ASD in a univariate analysis (Gardener, et al., 2009). Only in one of these the association remained statistically significant also after considering the confounding factors. Also, a metaanalysis of these nine studies did not show any significant association between the use of oxytocin during labour and incidence of ASD (Gardener, et al., 2009).

The decision to only include studies in which the already established perinatal risk factors for ASD were considered in the analysis was based on the fact that when disregarding these factors, the risk for bias is unacceptably high. The comparison between women with a spontaneous, unaugmented labour whose children do not suffer from ASD, and women whose labour was induced or augmented with oxytocin and have children who suffer from ASD, regardless of the known perinatal risk factors for ASD, could show that in children whose mothers underwent induced or augmented labour, ASD is present to a greater extent. Namely, such a result would be a consequence of the fact that in comparison to other labouring mothers, oxytocin was given to older labouring mothers, those suffering from diabetes, preeclampsia and primigravidas. Therefore, before making any conclusions on the effect of oxytocin during labour on the incidence of ASD, potential confounding factors should be carefully analysed. Consequently, research in which this was not considered was not included in

this literature review as it could lead to the formulation of wrong conclusions.

The main drawback of the current literature review is that it does not include a metaanalysis of included results. There was not enough information given for this. In future, it would be sensible to conduct such a metaanalysis, if possible, by using individualised data for each child and every childbirth separately. Until then, conclusions on the effects of oxytocin on labour induction and augmentation on the incidence ASD may only be given based on the studies that have been published to date.

Conclusion

The largest and, to date, the best methodically designed study did not show any association between the use of oxytocin and ASD. Moreover, studies which demonstrated the association showed that this potential association is weak and only statistically rather than clinically relevant. The demonstrated benefits of the medically indicated use of oxytocin during labour undoubtedly outweigh the theoretical risk for the occurrence of ASD. We believe that health care workers, especially midwives and obstetricians, should inform pregnant and labouring mothers about this. The latter are often exposed to misleading information on the dangers of synthetic oxytocin as a risk factor for ASD in children.

Slovenian translation/Prevod v slovenščino

Uvod

Spektroavtistične motnje (SAM) ali motnje avtističnega spektra so kompleksna razvojna motnja, ki se kaže predvsem kot kakovostno spremenjeno vedenje na področju socialne interakcije, besedne in nebesedne komunikacije in imaginacije ter ponavljajoče oz. nenavadno vedenje (Macedoni-Lukšič, 2006; Levy, et al., 2009; Macedoni-Lukšič, et al., 2009). Značilno vedenje vključuje izogibanje očesnemu kontaktu, težave s kontroliranjem čustev oz. razumevanjem in prepoznavanjem čustev drugih ter izrazito omejen obseg dejavnosti in interesov (Park, et al., 2016). Pogostnost SAM naj bi bila 1- do 2-% in se je v zadnjih dveh desetletjih, tudi zaradi natančnejše diagnostike in spremljanja teh motenj, izrazito zvišala (Park, et al., 2016). Pogostnost v Sloveniji za zdaj ni znana, ker pa so epidemiološke raziskave pokazale, da se pogostnost bistveno ne razlikuje med različnimi geografskimi oz. socialnimi okolji, so razmere pri nas najverjetneje podobne (Macedoni-Lukšič, et al., 2009).

Točnega vzroka za pojav SAM ne poznamo. Predvideva se, da so rezultat genetskih dejavnikov in dejavnikov iz okolja ter njihovega medsebojnega vpliva. Med dejavniki okolja so pomembni tudi dejavniki v nosečnosti ter ob in neposredno po porodu (Hultman, et al., 2002; Glasson, et al., 2004; Larsson, et al., 2005; Durkin, et al., 2008; Williams, et al., 2008; Bilder, et al., 2009; Gardener, et al., 2009; Burstyn, et al., 2010). Med slednjimi je bilo v zadnjih letih veliko pozornosti namenjene morebitni povezavi med uporabo sintetičnega oksitocina med porodom in pojavom SAM.

Oksitocin se v porodništvu uporablja, kadar želimo sprožiti krčenje maternice ob že zrelem maternicnem vratu (sprožiti porod) ter kadar želimo doseči porast maternične kontraktilnosti pri porodih, ki so se sicer začeli spontano, a potekajo prepočasi (želja pospešiti porod). Indikacije za sprožitev poroda lahko delimo na medicinske, kjer je koristnost sprožitve poroda za mati oz. plod dokazana, na primer pri hipertenzivnih boleznih v nosečnosti, hudem zastoju plodove rasti v maternici, predčasnem razpoku plodovih ovojev ali poterminski nosečnosti, in nemedicinske oz. tiste, pri katerih koristnost sprožitve poroda ni dokazana (American College of Obstetricians and Gynecologists, 2009). V Sloveniji je bilo med leti 2002 in 2011 9,8 % porodov sproženih s predrtjem plodovih ovojev in aplikacijo oksitocina, 9,6 % porodov je bilo sproženih z aplikacijo prostaglandina E2 za zorenje maternicnega vratu, 80,6 % porodov pa se je začelo spontano (Verdenik, et al., 2013). Med porodi, ki so se začeli spontano, je bil oksitocin uporabljen v 69 % pri prvorodnicah in v 43 % pri mnogorodnicah (Verdenik, et al., 2013).

Hipoteza o morebitni povezavi med uporabo oksitocina za sprožitev ali pospeševanje poroda in SAM temelji na dejstvu, da je oksitocin pomemben hormon v razvoju človekovega vedenja in njegovega delovanja v družbi (Ebstein, et al., 2009). Prav motnja v vedenju in socialnih interakcijah pa je eden od kriterijev SAM. Dodatna podpora tej hipotezi prihaja iz raziskav, ki so pokazale, da so genetske motnje v delovanju oksitocina povezane s SAM (Gregory, et al., 2009). Uporaba oksitocina med porodom bi bila torej lahko povezana z razvojem SAM.

Namen in cilji

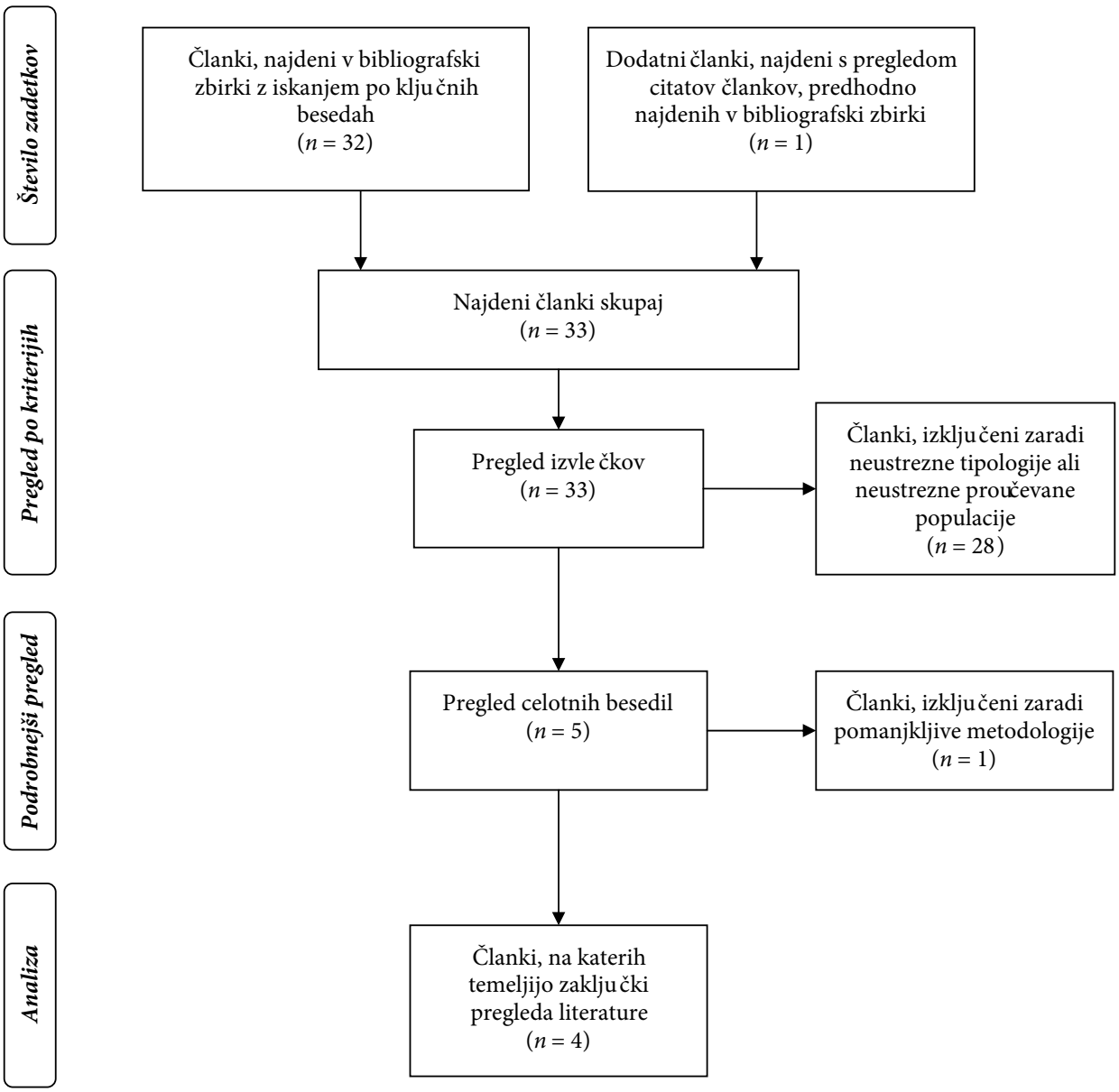
Predvsem v laični literaturi je v zadnjih letih pogosto zaslediti trditve o škodljivosti sintetičnega oksitocina, ki se uporablja za sprožitev in pospeševanje poroda; navajajo jih npr. spletne strani Porodna Hiša (2011), Autism Speaks (2013), Decoded Pregnancy (2013), Disability Scoop (2013). Kot stranski učinek tega zdravila je velikokrat navedena tudi domnevna vzročna povezava z nastankom SAM, zato smo se odločili za sistematični pregled novejših kliničnih raziskav, ki so obravnavale morebitno povezavo med uporabo oksitocina za sprožitev oz. pospeševanje poroda ter pojavnostjo SAM.

Metode

Uporabljen je bil sistematični pregled literature s področja povezave med uporabo oksitocina za pospeševanje ali sprožitev poroda in SAM, narejen po smernicah PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (PRISMA, 2017).

Metode pregleda

Uporabljena je bila metoda sistematičnega pregleda literature. Pregledali smo bibliografsko zbirko MEDLINE s pomočjo iskalnega sistema PubMed. Iskali smo klinične raziskave, ki so proučevale povezavo med uporabo oksitocina za sprožitev ali pospeševanje poroda in SAM. Iskali smo članke, objavljene v angleškem jeziku od 2013 do 2016. Za iskanje z Boolovima operatorjema smo uporabili ključne besede avtistična motnja (»Autistic Disorder«) ali (OR) spekter avtističnih motenj (»Autism Spectrum Disorder«) ali (OR) avtizem (»Autism«) in (AND) sprožitev poroda (»Labor Induction«) ali (OR) pospeševanje poroda (»Labor Augmentation«). S pregledom seznamov citatov v tako dobljenih člankih smo nato iskali še dodatne raziskave, ki bi lahko ustrezale našim vključitvenim kriterijem.



Slika 1: *PRISMA diagram poteka raziskave skozi faze sistematičnega pregleda literature (PRISMA diagram)*
Figure 1: *PRISMA Flow diagram depicting the flow of information through the different phases of systematic review*

Rezultati pregleda

Slika 1 prikazuje potek raziskave skozi faze pregleda. S pomočjo iskalnih kriterijev smo našli 32 člankov. En dodaten članek smo našli s pregledom citatov (Clark, et al., 2015). Po pregledu izvlečkov smo izključili vse pregledne članke, pisma urednikom in članke, ki so opisovali raziskave na živalih. Pregledali smo celotno besedilo preostalih petih člankov in ocenili kakovost raziskav (Gregory, et al., 2013; Clark, et al., 2015; Weisman, et al., 2015; Oberg, et al. 2016; Smallwood, et al., 2016). V končni pregled smo vključili štiri raziskave.

Ocena kakovosti pregleda in opis obdelave podatkov

Objavljena ni bila nobena randomizirana raziskava, ki bi ustrezala našim iskalnim kriterijem. V se raziskave, ki so bile primerne za oceno ustreznosti oz. kakovosti, so opazovalne raziskave. Štiri od petih raziskav, ki smo jih ocenjevali, so bile retrospektivne kohortne raziskave, narejene na podlagi pregleda velikih epidemioloških baz podatkov z ustreznim upoštevanjem motečih dejavnikov, kot so spol otroka, način poroda (vaginalni porod vs. carski rez), starost matere, pariteta, fetalni distres med porodom, medenična vstava in nekateri zapleti v nosečnosti (preeklampsija, nosečnostna sladkorna bolezen in zastoj plodove rasti) (Gregory, et al., 2013; Clark, et al., 2015; Weisman, et al., 2015; Oberg, et al., 2016). Vsi našteti dejavniki so namreč znani perinatalni dejavniki tveganja za SAM, zato jih je potrebno upoštevati, kadar preučujemo morebitno povezavo med uporabo oksitocina med porodom in SAM (Hultman, et al., 2002; Glasson, et al., 2004; Larsson, et al., 2005; Durkin, et al., 2008; Williams, et al., 2008; Bilder, et al., 2009; Gardener, et al., 2009; Burstyn, et al., 2010). Raziskava, ki so jo opravili Smallwood in sodelavci (2016), je zajemala bistveno manjši vzorec od ostalih (skupno 254 otrok, od tega 150 s SAM) in je bila zasnovana kot raziskava primer – kontrola. Skupina otrok s SAM in kontrolna skupina otrok brez SAM sta bili usklajeni le glede starosti otrok, ne pa tudi glede številnih že zgoraj navedenih znanih dejavnikov tveganja za SAM. Zaradi neupoštevanja potencialno motečih dejavnikov smo se odločili, da te raziskave ne vključimo v končno analizo, na podlagi katere smo želeli podati zaključke o vplivu oksitocina med porodom na tveganje za SAM.

Rezultati

Tabela 1 prikazuje značilnosti štirih opazovalnih raziskav, ki ustrezajo vključitvenim kriterijem našega sistematičnega pregleda literature.

Leta 2013 so Gregory in sodelavci (2013) objavili do takrat največjo epidemiološko raziskavo o morebitnem

Tabela 1: *Glavne značilnosti raziskav o vplivu uporabe oksitocina za sprožitev ali pospeševanje poroda na pojavnost SAM*
Table 1: *Main characteristics of the effect of the use of oxytocin on induction or augmentation of labour on incidence of ASD*

Avtor, leto/ Author, year	***Število vseh otrok/ Number of all children (Število otrok s SAM/ Number of children with SAM)***	***Ključne ugotovitve/Key findings***	
		Vpliv na pojavnost SAM/ Effect on incidence of SAM	***Razmerje obetov/ Odds ratio (95-% interval zaupanja/ 95-% confidence interval)***
Gregory, 2013	625042 (5500)	Sprožitev ali pospeševanje *vsi*	1,27 (1,01–1,52)*
		Sprožitev ali pospeševanje *dečki*	1,35 (1,01–1,66)*
		Sprožitev ali pospeševanje *deklice*	1,01 (0,67–1,53)
		Samo sprožitev *vsi*	1,13 (1,04–1,22)*
		Samo sprožitev *dečki*	1,18 (1,08–1,30)*
		Samo sprožitev *deklice*	0,95 (0,80–1,13)
		Samo pospeševanje *vsi*	1,16 (1,07–1,25)*
		Samo pospeševanje *dečki*	1,15 (1,05–1,25)*
		Samo pospeševanje *deklice*	1,18 (1,03–1,36)*
Clark, 2015	251404 (2543)	Sprožitev ali pospeševanje *dečki*	0,94 (0,77–1,14)
		Sprožitev ali pospeševanje *deklice*	0,79 (0,55–1,15)
		Samo sprožitev *dečki*	1,00 (0,88–1,12)
		Samo sprožitev *deklice*	0,86 (0,70–1,06)
		Samo pospeševanje *dečki*	0,98 (0,85–1,13)
		Samo pospeševanje *deklice*	0,98 (0,78–1,24)
Weisman, 2015	557040 (2110)	Samo pospeševanje *dečki*	1,13 (1,00–1,26)*
		Samo pospeševanje *deklice*	0,99 (0,77–1,27)
Oberg, 2016	1 362 950 (22077)	Samo sprožitev poroda *vsi*	1,19 (1,13–1,24)*
		Samo sprožitev poroda *sorojenci*	0,99 (0,88–1,10)

*Legenda/Legend: n – število/number; * – statistična značilnost intervala zaupanja/statistical significance of confidence interval*

vplivu oksitocina med porodom na pojavnost SAM. V njihovi perinatalni bazi podatkov iz Severne Karoline (Združene države Amerike – ZDA) sta bila sprožitev in pospeševanje poroda neodvisna dejavnika tveganja za SAM (razmerje obetov (RO) = 1,27, 95-% interval zaupanja (95-% IZ) = 1,01–1,52). Tudi ko so analizirali samo sprožitev in samo pospeševanje poroda, je bila povezava statistično značilna (sprožitev: RO = 1,13, 95-% IZ = 1,04–1,22; pospeševanje: RO = 1,16, 95-% IZ = 1,07–1,25). Objava te raziskave je sprožila burne odzive in številna poročila o škodljivosti oksitocina, predvsem v laičnih publikacijah. V znanstvenih krogih je bila raziskava sprejeta s precej več zadržkov. Zasnova raziskave je namreč na več mestih pomanjkljiva. Gre za analizo baze podatkov, ki ne omogoča natančnega upoštevanja vseh morebitnih motečih dejavnikov in dejanske analize uporabe oksitocina. V raziskavi so le predpostavljali, da so porode sprožili z oksitocinom, niso pa imeli podatkov o dejanskih metodah sprožitve. Prav tako ni bilo podatkov o odmerku oksitocina. Predpostavljati je mogoče, da porodnice s sproženim porodom prejmejo več oksitocina kot tiste s pospešenim porodom. Vendar razlik med morebitnim tveganjem za SAM pri sproženih in pospešenih porodih ni bilo (Gregory, et al., 2013).

Clark in sodelavci (2015) povezave med SAM in sprožitvijo ali pospeševanjem poroda z analizo perinatalne baze podatkov v zvezni državi Utah (ZDA) niso potrdili. Pomembne povezave s SAM prav tako niso našli niti omejeno le na sprožitev poroda (brez pospešenih porodov) niti le na pospeševanje poroda (brez sproženih porodov).

Weisman in sodelavci (2015) so objavili rezultate velike danske epidemiološke raziskave, v kateri prav tako niso našli povezave med sprožitvijo poroda in SAM. Prisotna je bila samo šibka povezava med pospeševanjem poroda z oksitocinom in SAM, in sicer le pri dečkih (RO = 1,13, 95-% IZ = 1,00–1,26).

Najnovejša raziskava s področja morebitne povezave med uporabo oksitocina med porodom in SAM je bila objavljena leta 2016. Švedski raziskovalci so na populaciji več kot 1.300.000 rojstev ob upoštevanju danes znanih motečih dejavnikov potrdili šibko povezavo med sprožitvijo poroda in SAM (RO = 1,19, 95-% IZ = 1,13–1,24). Velikost vzorca je omogočala tudi primerjavo sorojencev, pri katerih se je začetek poroda razlikoval (sprožen porod pri enem in spontan začetek poroda pri drugem). Analiza podatkov za sorojence, ki najbolje upošteva morebitne še nepotrjene moteče dejavnike, ni pokazala statistično pomembne povezave med sprožitvijo poroda in SAM (RO = 0,99, 95-% IZ = 0,88–1,10) (Oberg, et al., 2016).

Diskusija

Z našim pregledom literature smo identificirali štiri velike dobro zasnovane retrospektivne kohortne raziskave s področja povezave med sprožitvijo ali pospeševanjem poroda z oksitocinom in SAM, ki so bile objavljene v izbranem časovnem obdobju. Prva od teh raziskav je povezavo med sprožitvijo ali pospeševanjem poroda in SAM pokazala, druga je povezavo s SAM pokazala samo za pospeševanje poroda pri dečkih, tretja pa povezave med sprožitvijo ali pospeševanjem poroda in SAM ni pokazala. Četrta, časovno zadnja in največja raziskava na tem področju je za celotno populacijo sicer potrdila morebitno šibko povezavo med sprožitvijo poroda in SAM, vendar je analiza podatkov za sorojence pokazala, da ta povezava najverjetneje ni vzročna. Tudi sicer zasnova pregledanih raziskav (retrospektivne opazovalne kohortne raziskave) zanesljivih zaključkov o vzročnosti povezave ne dovoljuje niti v primerih, ko je le-ta statistično značilna.

Randomizirane raziskave, ki bi na to vprašanje ustrezno odgovorila, pač ne moremo pričakovati. Razlogov za to je več. Prvi je logistični, saj bi za takšno raziskavo morali analizirati ogromen vzorec porodnic in njihovih otrok, katerih razvoju bi morali slediti več let. Tudi stroški tovrstne raziskave bi bili izjemno visoki. Drugi razlog je etična oporečnost takšne raziskave. Ob prisotnih indikacijah za sprožitev ali pospeševanje poroda, ki smo jih omenili že v uvodu, so koristi uporabe oksitocina namreč dokazane; ob odsotnosti indikacij pa uporaba oksitocina med porodom ni smiselna (American College of Obstetricians and Gynecologists, 2009). Randomizirati porodnice, ki bi jim uporaba oksitocina koristila, in porodnice, ki tega zdravila ne potrebujejo, v dveh skupinah, tj. z in brez uporabe oksitocina, bi bilo torej neetično.

Dobra lastnost predstavljenega pregleda literature je, da smo članke iskali sistematično, z vnaprej določenimi iskalnimi kriteriji in kriteriji za kakovost. Pri tem smo upoštevali mednarodne standarde za prikaz rezultatov pregleda literature PRISMA (2017). Med vključitvenimi kriteriji velja v diskusiji omeniti dva: 1) časovni iskalni okvir smo omejili na članke, ki so bili objavljeni leta 2013 ali kasneje, in 2) vključili smo le raziskave, v katerih je bila povezava med uporabo oksitocina in SAM dokazana z multivariatno analizo in ustreznim upoštevanjem že znanih najpomembnejših perinatalnih dejavnikov tveganja (Gregory, et al., 2013; Clark, et al., 2015; Weisman, et al., 2015; Oberg, et al., 2016).

Odločitev, da bomo vključili le raziskave, objavljene od leta 2013 dalje, temelji na dejstvu, da so bile raziskave, objavljene pred tem, izvedene na bistveno manjšem vzorcu in so zato njihovi zaključki manj zanesljivi. Vseeno pa velja omeniti, da je bilo do leta 2013 objavljenih devet kohortnih raziskav, ki so v univariatni analizi pokazale povezavo med uporabo oksitocina in SAM (Gardener, et al., 2009). Samo pri eni od teh je povezava ostala statistično značilna tudi po upoštevanju motečih dejavnikov. Tudi metaanaliza teh devetih raziskav ni pokazala pomembne povezave med uporabo oksitocina med porodom in pojavnostjo SAM (Gardener, et al., 2009).

Odločitev, da bomo v pregled literature vključili le raziskave, v katerih so bili pri analizi vpliva oksitocina na SAM upoštevani že znani perinatalni dejavniki tveganja za SAM, temelji na tem, da je ob neupoštevanju teh dejavnikov tveganje za pristranost nesprejemljivo visoko. Primerjava žensk s spontanim, nepospešenim porodom, katerih otroci nimajo SAM, ter žensk, pri katerih je bil porod sprožen ali pospešen z oksitocinom in imajo otroke s SAM, ne glede na že znane perinatalne dejavnike tveganja za SAM, bi morda lahko pokazala, da je pri otrocih porodnic s pospešenim ali sproženim porodom SAM prisoten v večjem deležu. Takšen rezultat bi bil namreč tudi posledica dejstva, da je v primerjavi z ostalimi porodnicami oksitocin med porodom prejelo več starejših porodnic, tistih s sladkorno boleznijo, preeklampsijo in prvorodnic. Pred vsakršnim zaključkom o vplivu oksitocina med porodom na pojavnost SAM je zato treba pozorno analizirati morebitne moteče dejavnike. Posledično raziskav, v katerih to ni bilo storjeno, nismo vključili v naš pregled literature, saj bi lahko privedle do napačnih zaključkov.

Glavna slabost obstoječega pregleda literature je, da ne vsebuje metaanalize vključenih raziskav. Za slednjo v pregledanih člankih ni bilo podanih dovolj informacij. V prihodnje bi bilo smiselno takšno metaanalizo izvesti, po možnosti z uporabo individualiziranih podatkov za vsakega otroka in vsak porod posebej. Do takrat lahko zaključke o vplivu uporabe oksitocina za sprožitev ali pospeševanje poroda na nastanek SAM podamo le na podlagi pregleda do danes objavljenih raziskav.

Zaključek

Največja in do danes najbolje metodološko zasnovana raziskava ni pokazala povezave med uporabo oksitocina in SAM. Tudi raziskave, v katerih so povezavo našli, so pokazale, da je ta morebitna povezava šibka in le statistično, ne pa tudi klinično pomembna. Dokazane koristi medicinsko indicirane uporabe oksitocina med porodom tako nedvomno odtehtajo zgolj teoretično tveganje za nastanek SAM. Menimo, da bi morali zdravstveni delavci, predvsem babice in porodničarji, s tem seznaniti nosečnice in porodnice. Slednje so namreč danes iz različnih virov pogosto deležne zavajajočih informacij o nevarnosti sintetičnega oksitocina kot dejavnika tveganja za SAM pri otroku.

Conflict of interest/Nasprotje interesov

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This systematic literature review was exempt from ethical committee approval./Raziskava predstavlja pregled že objavljene literature in zato ni potrebovala posebnega dovoljenja komisije za etiko.

Author contributions/Prispevek avtorjev

Both authors made equal contributions to the design of the research, literature review and writing of all parts of the article./Oba avtorja sta enako prispevala k zasnovi raziskave, pregledu literature in pisanju vseh delov besedila članka.

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