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Intrapartum synthetic oxytocin, behavioral and emotional problems in children, and the role of postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding: A Dutch prospective cohort study

Elke Tichelman[a,b,*], Willemijn Warmink-Perdijk[a,b], Jens Henrichs[a], Lillian Peters[a,b], Francois G. Schellevis[c,d], Marjolein Y. Berger[b], Huibert Burger[b]

[a] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Midwifery Science, AVAG, Amsterdam Public, Health research institute, Amsterdam, the Netherlands
[b] University of Groningen, University Medical Centre Groningen, Department of General Practice and Elderly Care Medicine, the Netherlands
[c] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of General Practice and Elderly Care Medicine, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands
[d] NIVEL, Netherlands Institute for Health Services Research, Utrecht, the Netherlands

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ABSTRACT

Objective: To examine the association between intrapartum synthetic oxytocin and child behavioral and emotional problems and to assess if maternal depressive or anxious symptoms or mother-to-infant bonding play a mediating role in this association.

Design: Prospective cohort study.

Setting: Population-based Pregnancy Anxiety and Depression Study.

Participants: Pregnant women in their first trimester of pregnancy visiting a total of 109 primary and nine secondary obstetric care centers in the Netherlands between 2010 and 2014 were invited to participate. Follow-up measures used for the present study were collected from May 2010 to January 2019. Women with multiple gestations and with a preterm birth were excluded.

Measurements: Intrapartum synthetic oxytocin exposure status was based on medical birth records and was defined as its administration (Yes/No), either for labour induction or augmentation. Child behavioral and emotional problems were measured with the Child Behavior Checklist at up to 60 months postpartum. Maternal depressive symptoms, anxiety and mother-to infant bonding were measured with the Edinburgh Postnatal Depression Scale, State Trait Anxiety Inventory and the Mother-to-Infant Bonding Scale from 6 months postpartum. We used multivariable linear regression models to estimate standardized beta coefficients and unique variance explained.

Findings: 1,528 women responded. In total 607 women received intrapartum synthetic oxytocin. Intrapartum synthetic oxytocin administration was not associated with child behavioral and emotional problems, mother-to-infant bonding nor with postnatal anxiety. Intrapartum synthetic oxytocin was however significantly but weakly associated with more postnatal depressive symptoms (β=0.17, 95%CI of 0.03 to 0.30) explaining 0.6% of unique variance. Maternal postnatal depressive symptoms, postnatal anxiety symptoms and suboptimal mother-to-infant bonding were positively associated with child behavioral and emotional problems.

Key conclusions and implications for practice: We found no evidence that intrapartum synthetic oxytocin is associated with child behavioral and emotional problems, mother-to-infant bonding, or with postnatal anxiety symptoms. Because there was no association between intrapartum synthetic oxytocin and behavioral and emotional problems in children no mediation analysis was carried out. However, intrapartum synthetic oxytocin was positively but weakly associated with postnatal depressive symptoms. The clinical relevance of this finding is negligible in the general population, but unknown in a population with a high risk of depression

Introduction

Synthetic oxytocin is widely administered throughout labour and postpartum in modern obstetrics, i.e. intrapartum for labour induction, and labour augmentation, and postpartum for prevention of hemorrhage

* Corresponding author.
E-mail address: e.tichelman@umcg.nl (E. Tichelman).

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(World Health Organization, 2018). With an induction rate of approximately 25% of all term births in developed countries, and oxytocin-augmentation rates as high as 25 to 79% in some countries, intrapartum synthetic oxytocin use is ubiquitous (WHO, 2018; de Jonge et al., 2017).

Although widely used, intrapartum synthetic oxytocin could interfere with the natural process of birth. Natural oxytocin is involved in social bonding, childbirth and breastfeeding (Uvnäs-Moberg et al., 2019; Yang et al., 2013). During pregnancy, levels of natural oxytocin increase, cross the placenta (Wahl 2004), and correlate positively with prenatal mother-to-infant bonding in the third trimester (Eapen et al., 2014; Levine et al., 2007). The natural process of birth can be interfered by intrapartum synthetic oxytocin via several pathways, with potential impact on the child (Cadwell and Brimdyr, 2017). First, the administration of synthetic oxytocin may inhibit the action of maternal natural oxytocin immediately postpartum through desensitization of oxytocin receptors, and via negative feedback mechanisms (Cadwell and Brimdyr, 2017; Conti et al., 2008). Synthetic oxytocin, in contrast to natural oxytocin, does not have effects within the brain influencing neuroendocrine mechanisms and thereby maternal mood (Uvnäs-Moberg et al., 2019). Second, intrapartum synthetic oxytocin is able to cross the placenta (Wahl, 2004; Cadwell and Brimdyr, 2017) and may permanently alter and downregulate fetal oxytocin receptors (Wahl, 2004). Third, intrapartum synthetic oxytocin may elicit uterine hyperstimulation (excessive and unusually frequent contractions) which, in turn, has negative impact on fetal oxygen saturation and fetal heart rate (Cadwell and Brimdyr, 2017). The resulting fetal distress may have long-term consequences for development of the brain (Rees and Inder, 2005).

A possible distal effect of the exposure to intrapartum synthetic oxytocin is the occurrence of behavioral and emotional problems of the offspring, as demonstrated in animal models (Rault et al., 2013). Findings from literature suggest negative consequences of intrapartum oxytocin exposure on breastfeeding outcomes, lower APGAR scores, and deficits in gross and fine motor development (Torres et al., 2020; Gonzalez-Valenzuela et al., 2015). There are also studies suggesting that perinatal use of oxytocin may increase the risk of children developing Attention Deficit Hyperactivity Disorder or Autistic Disorder (Kurth and Haussmann, 2011; Weisman et al., 2015; Torres et al., 2020). A systematic review of human studies by Lønfeldt et al. reported little evidence for an association of intrapartum synthetic oxytocin with several child neurodevelopmental outcomes based on studies with a rather low-to-moderate quality (Lønfeldt et al., 2019). They revealed no evidence for an association with attention-deficit/hyperactivity disorder, but there was a modestly increased risk of autism spectrum disorders (Lønfeldt et al., 2019). There is mixed evidence for the association between intrapartum synthetic oxytocin and child behavioral and emotional problems during. The prospective study (n=2,900) by Guastella et al. observed no overall association between intrapartum synthetic oxytocin exposure measured in three categories (augmentation, induction or none exposure) and child behavioral and emotional problems during childhood (Guastella et al., 2018). Nevertheless, in a subsample of 542 children exposed to a higher intrapartum synthetic oxytocin dosage children had a modestly increased risk of child behavioral and emotional problems (Guastella et al., 2018). A large retrospective study with 330,107 participants, however, showed a slightly reduced cognitive ability in young adults exposed to synthetic oxytocin for labour augmentation measured dichotomously (yes/no). This study excluded births were the labour was induced. However, the difference found was small and not considered to be clinically relevant (Stokholm et al., 2018).

Postnatal depressive symptoms, postnatal anxiety symptoms and suboptimal mother-to-infant bonding, have shown to be predictors of an increased risk of child behavioral and emotional problems and may theoretically concern mediators of the association between exposure to intrapartum synthetic oxytocin and child behavioral and emotional functioning (Goodman et al., 2011; Stein et al., 2014; Glasheen et al., 2010; van Batenburg et al., 2013; Mason et al., 2011; Arguz Cildir et al., 2019). Yet, their associations with intrapartum synthetic oxytocin are less clear.

Conclusions regarding the relationship between intravenous synthetic oxytocin and postpartum depression cannot be made based on current evidence. There is mixed evidence (Gu et al., 2016; Kroll-Desrosiers et al., 2017; Hinshaw et al., 2008; Takács et al., 2018). Thul et al. rated the designs of the four studies as high quality (Thul et al., 2020). However, the designs and methodology are so different that it is difficult to compare between studies (Thul et al., 2020). In a randomized controlled trial Hinshaw showed a non-statistically significant difference within 412 nulliparous women. The rate of depression within 48 hours postpartum was 20% in the immediate oxytocin administration group versus 15% among the group with oxytocin withheld for up to 8 hours (Hinshaw et al., 2008).

Two studies using a strong design showed that peripartum – including intrapartum – synthetic oxytocin increases the risk of maternal postpartum depressive symptoms and postnatal anxiety (Gu et al., 2016; Kroll-Desrosiers et al., 2017). In a longitudinal study of 386 participants Gu et al. provided evidence that the total synthetic oxytocin dosage based on postpartum intravenous and intramuscular administration of synthetic oxytocin was associated with more depressive, anxious, and somatization symptoms in a graded way. (Gu et al., 2016). Kroll-Desrosiers et al. measured peripartum oxytocin exposure dichotomously (yes/no) in a large retrospective population-based study (n= 46,732) (Kroll-Desrosiers et al., 2017). Remarkably, using a prospective study (n=426) Takács et al. (2018) showed that intrapartum synthetic oxytocin measured dichotomously was associated with a lower risk of postpartum depressive symptoms (Takács et al., 2018). In all these studies, however, no adjustment for confounding by indication for oxytocin treatment was applied which hampers causal interpretation. Just like maternal depressive and anxious symptoms, mother-to-infant bonding could play a mediating role in an association between intrapartum synthetic oxytocin and child behavioral and emotional problems. Mother-to-infant bonding is defined as the emotions and feelings experienced by a mother towards her child (de Cock et al., 2016; Kinsey and Hupcey, 2013). Mother-to-infant bonding should not be confused with attachment, which refers to the connectedness between an infant and a caregiver characterized by the child using its caregiver as a secure base for exploration (Benoit, 2004). Mother-to-infant bonding, unlike attachment, is unidirectional (from mother to child) and starts to develop already during pregnancy, after which it further develops until early childhood (de Cock et al., 2016; Kinsey and Hupcey, 2013; Klaus et al., 1996). Indeed, natural oxytocin correlates with increasing perinatal mother-to-infant bonding (Eapen et al., 2014; Levine et al., 2007). However, results of a systematic review of correlates of prenatal and postnatal mother-to-infant bonding showed that intrapartum synthetic oxytocin has not been studied in relation to mother-to-infant bonding so far (Tichelman et al., 2019).

In sum, the long term effects of intrapartum synthetic oxytocin on child behavioral and emotional problems is uncertain. This is unfortunate as healthcare providers in maternal health care need to be able to inform women whether the use of intrapartum synthetic oxytocin would imply a risk for the offspring. Therefore, the first aim of this study is to investigate whether and to what extent the intrapartum use of synthetic oxytocin is associated with behavioral and emotional problems of children aged up to 60 months postpartum. The second aim is to assess whether maternal depressive or anxious symptoms or mother-to-infant bonding could mediate the association between intrapartum synthetic oxytocin and child behavioral and emotional problems.

Methods

Study design and participants

Participants were from the Pregnancy, Anxiety and Depression (PAD) Study (Meijer et al., 2013) together with the data of the PRegnancy Outcomes after Maternity Intervention for Stressful Emotions trial (PROMISES) (Meijer et al., 2011). The PAD study is a prospective population-based cohort study investigating among 5,784 women symptoms of and risk factors for anxiety and depression during pregnancy and the first years postpartum. The PAD study was set up to estimate the prevalence of depression and anxiety during pregnancy and served as a sampling frame for the PROMISES trial (Meijer et al., 2011). This randomized controlled trial demonstrated no beneficial effects of Cognitive Behavioral Therapy (CBT) on maternal symptoms nor on behavioral and emotional problems of the child among 282 women with at least moderate levels of anxiety or depression at the end of the first trimester of pregnancy (Burger et al., 2019).

All pregnant women in their first trimester of pregnancy visiting a total of 109 primary and nine secondary obstetric care centers in the Netherlands between 2010 and 2014 were invited to participate. Only a single inclusion criterion was applied (ability to read and speak Dutch). Follow-up measures used for the present study were collected from May 2010 to January 2019.

The eligible population for the present analysis consisted of all women with a child aged less than 60 months old by November 2016 (n=4,466). Women with multiple gestation and with a preterm birth (before 37 weeks of gestation) were excluded (respectively n= 231 and 31) because these conditions are associated with substantially increased risk of obstetric problems during pregnancy and adverse birth outcomes which could have a disproportionally strong effect on the results.

Ethical approval

Ethical Approval for the study was obtained from the medical ethical review board of the University Medical Center Groningen (METc2009.235). All participants gave informed consent.

Child behavioral and emotional problems

In the PAD study, child behavioral and emotional problems were measured between 45 and 60 months postpartum with the Dutch version of the Child Behavior Checklist (CBCL) for 1.5–5 year old children (Achenbach and Rescorla, 2000). Within the PROMISES trial the CBCL was administered 18 months postpartum. For each child one parent completed the 99 item CBCL and indicated how often during the last two months the child displayed emotional or behavioral problems by endorsing one of three item response options: 0 "Not true," 1 "Somewhat or Sometimes True," or 2 "Very True or Often True." The CBCL raw scores were transformed into two scales of : 1) Internalizing problems (emotionally reactive, anxious/depressed, somatic complaints and withdrawn behavior) (range 0-72) and 2) Externalizing problems (attention problems and aggressive behavior) (range 0-48). Higher scores indicate greater severity (Achenbach and Rescorla, 2000). Internal consistency of the scales in the present study is good (Cronbach's alphas of 0.82 and 0.90, respectively).

Intrapartum synthetic oxytocin

Intrapartum synthetic oxytocin exposure was defined as its administration either for labour induction or augmentation and was registered as yes/no. These data were extracted from medical birth records entered by gynecologists and midwives.

Postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding

Postnatal depressive symptoms were measured with the validated Dutch version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1996; Pop et al., 1992) at 6 months postpartum. Scores on this 10-item, 4-point Likert scale range from 0 to 30. Higher scores indicate more depressive symptoms. Internal consistency of the EPDS in the present study is good (Cronbach's alpha =0.87).

Postnatal anxiety symptoms were measured by State Trait Anxiety Inventory (STAI). The Dutch short version of the 6-item 4-point Likert scale (STAI-6) was used to determine anxiety at 6 months postpartum (Marteau and Bekker, 1992). Scores range from 20 to 80. Higher scores indicate more anxious symptoms (van der Ploeg, 2000). Internal consistency of the STAI at 6 months postpartum in the present study is good (Cronbach's alpha= 0.88).

To assess postpartum mother-to-infant bonding the Dutch version of Mother-to-Infant Bonding Scale (MIBS) was used (van Bussel et al., 2010; Taylor et al., 2005). This self-report questionnaire consists of 8 items (loving, resentful, neutral or felt nothing, joyful, dislike, protective, disappointed and aggressive) scored on a 4-point Likert scale ranging from "Very much " to "Not at all". Scores on the MIBS range between 0 and 24, with high scores indicating a poorer mother-to-infant bond. The MIBS was used between 6 and 45 months postpartum. The internal consistency of the MIBS between 6 and 45 months postpartum in the present study is acceptable (Cronbach's alpha= 0.67) compared to other studies where the reported Cronbach's alpha varied between 0.58 and 0.71. (Bussel et al., 2010; Matsunaga et al., 2017; Taylor et al., 2005; Wittkowski et al., 2007).

Maternal characteristics

Educational level, measured at baseline, was defined as the highest completed education, and recorded in five categories: elementary, lower tract of secondary, higher tract of secondary, higher vocational and university education. Cultural background (Dutch, non-Dutch) was reported by mothers at 13 weeks' gestation as well as data on prenatal depressive symptoms and prenatal anxiety using the EPDS and STAI-6.

Birth characteristics

Mode of birth (vaginal or cesarean section) and duration of first, second and third stage of labour measured continuously in minutes were extracted from medical records. Whether or not the child was exclusively breastfed for at least 6 months was assessed using an online questionnaire administered around 6 months postpartum.

Confounders

Potential confounders were identified prior to the analyses and were based on previous studies. They were selected if they could cause confounding by indication, i.e. a spurious association between intrapartum synthetic oxytocin on the one hand and child behavioral and emotional problems or maternal mental health factors on the other. Likewise, variables that could confound the association between maternal mental health factors and child behavioral and emotional problems were identified. Potential confounders comprised maternal characteristics (maternal age, parity, educational level, cultural background, and prenatal depressive and anxiety symptoms) as well as birth characteristics (mode of birth, duration of first and second stage of labour). We applied the following criteria to select confounders: causal knowledge as plausibility (prior probability), (literature-based) theoretically knowledge and, subsequently, an analysis of a relative 'change-in-estimate' of at least 10 percent of the estimate of the determinant of interest (Hernán et al., 2002; Van der Weele and Shpitser, 2013).

Table 1
Comparison of characteristics between participants exposed and not exposed to intrapartum synthetic oxytocin.

Characteristics Responders on CBCL n=1,528	No intrapartum SOT n= 921	Intrapartum SOT n=607	P-value
Maternal characteristics (first trimester of pregnancy)			
Educational attainment level, n (%)			0.12
elementary education	9 (1%)	8 (1%)	
lower tract of secondary education	23 (2%)	26 (4%)	
higher tract of secondary	269 (29%)	200 (33%)	
education	375 (41%)	250 (41%)	
higher vocational education	245 (27%)	123 (21%)	
university education			
Cultural background, non-Dutch, n (%)	37 (4%)	24 (4%)	0.87
Maternal age, mean	31	31	
Parity, nulliparous, n (%)	*334 (36%)*	*352 (58%)*	*<0.001*
Prenatal depressive symptoms (EPDS), mean	4.5	4.8	0.35
Prenatal anxiety symptoms (STAI), mean	33.0	33.6	0.24
Birth characteristics			
Mode of birth (sectio)	*165 (18%)*	*154 (25%)*	*0.02*
Duration of first stage of labour (min.) mean	*314*	*511*	*<0.001*
Duration of second stage of labour (min.) mean	*23*	*39*	*<0.001*
Duration of third stage of labour (min.) mean	13	13	0.72
Breastfeeding (6 months postpartum)	440 (48%)	238 (39%)	0.01

EPDS = Edinburgh Postnatal Depression Scale, STAI = State Trait Anxiety Inventory, CBCL = = Child Behavior Checklist, SOT= synthetic oxytocin. Reported p-values are based on: Chi square test and Student T-test were appropriate.

Table 2
Description of outcome variables of participants exposed and not exposed to intrapartum synthetic oxytocin.

Responders on CBCL n=1528	No intrapartum SOT n= 921	Intrapartum SOT n=607
Child behavioral and emotional problems (CBCL) (PROMISES 18 months and PAD 45 to 60 months postpartum)		
Child internalizing problems, mean	5.14	5.67
Child externalizing problems, mean	8.94	9.84
(EPDS and STAI 6 months postpartum, MIBS 6-45 months postpartum)		
Postnatal depressive symptoms (EPDS), mean	4.44	5.11
Postnatal anxiety symptoms (STAI), mean	32.43	33.60
Mother-to-infant-bonding (MIBS), mean	2.01	1.96

EPDS = Edinburgh Postnatal Depression Scale, STAI = State Trait Anxiety Inventory, MIBS = Mother-to-Infant Bonding Scale, CBCL = Child Behavior Checklist, SOT= synthetic oxytocin. Reported p-values are based on Student T-tests.

Table 3a
Univariable and multivariable association between intrapartum synthetic oxytocin and child internalizing and child externalizing problems.

	Child Internalizing problems $CI_{95\%}$ for *b*						Child externalizing problems $CI_{95\%}$ for *b*					
Variables	b	Lower	Upper	*β*	*p-value*	R^2	b	Lower	Upper	*β*	*p-value*	R^2
Univariable analyses												
Intrapartum SOT	0.53	-0.02	1.08	0.11	0.06	0.003	0.91	0.11	1.70	0.13	0.03	0.004
Multivariable analyses												
Intrapartum SOT*	0.08	-0.57	0.73	0.02	0.81	0.030	0.64	-0.32	1.60	0.09	0.18	0.012

Note. In the intrapartum oxytocin analysis no intrapartum SOT (synthetic oxytocin) is the reference group. b is unstandardized. *β* is standardized in Y.
*adjusted for maternal characteristics (parity) and birth characteristics (mode of birth, duration of first and second stage of labour).

Statistical analyses

Characteristics of responders and non-responders on the CBCL were descriptively compared. The fraction of missing data varied between 0% and 38%. To avoid potential bias and decreased statistical power, we imputed all missing data except for the child outcomes using multiple imputation by chained equations, under the assumption that the missing data mechanism was missing at random (MAR) or missing completely at random (White et al., 2011). We studied the missing data mechanism by predicting missingness (yes/no) of data for each of these variables from the other variables using logistic regression analyses (Schafer, 1999). The final imputation model included all variables used in the analyses and all variables that predicted missingness of a certain variable, or its value. Twenty datasets were im-

Table 3b
Univariable and multivariable association between intrapartum synthetic oxytocin and postnatal depressive symptoms, anxiety and mother-to-infant bonding.

	Postnatal depressive symptoms					Postnatal anxiety symptoms					Mother-to-infant bonding				
	$CI_{95\%}$ for *b*					$CI_{95\%}$ for *b*					$CI_{95\%}$ for *b*				
	b	Lower	Upper	*β*	*p-value*	R^2	b	Lower	Upper	*β*	*p-value*	R^2	b	Lower	Upper	*β*	*p-value*	R^2
Univariable analyses																		
Intrapartum SOT	0.67	0.19	1.15	0.16	0.01	0.006	1.17	-0.55	2.39	0.11	0.06	0.003	-0.05	-0.26	0.17	-0.03	0.67	0.000
Multivariable analyses																		
Intrapartum SOT*	0.70	0.13	1.28	0.17	0.02	0.011	1.10	-0.36	2.57	0.10	0.14	0.012	0.01	-0.23	0.25	0.01	0.94	0.007

Note. In the intrapartum oxytocin analysis no intrapartum SOT (synthetic oxytocin) is the reference group. *β* is standardized in Y.
*adjusted for maternal characteristics (parity) and birth characteristics (mode of birth, duration of first and second stage of labour).

puted by chained equations and pooled according to Rubin's rules (Rubin, 1987).

Characteristics and outcomes were compared between participants exposed and not exposed to intrapartum synthetic oxytocin using Chi-square test and Student T-tests where appropriate. A Pearson's correlation matrix was created for the main variables.

The primary analysis addressed the associations of intrapartum synthetic oxytocin administration with child internalizing and externalizing problems using univariable and multivariable linear regression models. In the multivariable analyses, adjustment was made for variables that could act as potential confounders in each specific association.

Additional analyses were performed to study the association between intrapartum synthetic oxytocin administration and postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding. Finally, we assessed the association between postnatal depressive symptoms, postnatal anxiety, mother-to-infant bonding and child behavioral and emotional problems. Standardized beta coefficients are reported to indicate effect size. To identify the unique variance contributed by each main predictor, we entered confounders first into the linear regression models followed by the respective predictor variable and assessed increase in explained variance. In case an overall association was observed between intrapartum synthetic oxytocin and child outcomes, a mediation analysis according to Preacher and Hayes was carried out and the proportion indirect effect estimated. Finally, we repeated our analyses excluding PROMISES data as a sensitivity analysis to include only measurements behavioral and emotional problems in children ages 45-60 months. The level of significance was set at p=0.05, two sided. Statistical analyses were performed with SPSS Statistics 25.0 (SPSS inc. Chicago, Illinois).

Findings

Out of a total of 4,466 participants, 1,528 (34%) completed the questionnaires on the CBCL. Reasons for non-response were mainly uncommunicated changes in home or email address. Out of the 1,528 women 176 participants of the PROMISES trial were included.

Non-responders on CBCL did not differ from responders on CBCL on educational attainment level, cultural background, parity, prenatal depressive symptoms, mode of birth, gestational age at birth, breastfeeding six months postpartum, intrapartum synthetic oxytocin administration, postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding.

Comparison of characteristics between participants with and without intrapartum synthetic oxytocin is presented in table 1. Participants exposed to intrapartum synthetic oxytocin were more likely to be nulliparous women, to have a cesarean section or to have a longer duration of the first and second stage of labour.

Description of outcome variables of participants with and without intrapartum synthetic oxytocin is presented in table 2. Participants exposed to intrapartum synthetic oxytocin had higher levels of postpartum depressive symptoms (mean 5.11 versus 4.44) and their children had higher externalizing problems scores (mean 9.84 versus 8.94).

Postnatal depressive symptoms, postnatal anxiety, mother-to-infant bonding and child behavioral and emotional problems correlated positively with each other. The strongest correlation was 0.83 between maternal postnatal depressive symptoms and maternal postnatal anxiety symptoms (Supplementary material table S1).

Intrapartum synthetic oxytocin was significantly associated with more child externalizing problems in the univariable analysis (p= 0.03). The association with child internalizing problems was marginally statistically significant (p=0.06). When adjusted for confounders, these associations were no longer statistically significant. After controlling for confounders, women who received intrapartum synthetic oxytocin had significantly higher levels of maternal depressive symptoms (β = 0.17, 95% CI of 0.03 to 0.30) than women not receiving synthetic oxytocin (Table 3a). Administration of intrapartum synthetic oxytocin explained a small amount of unique variance (i.e., 0.6%). No significant associa-

Table 4
Univariable and multivariable association between postnatal depressive symptoms, anxiety, mother-to-infant bonding and child internalizing and child externalizing problems.

	Child internalizing problems $CI_{95\%}$ for *b*						Child externalizing problems $CI_{95\%}$ for *b*					
Maternal mental health variables	b	Lower	Upper	*β*	*p-value*	R^2	b	Lower	Upper	*β*	*p-value*	R^2
Univariable analyses												
Postnatal depressive symptoms	0.22	0.15	0.28	0.04	<0.001	0.035	0.34	0.25	0.43	0.06	<0.001	0.042
Postnatal anxiety symptoms	0.10	0.07	0.12	0.02	<0.001	0.046	0.16	0.13	0.20	0.02	<0.001	0.061
Mother-to-infant bonding	0.44	0.27	0.61	0.09	<0.001	0.025	0.83	0.60	1.05	0.09	<0.001	0.043
Multivariable analyses												
Postnatal depressive symptoms*	0.19	0.11	0.28	0.04	<0.001	0.054	0.23	0.11	0.36	0.03	<0.001	0.075
Postnatal anxiety symptoms**	0.11	0.07	0.14	0.02	<0.001	0.065	0.12	0.08	0.17	0.01	<0.001	0.094
Mother-to-infant bonding ***	0.40	0.23	0.57	0.08	<0.001	0.058	0.72	0.49	0.94	0.10	<0.001	0.071

Note. *β* is standardized in Y.
*Adjusted for maternal characteristics (maternal age, educational level, cultural background and prenatal depressive symptoms).
**Adjusted for maternal characteristics (maternal age, educational level, cultural background and prenatal anxiety).
***Adjusted for maternal characteristics (parity and prenatal depressive symptoms), Mother-to-infant bonding; higher values indicate poorer bonding.

tion was found between intrapartum synthetic oxytocin and postnatal anxiety and mother-to-infant bonding (Table 3b).

Table 4 shows that postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding were univariably, and multivariably associated with both child internalizing and externalizing problems. Amounts of unique explained variances added by these factors were small. Maternal postnatal depressive symptoms added respectively 3.5 percent and 3.7 percent unique variance to the final models of child internalizing problems and externalizing problems. Maternal postnatal anxiety symptoms explained respectively 3.5 percent and 2.4 percent of unique variance in the final models of child internalizing problems and externalizing problems. Mother-to-infant bonding added respectively 2.0 percent and 3.2 percent unique variance to the final models of child internalizing problems and externalizing problems.

The sensitivity analysis showed similar results. The only difference, when excluding PROMISES data, is that the adjusted association between intrapartum synthetic oxytocin and postnatal maternal depressive symptoms is approaching statistical significance (b=0.52, 95% CI; -0.03-1.07, *β*=0.12, p-value= 0.06). Because there was no association between intrapartum synthetic oxytocin and behavioral and emotional problems in children no mediation analysis was carried out.

Discussion

This large prospective study did not show that intrapartum synthetic oxytocin was associated with internalizing or externalizing problems of children aged up to 60 months, maternal postnatal anxiety or with mother-to-infant bonding. However, intrapartum synthetic oxytocin was associated with more maternal postnatal depressive symptoms. The effect size was nevertheless small as well as the explained unique variance. Postnatal depressive symptoms, postnatal anxiety and suboptimal mother-to-infant bonding were positively but modestly associated with both child internalizing and externalizing problems.

This study is one of the few prospective studies addressing the association between intrapartum synthetic oxytocin exposure and child internalizing and externalizing problems. While intrapartum synthetic oxytocin was univariably associated with both child internalizing and externalizing problems, these associations almost disappeared after adjustment for confounders. The result of no overall association is in line with the overall findings of the longitudinal study by Guastella (Guastella et al., 2018) and with the findings of a recent register-based cohort study including 677,629 singletons showed results in the same direction, that intrapartum synthetic oxytocin measured dichotomously (induction or augmentation versus no intrapartum oxytocin) was not associated with childhood emotional disorders (HR = 1.05, 95% CI 0.99, 1.11) after adjustment for maternal history of psychopathology, antidepressants during pregnancy, cohabitation status, highest educational attainment, smoking status during pregnancy, and indications for labor stimulation (Lønfeldt et al., 2020). It is likely that a large number of factors coalesce to increase an individual's risk for behavioral and emotional problems in children.

Secondly, we addressed the role of postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding, in the association between synthetic oxytocin and child behavioral and emotional problems. Our results show that administration of synthetic oxytocin is significantly but weakly associated with higher levels of maternal postnatal depressive symptoms. The effect size was small and explaining only a small amount of unique variance (i.e., 0.6%). Similarly, a previous large-scale retrospective study reported that peripartum synthetic oxytocin administration was associated with a 32% significantly increased risk of postpartum depression or anxiety disorder (Kroll-Desrosiers et al., 2017). Nevertheless, based on our findings, the clinical relevance of intrapartum synthetic oxytocin administration seems negligible in the general population as compared to other risk factors for postnatal depression. However, in a population with a high risk of a minor or major postpartum depression, the clinical impact of synthetic oxytocin may be worth investigating. Moreover, in our study there was no evidence that intrapartum synthetic oxytocin was associated with postnatal anxiety although significance was approached in the univariable analysis. This is in contrast with previous studies (Gu et al., 2016; Kroll-Desrosiers et al., 2017). Our results could be partly explained by the fact that the current study is the first adjusting for confounders by indication. We assumed duration of labour was a confounder by indication because longer duration of labour is associated with a higher likelihood to receive intrapartum synthetic oxytocin and duration of labour has been associated with poorer child outcomes. In our study, adjustment for duration of labour hardly affected the magnitude of the association of oxytocin administration with child internalizing and externalizing problems.

To the best of our knowledge, our study was the first study examining the association between intrapartum synthetic oxytocin and mother-to-infant bonding. The absence of evidence of this association we observed may be explained by the difference in biologic behavior between natural oxytocin and synthetic oxytocin. Synthetic oxytocin, in contrast to natural oxytocin, does not pass the maternal blood brain barrier and thereby is less likely to directly influence mother to infant bonding (Uvnäs-Moberg et al., 2019). Maternal postnatal depressive symptoms, maternal postnatal anxiety symptoms and mother-to-infant bonding explained unique but small amounts of variance in the final models of child internalizing and externalizing problems. The result regarding depressive symptoms is in line with that from previous longitudinal studies providing evidence for associations between postnatal depression, de-

pressive symptoms of the mother and emotional problems throughout childhood, including internalizing disorders, as summarized in review papers (Goodman et al., 2011; Stein et al., 2014). Fewer studies have been published examining associations between postnatal anxiety and child emotional problems than for perinatal depression. Their results are in line with our findings (Glasheen et al., 2010; van Batenburg et al., 2013). The results of our study, regarding the so far rarely studied association between postpartum mother-to-infant bonding and child behavioral and emotional problems, are similar to those from two previous studies (Arguz Cildir et al., 2019; Mason et al., 2011). The finding that mother-to-infant bonding contributes to child behavioral and emotional problems up to 60 months of age is also in line with the recent review on the role of antenatal and postnatal maternal bonding in infant development up to 24 months of age (Le Bas et al., 2020). This review focused on physical, psychological and social infant development. The authors included nineteen articles. All mean effects were in the same direction with higher bonding contributing to higher attachment quality, lower colic rating, easier temperament and positive infant mood (Le Bas et al., 2020).

Strengths and limitations

Our study contributes to the knowledge on some relatively understudied topics, concerning long term consequences of synthetic oxytocin and the association between mother-to-infant bonding and behavioral and emotional problems in children. It is a strength of this study to have investigated postnatal anxiety as well. Postnatal anxiety is relatively understudied as compared to postnatal depression in relation to child outcomes. By using a broad range of variables and a large sample from the general population, the generalizability of the results is increased. Finally, the longitudinal design of the study contributes to the plausibility of the associations being temporal (Schunemann et al., 2011). No randomized studies have evaluated long term consequences for child development of intrapartum synthetic oxytocin administration. Observational studies form an alternative to investigate causal relationships when proper adjustment is made for confounding by indication (Black, 1996). Therefore, a proper selection of confounders was made in our analysis of each association. Also, confounding by indication was examined and corrected for. By applying strict criteria for confounders, we tried to avoid controlling for too many potential confounders, because this can lead to aggravate problems of data sparsity or multicollinearity (Greenland et al., 2016).

Our study also has limitations. First, the response rate was 34% for the main outcome which is considered low. We assumed that imputation of the outcome with only 34% of values available would not lead to credible results. However, this should be put into perspective as many longitudinal cohort studies with a long follow up period are dealing with the problem of considerable loss to follow-up (Arguz Cildir et al., 2019, Eyre et al., 2019). Nevertheless, in our study we expect that the potential for selection bias of the association has been limited because non-responders on the outcome CBCL did not significantly differ from responders on the CBCL with respect to the determinant intrapartum synthetic oxytocin administration, and with respect to the other outcomes, i.e. levels of postnatal depressive symptoms, postnatal anxiety and mother-to-infant bonding. Second, the dose of intrapartum synthetic oxytocin was not recorded in medical records and a dose-response relationship could not be investigated. Guastella et al. showed in a subsample of 542 children a weak positive dose-response relationship between children exposed to a higher intrapartum synthetic oxytocin dosage and child behavioral and emotional problems (Guastella et al., 2018). However, when measured in three categories (augmentation, induction or none exposure) the same study showed no overall association. With the categorization of data information has been lost. In our study even more data has been lost because we dichotomized our data. In line with the recommendations by Lefevre and Sirigu, future investigations should also focus more on the dose-response relationship and severity of social disorders and developmental comorbidity. It would be informative to also study the role of maternal behaviour components in the future (Lefevre and Sirigu, 2016). We measured postnatal depressive symptoms and postnatal anxiety, but information on observed maternal behaviour was not available. Addressing the role of the latter in future research might be of value (Torres et al., 2020).

Third, we could not distinguish between induction and augmentation of labour. Induction of labour is a different intervention compared to augmentation. Especially, since induction is an intervention introducing birth therfore these children are theoretically as a result born relatively prematurely. Studies show that cerebral ripening continues at term (Engle and Kominiarek, 2008). As it is known that premature babies have a higher chance of developmental disorders (Engle and Kominiarek, 2008), induced labour could therefore theoretically lead to poorer developmental outcomes. For this reason we excluded women with a preterm birth (before 37 weeks of gestation). When inducing labor, the period of oxytocin infusion is expected to be longer than with augmentation of labor. However, with the adjustment for duration of labour we tried to tackle this issue.

Finally, the wide variability in the timing of measures is an important limitation. For this reason, we performed a sensitivity analysis with a breakdown of sample sizes based on whether mother- to-infant bonding was measured at 18 months or at older ages of 45-60 months. We repeated our analyses excluding PROMISES data in which mother- to-infant bonding was measured at 18 months as a sensitivity analysis. Despite the wide variability in the timing of some measures, the measurement of the analyzed variables were in chronological order. Our second aim was to assess if maternal depressive or anxious symptoms or mother-to-infant bonding could play a mediating role in an association between intrapartum synthetic oxytocin and child behavioral and emotional problems. For this reason, it is important that the timeline of the variables is chronological within a longitudinal study.

Implications

Nowadays, health care providers focus more on the short-term consequences in the assessment of the safety of synthetic oxytocin (Simpson, 2011). However, there is an additional need for information on longer term outcomes. At present, maternal health care providers may refer to studies including ours showing that there is no evidence that synthetic oxytocin affects behavioral and emotional problems in children. However, we agree with other authors that there is still insufficient evidence of high quality to modify obstetric guidelines for the use of oxytocin, which state that synthetic oxytocin should only be used when clinically indicated (Lønfeldt et al., 2019). We recommend in future investigations to focus more on the dose-response relationships, the calculation of the exact total dosage oxytocin and the distinction between induction and augmentation of labour.

It is well known that postnatal maternal depressive symptoms and anxiety are associated with child behavioral and emotional problems which was confirmed by the present study. We added knowledge that poor mother-to-infant bonding was linked to poorer outcomes in the child. Therefore, healthcare providers for mothers may now pay attention to mother-to-infant bonding as well during their work. In summary, a high level of maternal postnatal depressive symptoms, anxious symptoms or suboptimal mother-to-infant bonding, could be an indication for more close monitoring for child behavioral and emotional problems.

Future research should aim for high quality studies to show whether intrapartum synthetic oxytocin does or does not harm maternal and child long-term mental health, especially in a population with a high risk of a minor or major postpartum depression. For example, research should focus on longer follow-up, test-administered neurodevelopmental outcomes and the role of parenting or mother's behavior. We recommend in future studies to properly select confounders including confounders by indication.

Conclusion

There was no evidence that intrapartum synthetic oxytocin was associated with child internalizing and externalizing problems of children aged up to 60 months. However, intrapartum synthetic oxytocin was positively but weakly associated with postnatal depressive symptoms. The clinical relevance of this finding seems negligible in the general population, but unknown in a population with an increased risk of depression and needs further study. Moreover, this is one of the few studies demonstrating that poor mother-to-infant bonding is also associated with more child behavioral and emotional problems.

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Credit author statement

ET, WDBW, JH, LLP, FGS, MYB, and HB made all significant contributions to the conception and design of the study and interpretation of data. ET and HB were involved in the acquisition, analysis and data analysis. ET and WDBW wrote the first draft of the article. All authors commented on the paper and gave their final approval for the version to be published.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.midw.2021.103045.

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