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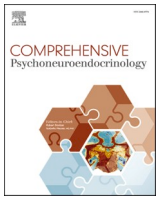

Exogenous oxytocin administered to induce or augment labour is positively associated with quality of observed mother-infant bonding

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ABSTRACT

Oxytocin is a key hormone in the transition to motherhood. The maternal endogenous oxytocin system facilitates many physiological and biological adaptations, including breastfeeding, maternal wellbeing, and brain plasticity. Additionally, maternal endogenous oxytocin works as a finetuned orchestrator prior to, during, and after the birth of a child to support birth progression and mother-infant bonding. Exogenous oxytocin may be administered to induce or augment labour when this is not progressing naturally and is a common obstetric intervention worldwide. However, the lasting impact of these widely varying levels of systemic exogenous oxytocin on mother-infant bonding is currently unknown. This study aimed to investigate the association between exogenous oxytocin administered to induce or augment labour and quality of observed mother-infant bonding.

Thirty-eight mother and infant dyads participated (mothers aged 24–48 years; infants aged 2–5 months). Mother-infant bonding quality was assessed via the Recorded Interaction Task and hospital birth records were consulted to obtain exogenous oxytocin administration data. Demographic information and possible confounding factors were collected from dyads, and salivary oxytocin concentration was measured for both mother and infant.

Mother's perception of infant sleep difficulty was identified as a confounding factor for quality of mother-infant bonding. After controlling for the confounding factor, receiving exogenous oxytocin to induce or augment labour, as opposed to not, was found to be significantly positively associated with higher quality of observed mother-infant bonding ($p = 0.029$). These novel findings highlight the need for further exploration, both of the impact of the treatment and of the mechanisms of action of intrapartum exogenous oxytocin on the endogenous oxytocin system. It is argued that particular focus be given to investigate action on the central oxytocin receptors, and if this may play a role in subsequent mother-infant bonding outcomes. It is vital to understand the full breadth and the clinical implications of this commonplace procedure.

1. Introduction

Oxytocin, produced in the hypothalamus, is a nonapeptide that acts both as a neurotransmitter and a hormone. The actions of oxytocin in each capacity are mediated by the oxytocin receptor (OTR), which is distributed widely throughout the brain and peripheral tissues (for review see Sharma et al., 2020). As such, oxytocin is implicated in many behavioural and physiological processes. Of note, oxytocin has a well-established role in social behaviours including trust and affiliation, trauma responses, addiction and response to subsequent treatment, mood disorders including depression and anxiety, psychiatric disorders such as schizophrenia and borderline personality disorder, and autism spectrum disorders [1–5]. Oxytocin is also involved in erectile function and sexual behaviour, immunologic and anti-inflammatory processes including wound healing, and appetite and eating disorders [6,7]. Finally, of frequent focus in the literature is oxytocin's role in various maternal physiological processes and behaviours, including childbirth and induction of labour, milk ejection and breastfeeding, maternal

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wellbeing, maternal brain plasticity and adaptation, and mother-infant bonding [7].

Oxytocin is a key hormone during childbirth. Its importance in contributing to labour initiation, labour progression, and birth is further highlighted by the frequent use of exogenous oxytocin to artificially induce labour [8]. The administration of exogenous oxytocin (for example Pitocin or Syntocinon) to assist in induction of labour developed as a practice across the 20th century (for review see Ref. [9]). It remains a common intervention. For example, in Australia, approximately 74 % of mothers who have an induced labour receive exogenous oxytocin [10]. Oxytocin administration for augmentation of labour, even after spontaneous onset, and for prevention and management of postpartum haemorrhage (PPH) during the third stage of labour are also common [11]. Whilst recommendation and dosage for exogenous oxytocin use in PPH management is relatively well established, recommendations and guidelines for use in labour induction and augmentation vary worldwide [12]. Given the wide and frequent use of exogenous oxytocin during the intrapartum period, there has been an increased call for further investigation into the practice, including the effect on long-term outcomes, specifically those in which the endogenous oxytocin system is implicated [8,9,13–15].

Mother-infant bonding is primed and facilitated by the endogenous oxytocin system. The term itself refers to the reciprocal early emotional bond between a mother and their infant [13,16]. For mothers, development of a strong bond is linked to more positive parenting behaviours and can further increase maternal sensitivity, whereas weaker bonds may lead to lack of maternal feelings, including avoidance and hostility, and possible long-term detriment to the mother-child relationship [17]. Outcomes for the infant, and later child, are also impacted by the mother-infant bond quality, including effect on behavioural and emotional development [18].

Mother-infant bonding outcomes following intrapartum administration of exogenous oxytocin have received limited attention [13,19]. Exogenous oxytocin administered directly to neonatal prairie voles within 24 h of birth inhibited pair bonding in a dose-dependent manner [20]. Although intrapartum exogenous oxytocin is generally understood to not cross the placenta, the results nevertheless support the pressing necessity to explore the relationship of intrapartum exogenous oxytocin and bonding in humans [20,21].

Existing literature based on human populations has focused on mother-infant bonding as a facilitator of other outcomes following intrapartum exogenous oxytocin. Tichelman et al. [18] examined the association between intrapartum exogenous oxytocin and various behavioural and emotional problems in the later child, with a focus on how mother-infant bonding may mediate such a relationship. No association between intrapartum exogenous oxytocin and 'mother-to-infant bonding', as measured by the Mother-to-Infant Bonding Scale (MIBS), was reported [18]. Of note is the use of the word 'to' present in the bonding terminology used. This specific language reflects the measurement tool employed; the MIBS is a self-report questionnaire consisting of 8-items and as such reflects the reporting of the mother's perceived bonding to their infant, rather than a reciprocal process. The MIBS was also employed in a recent study by Kunimi et al. [22] to explore the association between intrapartum exogenous oxytocin and adverse mother-infant bonding outcomes, such as mother's displays of rejection or lack of affection towards their infant. Only specific sub-scales of the MIBS, "lack of affection" and "anger/rejection", were examined.

The accurate assessment of overall mother-infant bonding quality will be vital in determining any association with intrapartum exogenous oxytocin administration. Claims have been made in support of observational methods being the 'gold standard' in the assessment of mother-infant bonding [23]. The Recorded Interaction Task (RIT)employs observational methods to assess both maternal and infant bonding behaviours and determine an overall bonding quality score [24]. The aim of the current study was to investigate the association between administration of exogenous oxytocin to induce or augment labour, and quality of mother-infant bonding, as assessed using the RIT.

2. Methods

2.1. Ethics

Ethical approval was granted by the Women's and Children's Health Network Human Research Ethics Committee (HREC/17/WCHN/106) and the University of South Australia's Human Research Ethics Committee (200594) prior to study commencement. Written informed consent was obtained from all mothers, on behalf of themselves and their infant, prior to participation and data collection.

2.2. Participants

Mother-infant dyads were recruited in South Australia across 2020 and 2021 via social-media advertising, state-run health service mother's groups, and an early parenting expo event. Limited presence of COVID-19 in the local and wider communities allowed for implementation of such recruitment methods. Inclusion criteria were primiparous mothers aged over 18, infants aged between two and five months (inclusive), and the ability to understand and communicate in English (all communication, tools, and data collection were administrated in English). Mothers with previous births and with multiple gestation were excluded due to the possible influence of these variables on the endogenous oxytocin system and mother-infant bonding [25].

2.3. Procedure

Mother-infant dyads attended one appointment for data collection at a clinical trial facility. Saliva samples, for analysis of current salivary oxytocin concentrations, were collected from mothers via passive drool. Where possible, saliva samples were also obtained from infants by collecting passive drool from the chin and mouth. Following saliva collection, mothers provided demographic information and completed the following standardised tests: the Edinburgh Postnatal Depression Scale (EPDS), which ranges from 0 to 30 with higher scores indicating higher presence of depressive symptoms; the Depression Anxiety Stress Scale-21 (DASS-21), which has three subscales (depression, anxiety and stress) each ranging from 0 to 21 points with higher values representing higher symptoms, and a total score which is the sum of the three subscales; and the Interpersonal Support Evaluation List 12 item scale (ISEL), which ranges from 0 to 48, with a higher score representing greater perception of social support. The EPDS, DASS-21, and ISEL yielded data relating to mother's recent mood and emotional state, and perception of their current social support, factors that are implicated with the endogenous oxytocin system. The strong psychometric properties of each scale – the EPDS, DASS-21, and ISEL – for the assessment of such data are well documented [26–28] Finally, together, mother-infant dyads completed the Recorded Interaction Task.

2.3.1. Demographic information

Demographic data included mother's date of birth, marital status, level of education, and employment status, and infant's date of birth and sex. Information pertaining to factors which may affect endogenous oxytocin concentration was collected, as well as factors reported to be associated with mother-infant bonding quality [13]. This included mother and infant's ethnicity, current diagnosed medical conditions (including mental health conditions), current medications (prescribed and non-prescribed), current alcohol use, breastfeeding status, difficulties associated with breastfeeding or bottle feeding, infant bed-sharing status, and mother's perception of their infant's current level of sleeping difficulty (via simple Likert scale).

2.3.2. Recorded Interaction Task

The novel RIT employs observational methods to assess mother-infant bonding [24]. Mother-infant dyads completed the RIT by performing a nappy change interaction which was video recorded. Mothers were advised to hold their infant in front of their chest, and after the video recording started, place their infant on the changing mat and change their infant's nappy as they would normally do so. Recording was undertaken sensitively, and the recording device situated in a way that captured both mother and infant's faces during the interaction. Recording stopped following completion of the nappy change, and mothers were given the option to view their video recording before proceeding. Video recordings were later viewed and scored by a trained assessor using the RIT observation scoring sheet. Items on the RIT observation scoring sheet consider both maternal and infant behaviours including sensitivity, handling, and vocal and visual behaviours. Items were scored depending on how frequently they were observed throughout the video recording, on a Likert scale of 1 (never) to 5 (always). Maternal and infant behaviour ratings were combined, with the final scores obtained reflecting observed mother-infant bonding on a possible range of 17 (poorer bonding) to 85 (strong bonding). The RIT demonstrates sufficient content and face validity in the assessment of mother-infant bonding (n = 15) [24], strong intra-rater reliability (ICC>0.86) and fair inter-rater reliability (ICC = 0.55–0.89) (n = 15) [29].

2.3.3. Salivary oxytocin analysis

Mother and infant saliva samples were analysed to determine current peripheral oxytocin concentrations. Saliva samples were collected prior to feeding, to mitigate the oxytocin flux which occurs during this interaction, and between 1 and 4pm to minimise the effect of diurnal oxytocin fluctuation. Saliva samples were immediately ice-chilled and centrifuged at 4 °C at 1600g for 15 min. Samples were stored at −80 °C until assayed in one batch.

Saliva samples were assayed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Arbor Assays, Ann Arbor, MI). Using kit supplied materials and following manufacturer instructions, oxytocin was extracted from samples, reconstituted in assay buffer, and analysed in duplicate. Optical density of samples was measured at 450 nm (Multiskan™ FC Microplate Photometer, Thermo Scientific™).

2.4. Pregnancy and birth records

All mothers consented to their pregnancy and birth records being accessed following their data collection appointment. Information obtained from records included, past pregnancy, pregnancy complications, antenatal EPDS scores, intrapartum progress complications, mode of delivery, duration of labour, pain management, gestational age, 1-min and 5-min Apgar scores, birth weight, birth length, head circumference, and nursery or intensive care unit admission.

Information regarding intrapartum exogenous oxytocin administration was also recorded. Data points included whether exogenous oxytocin was administered to either induce or augment labour and whether exogenous oxytocin was administered for third stage labour and PPH management. For mothers who received exogenous oxytocin to induce or augment labour, the following related data were also collected: oxytocin concentration (IU/L); dosing regimen including rate of administration (ml/hr), duration of administration (hours), and total volume of solution administered (ml); and total dose of oxytocin administered (IU).

2.5. Statistical analysis

A sample size of 27 achieves 81 % power to detect a partial ρ^2 of at least 0.02 attributed to 1 independent variable when the significance level (alpha) is 0.05 and the actual value of ρ^2 is 0.40. The influence of an additional five independent variables was removed.

A baseline simple linear regression model was run, including exogenous oxytocin administration as the single predictor variable and mother-infant bonding quality (RIT total score) as the outcome measure. Following this, a series of multivariable regressions were run, adding each of the potential confounding variables into the baseline model in turn to assess its impact on the regression coefficient for exogenous oxytocin. Potential confounding variables were data related to participant demographics (outlined in section 2.3), pregnancy and birth data (outlined in section 2.4), and salivary oxytocin concentrations. A total of 43 potential confounding variables were tested. Variables that modified the regression coefficient for exogenous oxytocin by 20 % or more, were considered a confounding variable. At the end of this exercise, a final multivariable model was undertaken, including exogenous oxytocin administration as the main exposure variable and all confounding variables. Participants whose mode of delivery was by elective caesarean section were excluded from the regression analyses described above, as such individuals never had the chance to undergo labour, whether with or without exogenous oxytocin. The Shapiro-Wilk test was performed and showed that RIT total score had no significant departure from normality (p = 0.252). Chi-square tests were performed to determine if the group of participants who received synthetic oxytocin to induce or augment labour was comparable to the group of participants who did not receive synthetic oxytocin for this purpose. The two groups showed no significant differences in their demographics or other variables (p > 0.157), so were assumed comparable.

Bivariate Pearson's correlations were conducted to explore the relationship between exogenous oxytocin doses and mother-infant bonding quality (RIT total score). The RIT total score was first compared the dose of exogenous oxytocin administered to induce or augment labour, and secondly compared to the total dose of exogenous oxytocin administered in the intrapartum period (to induce or augment labour and for PPH management or treatment combined).

A series of bivariate Pearson's correlations were conducted to determine the relationship between mother and infant salivary oxytocin concentrations and the following variables: mother-infant bonding quality (RIT total score), dose of exogenous oxytocin administered to induce or augment labour, and total dose exogenous oxytocin administered during the intrapartum (including to induce or augment labour and for PPH management or treatment). The distribution of mother's rating of infant sleep difficulty across bed sharing responses was determined by an independent-samples Mann-Whitney *U* test.

All analyses were undertaken by IBM SPSS Statistics software (IBM Corp, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY).

3. Results

3.1. Participants

Thirty-eight mother-infant dyads were recruited and participated in the current study. All mothers were primipara. The mean (SD) age of mothers was 34 (4.8) years. The mean (SD) age of infants was 3.7 (1.2) months. An equal number of male (n = 19) and female (n = 19) infants participated.

Table 1 presents demographic information relating to mother participants. The majority of mothers were White (n = 34), married or in a de facto relationship (n = 37), educated at a tertiary level (n = 36), and employed (n = 35). Although most of the mothers abstained from alcohol (n = 27), those who did drink had reasonably low consumption (maximum 3 drinks per week, n = 1). No mothers who participated reported intake of any other recreational drugs (licit or illicit).

Mother's responses to the ISEL-12, EPDS, and DASS-21 (including DASS-21 sub-scales) are summarised in Table 2. Overall, as indicated by the ISEL-12, mother's perceived social support was high. The majority of responses to the EPDS indicated little to no depressive symptoms (n = 27) [30]. The majority of mother's scores on the DASS-21 depression sub-scale also indicated no depressive symptoms (n = 34) [31].

Table 1
Demographic information, mothers (n = 38).

Demographic	n	(%)
Age (years)		
20-24	1	2.6
25-29	5	13.2
30-34	18	47.4
35-39	11	28.9
40-45	1	2.6
45-50	2	5.3
Ethnicity		
White	34	89.5
Asian	2	5.3
African	1	2.6
Hispanic	1	2.6
Marital status		
Married or engaged	24	63.2
De facto	13	34.2
Single	1	2.6
Highest level education		
Tertiary	36	94.7
Secondary	2	5.3
Employment status		
Employed, working	2	5.3
Employed, maternity leave	33	86.8
Volunteer	1	2.6
Unemployed	2	5.3
Diagnosed medical conditions		
None	22	57.9
Mental health disorder	6	15.8
Physiological disorder	8	21.1
Mental health and physiological disorder	2	5.3
Prescribed medication use		
None	23	60.5
Progestogen-only contraception pill	5	13.2
Antidepressant	5	13.2
Other[a]	5	13.2
Unprescribed medication/supplementation		
	19	50
Vitamin/mineral supplementation	15	39.5
Other[b]	4	10.5
Alcohol use per week		
No alcohol consumption	27	71.1
Up to one standard drink	5	13.2
Two standard drinks	5	13.2
Three standard drinks	1	2.6

[a] Includes anti-inflammatory, antiemetic, proton pump inhibitor, bronchodilator, and betablocker medications.
[b] Includes laxative, antihistamine, paracetamol, and ibuprofen medications.

Table 2
Mother's scores (mean, SD) obtained on the ISEL, EPDS, and DASS-21 questionnaires (n = 38).

Scale (score range)	Mean	SD
ISEL (0-48)	44	4.3
EPDS (0-30)	5	3.5
DASS-21		
Total (0-63)	8	5.3
Depression scale (0-21)	1	1.5
Anxiety scale (0-21)	1	1.8
Stress scale (0-21)	5	3.0

Abbreviations: ISEL, Interpersonal Support Evaluation List 12 item scale; EPDS, Edinburgh Postnatal Depression Scale; DASS-21, Depression Anxiety Stress Scale-21.

Demographic information relating to infant participants, as reported by their mothers, are presented in Table 3. Twenty-five mother's reported experiencing difficulties associated with either breast or bottle feeding their infant, including feeding anxiety, pain and/or nipple soreness, milk under or oversupply, difficulty latching, reflux or aspiration, and mastitis. The majority of mother's (n = 30) did not perceive their infant to have overly problematic sleeping difficulties, as reflected by lower scores of 1–4 on the Likert scale. A trend was identified between perceived sleep difficulty and bed sharing status. Six mothers reported they and/or the second parent bed shared with the infant, though three noted this was an infrequent occurrence. The distribution of sleep difficulty ratings was significantly higher for those who indicated they bed shared with their infant (p = 0.017).

Table 3
Demographic information, infants (n = 38).

Demographic	n	%
Age (weeks)		
8-12	10	26.3
13-16	12	31.6
17-21	9	23.7
22-25	7	18.4
Ethnicity		
White	28	73.7
Mixed/multiple ethnic backgrounds	10	26.3
Feeding status		
Exclusively breastfeeding	27	71.1
Combination breastfeeding/formula	7	18.4
Exclusively formula fed	3	7.9
Information missing	1	2.6
Diet includes solids		
No	33	86.8
Yes	4	10.5
Information missing	1	2.6
Feeding difficulties (as reported by mother) [a]		
No	12	31.6
Yes	25	65.8
Information missing	1	2.6
Sleep difficulty (as perceived by mother) [b]		
1-2	19	50.0
3-4	11	28.9
5-6	3	7.9
7-8	4	10.5
9-10	0	0
Information missing	1	2.6
Bed share status		
No	31	81.6
Yes	6	15.8
Information missing	1	2.6

[a] Includes difficulties associated with either breast or bottle feeding, including feeding anxiety, pain and/or nipple soreness, milk under or oversupply, difficulty latching, reflux or aspiration, and mastitis.
[b] Sleep difficulty reported on a 10-point Likert scale, from 1 "not a problem" to 10 "very problematic".

RIT total scores, demonstrating mother-infant bonding quality, ranged from 46 to 72, with a mean (SD) of 60.1 (7.1), demonstrating reasonably strong bonding across the sample. The RIT does not have a diagnostic cut-off score for disrupted bonding. Nonetheless, the fact that no scores fell in the lower 42 % of the possible range supports the inference that no dyads in the current sample were showing disrupted bonding.

Salivary oxytocin concentrations were obtained for 36 mothers and 26 infants. For two mothers, oxytocin concentrations were non-detectable. Difficulty in obtaining sufficient volume of passive drool from infants contributed to the lower number of infant samples. Maternal salivary oxytocin concentrations ranged from 17.8 to 93.7 pg/ml, with a mean (SD) of 48 pg/ml (16.3). Infant salivary oxytocin concentrations ranged from 9.4 to 80.6 pg/ml, with a mean (SD) of 40 pg/ml (18.1). The wide range of oxytocin concentrations in this sample is presented in Fig. 1.

3.2. Pregnancy and birth records

Participants gave birth across nine hospitals in South Australia. Pregnancy and birth data are summarised in Table 4. Five participants were gravida two, however all (n = 38) were parity one. Twenty-seven mothers completed the EPDS during pregnancy, the majority of which demonstrated no or minimal depressive symptoms (n = 19). Almost 40

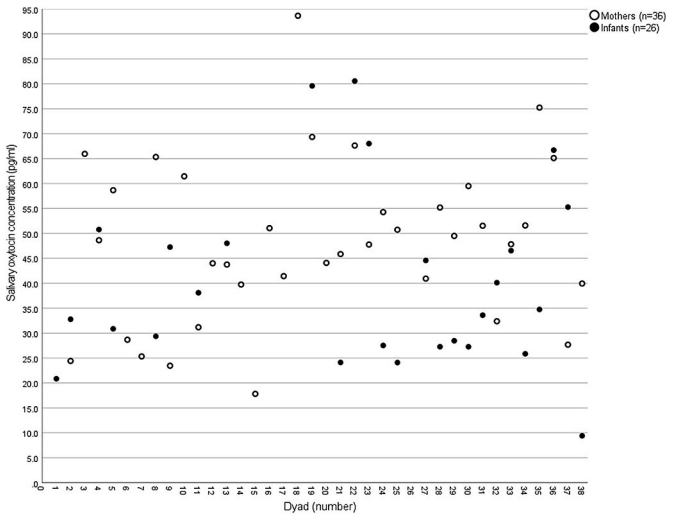

Fig. 1. Salivary oxytocin concentrations of mother-infant dyads (n = 38).

% of participants experienced complications during pregnancy. Complications included IVF, gestational diabetes, gestational hypertension, chorioamnionitis, advanced maternal age, premature labour, prolonged pregnancy, preeclampsia, and breech presentation.

Twenty-seven mothers experienced complications or disruptions of some sort to their progress during the intrapartum period (including induction or augmentation of labour via any method, transport to theatre for support in delivery or change in delivery mode, foetal distress, bladder catheterisation, incoordinate contractions, and maternal fatigue). One or more obstetric complications were recorded for 25 participants. Complications included episiotomy (n = 11), spontaneous tear (perineal, vaginal, labial, and/or cervical) (n = 15), and PPH (n = 4). Majority of births were vaginal (n = 26), and emergency lower-uterine segment caesarean section (LSCS) was more common (n = 8) than elective LSCS (n = 4). Twenty-seven participants experienced active labour, averaging 8.0 h. Pain management was used by the majority of participants (n = 35), inclusive of those who received spinal or epidural anaesthesia for LSCS. The majority of participants (n = 36) also received PPH management as a 10 IU oxytocic intramuscular injection (carbetocin n = 10, duratocin n = 1, syntocinon n = 16, syntometrine n = 9). Following birth, eight infants were admitted to the hospital nursery or neonatal intensive care unit.

Infant birth data, including birth weight, length, and head circumference, are presented in Table 5. Mean gestational age was 38:6 (weeks: days). Apgar scores were recorded at 1 min and 5 min post-birth for all infants (n = 38), and also at 10 min (n = 2).

3.3. Exogenous oxytocin

Fifteen mothers (39.5 %) received exogenous oxytocin to induce or augment labour. Exogenous oxytocin was prepared as a 10 IU/L solution in all but one instance, wherein a 20 IU/L solution was prepared. Dosing regimen and total dose administered varied widely. Initial rate of administration of the prepared solution was 12 ml/h for the majority of participants (n = 13), and the rate was often incremented every 30–60 min by 12 ml/h. The maximum rate received was 156 ml/h, which equates to a dosing rate of 26 mIU/minute. The mean (SD) length of administration was 7.3 h (4.1) and ranged from 1.5 h to 17 h. The mean (SD) total volume of exogenous oxytocin solution (10 IU/L) administered was 428.6 ml (356.4) and ranged from 30 ml to 1123 ml.

As noted, the majority of participants received a routine 10 IU dose of exogenous oxytocin for PPH management. Three participants received a further 40 IU oxytocin in response to PPH occurring. When considering all exogenous oxytocin administered across the intrapartum period, including for induction and augmentation, and PPH management or treatment, the mean (SD) dose received in the current sample (n = 38) was 14.9 IU (10.4).

Table 4
Mother's pregnancy and birth data (n = 38).

	n	%
Gravida		
1	33	86.8
2	5	13.2
Antenatal EPDS score		
N/A	11	28.9
0–6 (no/minimal depression)	19	50.0
7–13 (mild depression)	7	18.4
14–19 (moderate depression)	0	0
20–30 (severe depression)	1	2.6
Pregnancy complications [a]		
No	15	39.5
Yes	23	60.5
Intrapartum progress complications [b]		
No	11	28.9
Yes	27	71.1
Exogenous oxytocin to induce/augment labour		
No	23	60.5
Yes	15	39.5
Obstetric complications [c]		
None	13	34.2
Yes	25	65.8
Mode of delivery		
Vaginal, unassisted	23	60.5
Vaginal, assisted (forceps or ventouse)	3	7.9
LSCS, emergency	8	21.1
LSCS, elective	4	10.5
Duration of labour (hours)		
No labour	4	10.5
No progression	8	21.1
<5	8	21.1
5-10	11	28.9
10-15	3	7.9
15-20	4	10.5
Pain management [d]		
No	3	7.9
Yes	35	92.1
Oxytocin for PPH prevention		
No	2	5.3
Yes	36	94.7
Infant nursery admission		
No	30	78.9
Yes	8	21.1

Abbreviations: LSCS, Lower segment caesarean section; PPH, Postpartum haemorrhage.

[a] Includes IVF, gestational diabetes, gestational hypertension, chorioamnionitis, advanced maternal age, premature labour, prolonged pregnancy, preeclampsia, and breech presentation.

[b] Includes induction or augmentation of labour via any method, transport to theatre for support in delivery or change in delivery mode, foetal distress, bladder catheterisation, incoordinate contractions, and maternal fatigue.

[c] Includes episiotomy, spontaneous tear (perineal, vaginal, labial, and/or cervical), and PPH.

[d] Includes spinal and epidural anaesthesia, gas (N_2O/O_2), Transcutaneous electrical nerve stimulation (TENS), hydrotherapy, morphine, and fentanyl.

Table 5
Infant's birth data (n = 38).

	Mean	SD
Gestation (weeks:days)	38:6	1:4
Apgar (1 min)	8.1	1.5
Apgar (5 min)	8.8	0.7
Birth weight (g)	3374.8	498.7
Birth length (cm)	50.0	2.9
Head circumference (cm)	34.6	1.6

Abbreviations: Apgar, Appearance, pulse, grimace, activity, respiration score.

3.4. Oxytocin and mother-infant bonding

Four participants gave birth by elective caesarean section and thus never had the chance to undergo labour, whether with receipt of endogenous oxytocin or not. As such, these participant's data were excluded from the following regression analyses. The baseline simple linear regression model (Model 1, Table 6) found no statistically significant relationship between receiving exogenous oxytocin to induce or augment labour and the quality of mother-infant bonding (RIT total score) ($p = 0.067$). The subsequent series of multivariable regressions identified one confounding variable: mother's perception of infant sleep difficulty.

The relationship between receiving exogenous oxytocin to induce or augment labour and quality of mother-infant bonding was found to be statistically significant in the final multivariate regression model (Model 2, Table 6), after adjusting for the single confounding variable ($p = 0.029$). This is presented in Fig. 2. Receiving exogenous oxytocin to induce or augment labour, as opposed to not, was associated with an increased quality of mother-infant bonding of five points on the RIT.

A weak, but significant, positive correlation was identified between the dose of endogenous oxytocin administered to induce or augment labour and RIT total score ($r = 0.335$, $n = 38$, $p = 0.040$). However, no significant association was found between the total dose of exogenous oxytocin administered in the intrapartum period (to induce or augment labour and for PPH management or treatment combined) and RIT total score ($r = 0.062$, $n = 38$, $p = 0.711$) (Table 7).

No significant correlation was found between mother salivary oxytocin concentrations and infant salivary oxytocin concentrations ($r = 0.185$, $n = 25$, $p = 0.377$). Neither mother nor infant salivary oxytocin concentrations were significantly correlated with mother-infant bonding quality. Similarly, neither mother nor infant salivary oxytocin concentrations were significantly correlated with any intrapartum exogenous oxytocin dose (Table 7).

4. Discussion

The current study aimed to investigate the relationship between administration of exogenous oxytocin to induce or augment labour, and the subsequent quality of mother-infant bonding at two to five months postpartum. Mother-infant bonding was assessed by observational methods, using the RIT. Possible confounding variables for mother-infant bonding were also collected and considered during analyses.

A significant positive relationship was found between administration of exogenous oxytocin to induce or augment labour and quality of mother-infant bonding. Mothers who received exogenous oxytocin for induction or augmentation were likely to be approximately five points higher in their bonding score on the RIT ($p = 0.029$). The RIT has a possible scoring range of 17–85, meaning five points equates to a 7.4 % difference in bonding quality. It is important to note that such effect was observed only when an additional confounding factor was controlled for, mother's perception of infant sleep difficulty. Infant sleep difficulty is reported to be negatively associated with mother-infant bonding quality [32].

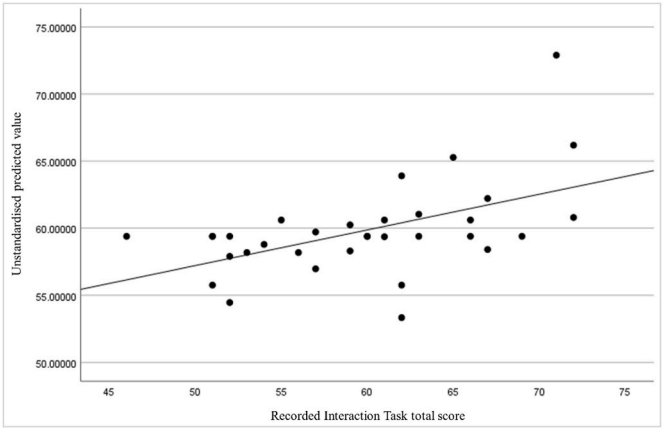

Fig. 2. Scatter plot of multivariate linear regression model for predictors (Model 2, Table 6) of the Recorded Interaction Task total score (observed mother-infant bonding).

To the best of our knowledge, this study is the first to investigate the relationship between intrapartum synthetic oxytocin and observed mother-infant bonding, and report a significant positive relationship. As introduced above, Kunimi et al. [22] addressed a comparable aim: to investigate the association between synthetic oxytocin use for labour induction and adverse mother-infant bonding. The authors found no significant difference in adverse mother-infant bonding between mothers who received synthetic oxytocin to induce labour, and mothers who had their labour induced via other methods ($n = 19700$) [22]. Differing results may be attributed to the differences in each study's exact focus and subsequent methodology implemented. For example, the current study focussed on the quality of observed mother-infant bonding, whereas the focus of Kunimi et al. [22] was narrowed to adverse mother-infant bonding, as measured by specific sub-scales of the MIBS. Additionally, Kunimi et al. [22] only considered mothers who had been induced (by synthetic oxytocin or otherwise), and those who had a spontaneous labour, or no labour, were excluded. Also not considered in analysis was synthetic oxytocin administered at any other point during the intrapartum period, namely, to prevent, manage, or treat postpartum haemorrhage. The current study, however, did consider mothers who had spontaneous labour or no labour, and included data related to all intrapartum synthetic oxytocin administration. The extremely large sample size of Kunimi and colleagues' study should not be ignored when considering the differing findings, though neither should the wider scope of considerations in the current study, and the use of observed mother-infant bonding measures rather than mother's self-reported perception of bonding.

The positive relationship between exogenous oxytocin administration and mother-infant bonding was unexpected. Like mother-infant bonding, breastfeeding is a process in which the role of endogenous oxytocin is well established, however, the relationship between intrapartum exogenous oxytocin administration and breastfeeding is frequently reported as being negative [33–37]. Despite some opposing observations of positive breastfeeding outcomes following exogenous oxytocin administration [25], the recurrent negative associations set the anticipation for a similar trend to be observed for mother-infant bonding in the current study.

In the assessment of intrapartum exogenous oxytocin administration

Table 6
Regression coefficients for simple (Model 1) and multivariate (Model 2) linear regression quality of mother-infant bonding as assessed by RIT Total score ($n = 34$).

Model	Adjusted R Square	Variable	Regression coefficient (B)	95 % CI for B		Sig. (p)
				Lower	Upper	
1[a]	0.076	Exogenous oxytocin[c]	4.367	−0.316	9.049	0.067
2[b]	0.123	Exogenous oxytocin[c]	5.277	0.573	9.982	0.029
		Sleep difficulty[d]	−0.976	−2.190	0.239	0.111

[a] Baseline simple linear regression model. Predictor variable: Exogenous oxytocin. Dependent variable: RIT Total score.
[b] Final multivariate linear regression model. Predictor variables: Exogenous oxytocin, Sleep difficulty. Dependent variable: RIT Total score.
[c] Received exogenous oxytocin to induce or augment labour.
[d] Mother's rating of infant sleep difficulty.

Table 7
Bivariate Pearson's correlations.

		Infant oxytocin	Mother-infant bonding[c]	Exogenous oxytocin induce/augment dose[d]	Exogenous oxytocin dose total[e]
Mother oxytocin [a]	Pearson correlation coefficient (r)	0.185	−0.180	−0.105	−0.246
	Sig. (p)	0.377	0.295	0.542	0.148
	n	25	36	36	36
Infant oxytocin [b]	Pearson correlation coefficient (r)		0.071	0.166	0.094
	Sig. (p)		0.729	0.417	0.649
	n		26	26	26
Mother-infant bonding [c]	Pearson correlation coefficient (r)			0.335	0.062
	Sig. (p)			0.040	0.711
	n			38	38

[a] Mother salivary oxytocin concentrations.
[b] Infant salivary oxytocin concentrations.
[c] Mother-infant bonding quality (RIT total score).
[d] Dose of exogenous oxytocin received to induce or augment labour.
[e] Dose of total exogenous oxytocin received during intrapartum period (to induce or augment labour, and for PPH management or treatment).

and impact on postpartum breastfeeding outcomes, the concentration of maternal endogenous oxytocin is also frequently considered. However, this is also an area of inconsistent results. Gu et al. [34] and Prevost et al. [25] both found that higher quantities of exogenous oxytocin administration during the intrapartum period predicted higher maternal plasma oxytocin concentrations in the postpartum period. However, as detailed above, each study then reported conflicting impacts on breastfeeding. Dissimilar again, Jonas et al. [38] reported that receiving higher doses of exogenous oxytocin during the intrapartum period resulted in lower maternal plasma oxytocin concentration, but only in response to infant suckling. The current study observed a differing result again; there was no significant correlation between exogenous oxytocin administration during the intrapartum period and maternal or infant endogenous oxytocin in the postpartum period. Of note, previous research detailed above analysed plasma oxytocin concentrations, whereas the current protocol assessed salivary oxytocin concentrations [25,34,38]. A correlation between plasma and salivary oxytocin concentrations has been reported when sampling does not follow intranasal oxytocin administration [39–41]. However, concerns regarding the reliability of both plasma and saliva samples in representing peripheral oxytocin concentrations have been raised [41,42]. Ultimately, this highlights – and supports similar previous assertions [40,43] – the need for a standardised methodology for peripheral oxytocin measurement, including biological sample, number of samples required, and analytical process, that can then be applied to future research investigating the above associations.

Whilst the previous research discussed above is inconsistent in methodology and variables collected and compared, and as such inconsistent in outcomes, the majority still observed less favourable breastfeeding outcomes in those who received exogenous oxytocin to induce or augment labour. Hypotheses as to why intrapartum exogenous oxytocin may impact not only breastfeeding, but any postpartum behaviours in which the endogenous oxytocin system is implicated, have been put forth by various groups.

Following their observation of negative breastfeeding and primitive neonatal reflex outcomes in infants whose birth was induced or augmented by exogenous oxytocin, Marin Gabriel et al. [35] and Olza Fernandez et al. [36] argued this was likely due to exogenous oxytocin crossing the placenta and the infant blood-brain barrier. This would rely however on sufficient oxytocin concentrations crossing two barriers, being the placenta and blood-brain barrier, that are known to be reasonably impermeable to the molecule [44,45].

Other hypotheses focus on maternal physiology. Bell et al. [21] and Uvnäs-Moberg et al. [8] discussed the possibility of maternal OTR desensitisation following prolonged exposure to exogenous oxytocin during the intrapartum period. The impact this may have on postpartum behaviours however would also need to consider the location of the OTRs implicated in that behaviour. Breastfeeding outcomes may likely be influenced by OTR expression on mammary epithelial cells, being the target of circulating oxytocin in this process [46,47]. Mother-infant bonding on the other hand is likely influenced by expression of neuronal OTRs (or in the periphery through stress regulation). Whilst desensitisation of the OTR has been observed on myometrial cells and fibroblasts, it is not currently known whether neuronal OTRs behave in the same way upon continued exposure [21,46].

The discussion and hypotheses of exogenous oxytocin's mode of action may, in part, be the reasoning as to why the results of the current study were in the opposite direction to previous research investigating breastfeeding outcomes. Exogenous oxytocin may only be responsible for lasting impact and OTR desensitisation in the periphery. Thus, breastfeeding outcomes may suffer. Mother-infant bonding, however, is primed by the central endogenous oxytocin system [7]. This distinction may be key in the continued investigation of the impact of intrapartum exogenous oxytocin administration on postpartum outcomes in which the endogenous oxytocin system is implicated.

Substantial research would be required to adequately address this. Firstly, the low permeability of the blood-brain barrier to oxytocin has already been stated [44,45]. Should intrapartum exogenous oxytocin exert differing effects on central vs peripheral OTRs, the route of exogenous oxytocin into the brain would need to be established. Secondly, the mode of action of exogenous oxytocin in disrupting breastfeeding would need to be confirmed. Many studies, like the current report, focus on either case control or cohort study designs to assess the relationship between intrapartum exogenous oxytocin and postpartum outcomes [33]. Given the inconsistent results within outcomes and across outcomes, it may be appropriate to investigate and confirm the exact exogenous oxytocin mode, or modes, of action prior to subsequent studies repeating methods of previous studies. Nonetheless, the significant results of the current study should not be ignored. The higher quality of observed mother-infant bonding in dyads who received intrapartum exogenous oxytocin, has potential to inform future investigations and clinical application.

Another plausible explanation for the results of this study may be in relation to the reason for exogenous oxytocin administration in the first place, that is, to shorten labour. Longer labour duration has been positively correlated with lower levels of mother-infant bonding [48]. Whilst this associated was observed via use of the MIBS, focusing solely on the mother's feelings towards the infant, without consideration of bonding's reciprocal nature, there is merit in further exploration of this hypothesis also.

This investigation had several strengths worth noting, including being the first to examine the relationship between administration of exogenous oxytocin to induce or augment labour and mother-infant bonding. In addition, the assessment of mother-infant bonding employed observational methods by means of the RIT, which has recently undergone rigorous validity and reliability testing to confirm its use in the current population [24,29]. A further strength was the large range of variables that were collected and controlled for, in order to determine the specific relationship between the dependent variable and outcome.

The current study is not without limitations. Although many variables were considered, there were some factors that could not be controlled. Of note was the inability to control for exogenous oxytocin administered for PPH management and/or treatment. This is a universally common practice, and recommended by the World Health Organisation [11]. Whilst mothers who received exogenous oxytocin to induce or augment labour could be grouped separate from those who did not receive oxytocin for this purpose, it was not possible to further group mothers who received no exogenous oxytocin at all during the intrapartum period. However, administration of exogenous oxytocin for PPH management was still considered as a potential confounding variable during multivariable regression analysis.

To address this limitation, future studies may focus on much larger samples to gain sufficient power so that the following groups may be compared: received exogenous oxytocin for labour induction and augmentation and PPH management, received exogenous oxytocin for labour induction and augmentation but not for PPH management, did not receive exogenous oxytocin for labour induction and augmentation but did for PPH management, and received zero exogenous oxytocin during the intrapartum period. However, due to recommended clinical practices, this may not be easily achievable. Further refinement of participant groups into those who received exogenous oxytocin for labour induction versus for labour augmentation may also be warranted.

The observational methodology of the RIT, as said, is a strength to the current study. However, also worth addressing is the novelty of the RIT tool, and the possible limitations this enacts on the current study. Whilst the instrument has demonstrated validity and reliability, this testing was conducted with samples of 15 mother-infant dyads [24,29]. Aside from this testing, the current study is the first to implement the RIT for the assessment of mother-infant bonding. This is an important consideration when reflecting upon the presented results. Future research is warranted to further support the validity of the RIT in assessing mother-infant bonding, for example comparison against established observational methods of mother-infant interaction. This too would strengthen the results currently reported. Of additional consideration regarding the RITs use in this study is that there was one coder.

A further limitation, with regard to measuring postpartum endogenous salivary oxytocin concentrations, was that sampling occurred at only one single time point and that difficulty was experienced in obtaining sufficient passive drool from infant participants. As discussed, inferences made in reference to single measures of salivary oxytocin should be made with caution [41,42]. Finally, the homogeneity of the sample should be considered. Whilst the following variables were controlled for in statistical analysis, the majority of the mothers in the current sample were White, married, well educated, employed, had strong social supports, and stable mental wellbeing. Subsequent investigations may ensure the sample includes wider representation. Additionally, such investigations may also seek to collect extra information regarding factors known to impact endogenous oxytocin concentrations that the current study was unable to capture, for example any early life adversity experienced by mothers.

5. Conclusions

The current study identified higher quality mother-infant bonding between dyads who received exogenous oxytocin to induce or augment labour, though, notably, only after adjusting for mother's perception of infant sleep difficulty. It is the first study to investigate such a relationship and has identified several areas for further exploration. These include investigating the mechanisms of action of intrapartum exogenous oxytocin on the endogenous oxytocin system, particularly on central versus peripheral OTRs, and the impact of exogenous oxytocin administered by alternative methods, for example intranasally, on quality of mother-infant bonding.

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Conflicts of interest/competing interests

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics approval

Ethics approval was granted by the Women's and Children's Health Network Human Research Ethics Committee (HREC/17/WCHN/106) and the University of South Australia's Human Research Ethics Committee (200594).

Consent to participate

Written informed consent was obtained from all mother-infant dyads prior to study participation.

Consent for publication

All authors have read and approved the final manuscript and consented to its submission for consideration of publication.

CRediT authorship contribution statement

Hannah Edwards: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Femke TA. Buisman-Pijlman:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Adrian Esterman:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Craig Phillips:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sandra Orgeig:** Writing – review & editing, Supervision. **Andrea Gordon:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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