【 資 料 一 覧 】

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資料1

事　務　連　絡
令和２年２月４日

公益財団法人日本医療機能評価機構
理　事　長　河北　博文　　殿

厚生労働省医政局総務課医療安全推進室
厚生労働省保険局保険課

産科医療補償制度の見直しに関する検討について

医療安全の推進につきまして、平素から格別のご協力、ご高配を賜り厚く御礼申し上げます。

平成２１年より、安心して産科医療が受けられる環境整備の一環として、分娩に係る医療事故により障害等が生じた患者に対する救済及び紛争の防止・早期解決を図るとともに、原因分析を通じて産科医療の質の向上を図ることを目的とした産科医療補償制度が円滑に運営されておりますが、平成３０年７月２５日付で産科医療補償制度運営委員会委員長より「産科医療補償制度の見直しに関する検討についての要望」をいただいたところです。

今後も本制度が安定的に運営されるためには、制度の運営状況・実績等について、定期的に検証を行い、必要に応じて見直しを図ることが重要であると考えております。

つきましては、貴機構において医療関係団体、患者団体、保険者等の関係者の意見を聴取し、制度のあり方に関する検討を進め、検討結果をご報告いただきますようお願いいたします。

なお、厚生労働省では、その検討結果を踏まえ、対応を進めていきます。

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資料2

産科医療補償制度の見直しに関する検討会の設置および産科医療補償制度運営委員会規則の一部改訂について

（１）産科医療補償制度運営委員会規則の一部改訂

改正	現行
第２条　委員会は、業務を執行する理事の諮問に応じて、産科医療補償制度の運営（削除）に関する事項を審議する。	第２条　委員会は、業務を執行する理事の諮問に応じて、産科医療補償制度の運営および制度の見直しに関する事項を審議する。

（２）産科医療補償制度の見直しに関する検討会規則

公益財団法人日本医療機能評価機構
産科医療補償制度の見直しに関する検討会規則

（目的）

第１条　この規則は、公益財団法人日本医療機能評価機構（以下「機構」という。）定款第４６条並びに委員会等設置規則第３条の規定に基づき、産科医療補償制度の見直しに関する検討会（以下「検討会」という。）の組織及び運営に関する事項を定めることを目的とする。

（審議事項）

第２条　検討会は、「産科医療補償制度の見直し関する検討について」（令和２年２月４日付厚生労働省事務連絡）に基づき理事長の諮問に応じて設置し、産科医療補償制度の見直しに関する事項を審議する。

（組織等）

第３条　検討会は、１５人以内の構成員をもって組織する。

２　構成員は、医療関係団体、患者団体、保険者、学識経験者等の中から理事長が委嘱し、その任期は２年以内とする。ただし、再任を妨げない。

３　補欠又は増員により委嘱された構成員の任期は、前任者又は現任者の残任期間とする。

４　構成員のうち１人を座長とし、理事長が指名する。

５　座長は会務を総理する。

６　座長は、あらかじめ座長代理を指名しておくことができる。

（議事運営）

第４条　検討会は、座長が招集する。

２　検討会は、構成員の過半数の出席がなければ、開会することができない。

３　検討会の議事は、出席した構成員の過半数をもって決し、可否同数のときは、座長の決するところによる。

（会議の公開）

第５条　検討会の審議は、公開とする。ただし、個人情報を保護する必要がある事項等を審議する場合は、非公開とすることができる。また、検討状況については、厚生労働省医政局総務課・保険局保険課に適時報告する。

（守秘事項）

第６条　構成員は、非公開の検討会の審議の内容を他に漏らしてはならない。構成員を退いた後においても同様とする。

（庶務）

第７条　検討会の庶務は、厚生労働省医政局総務課および保険局保険課の協力を得て、機構において行う。

（雑則）

第８条　この規則に定めるもののほか、検討会の運営等に関し必要な事項は、検討会において定めることができる。

附　則

この規程は 2020 年 3 月 6 日から施行する。

資料3

制度開始以降の審査件数および審査結果の累計（詳細版）

（2020 年 6 月 5 日現在）

児の生年	補償対象基準	審査件数	補償対象（※１）	補償対象外			継続審議
				補償対象外	再申請可能（※２）	計	
2009 年（※３）	2,000ｇ以上かつ 33 週以上	433	362	71	0	71	0
	28 週以上かつ所定の要件	127	57	70	0	70	0
	その他(28 週未満)	1	0	1	0	1	0
	計	561	419	142	0	142	0
2010 年（※３）	2,000ｇ以上かつ 33 週以上	381	311	70	0	70	0
	28 週以上かつ所定の要件	142	71	71	0	71	0
	計	523	382	141	0	141	0
2011 年（※３）	2,000ｇ以上かつ 33 週以上	350	279	71	0	71	0
	28 週以上かつ所定の要件	152	76	76	0	76	0
	計	502	355	147	0	147	0
2012 年（※３）	2,000ｇ以上かつ 33 週以上	383	302	81	0	81	0
	28 週以上かつ所定の要件	134	60	74	0	74	0
	計	517	362	155	0	155	0
2013 年（※３）	2,000ｇ以上かつ 33 週以上	324	267	57	0	57	0
	28 週以上かつ所定の要件	152	84	68	0	68	0
	計	476	351	125	0	125	0
2014 年（※３）	2,000ｇ以上かつ 33 週以上	324	251	73	0	73	0
	28 週以上かつ所定の要件	145	75	70	0	70	0
	計	469	326	143	0	143	0
2015 年	1,400ｇ以上かつ 32 週以上	330	280	40	6	46	4
	28 週以上かつ所定の要件	77	53	23	1	24	0
	計	407	333	63	7	70	4
2016 年	1,400ｇ以上かつ 32 週以上	231	207	9	15	24	0
	28 週以上かつ所定の要件	44	29	11	3	14	1
	計	275	236	20	18	38	1
2017 年	1,400ｇ以上かつ 32 週以上	183	166	4	13	17	0
	28 週以上かつ所定の要件	28	17	10	1	11	0
	計	211	183	14	14	28	0
2018 年	1,400ｇ以上かつ 32 週以上	87	76	2	7	9	2
	28 週以上かつ所定の要件	11	9	2	0	2	0
	計	98	85	4	7	11	2

2019 年	1,400 g 以上かつ 32 週以上	8	8	0	0	0	0
	28 週以上かつ所定の要件	1	1	0	0	0	0
	計	9	9	0	0	0	0
合　計		4,048	3,041	954	46	1,000	7

（※１）「補償対象」には、再申請後に補償対象となった事案や、異議審査委員会にて補償対象となった事案を含む。

（※２）「補償対象外（再申請可能）」は、審査時点では補償対象とならないものの、将来、所定の要件を満たして再申請された場合、改めて審査するもの。

（※３）2009 年から 2014 年の出生児は、審査結果が確定している。

内容は以下URLで閲覧できます。
https://jcqhc.or.jp/wp-content/uploads/2020/03/news_letter_202003.pdf

資料4

2020年3月1日発行（第19巻6号） 隔月発行

評価機構

2020 3 月号 NEWS LETTER

特 集

産科医療補償制度の運営状況等について

人の安心 医療の安全 JQ

公益財団法人 日本医療機能評価機構
Japan Council for Quality Health Care

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資料5

重度脳性麻痺児とそのご家族を支援するとともに
産科医療の質の向上をめざした制度です

内容は以下URLで閲覧できます。
http://www.sanka-hp.jcqhc.or.jp/documents/news/sanka_news_08.pdf

2020年4月1日発行
第 8 号

産科医療補償制度ニュース

制度の運営状況

特 集

脳性麻痺児の看護・介護の実態把握に関する調査

人の安心、医療の安全 JQ
公益財団法人 日本医療機能評価機構
Japan Council for Quality Health Care

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資料6

産科医療補償制度　補償対象基準の確認のお願い

〇本制度の補償対象基準等は、2015 年に見直しが行われ、要件が広がっています。

〇新基準が適用される 2015 年以降に生まれた児が 2020 年より順次補償申請期限を迎えていますので、補償申請期限漏れのないようあらためて新基準をご確認ください。

【お子様の出生年と補償申請期限の関係】

児の出生年	2015 年	2016 年	2017 年	2018 年
補償申請期限	2020 年の満 5 歳の誕生日まで	2021 年の満 5 歳の誕生日まで	2022 年の満 5 歳の誕生日まで	2023 年の満 5 歳の誕生日まで

【補償対象基準の新旧比較】

	旧基準	**新基準**
1.補償対象基準	次の①または②いずれかの基準を満たして出生したこと	
	①出生体重 2,000g 以上かつ在胎週数 33 週以上	①　出生体重 **1,400g** 以上かつ在胎週数 **32 週**以上
	②　在胎週数 28 週以上であって、以下の（1）、（2）のいずれかの場合に該当する児 （1）低酸素状況が持続して臍帯動脈血中の代謝性アシドーシス（酸性血症）の所見が認められる場合（pH 値が 7.1 未満）	
	（2）胎児心拍数モニターにおいて特に異常のなかった症例で、通常、前兆となるような低酸素状況が前置胎盤、常位胎盤早期剥離、子宮破裂、子癇、臍帯脱出等によって起こり、引き続き、次のいずれかの胎児心拍数パターンが認められ、かつ、心拍数基線細変動の消失が認められる場合 イ　突発性で持続する徐脈 ロ　子宮収縮の 50%以上に出現する遅発一過性徐脈 ハ　子宮収縮の 50%以上に出現する変動一過性徐脈	**（2）低酸素状況が常位胎盤早期剥離、臍帯脱出、子宮破裂、子癇、胎児母体間輸血症候群、前置胎盤からの出血、急激に発症した双胎間輸血症候群等によって起こり、引き続き、次のイからチまでのいずれかの所見が認められる場合** イ　突発性で持続する徐脈 ロ　子宮収縮の 50%以上に出現する遅発一過性徐脈 ハ　子宮収縮の 50%以上に出現する変動一過性徐脈 **ニ　心拍数基線細変動の消失** **ホ　心拍数基線細変動の減少を伴った高度徐脈** **ヘ　サイナソイダルパターン** **ト　アプガースコア 1 分値が 3 点以下** **チ　生後 1 時間以内の児の血液ガス分析値（pH 値が 7.0 未満）**
2.除外基準	先天性や新生児期の要因によらない脳性麻痺であること	
3.重症度の基準	身体障害者手帳 1・2 級相当の脳性麻痺であること	

［お問い合わせ先］
産科医療補償制度専用コールセンター
0120-330-637＜受付時間：午前９時～午後５時（土日祝日・年末年始を除く）＞

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令和２年４月１日（毎月１日発行）　日産婦医会報　（第三種郵便物認可）

医療安全に向けた会員支援：産科医療補償制度との連携について

日産婦医会医療安全部会

日産婦医会医療安全部会（以下、部会）では、安全な産婦人科医療の実現を目指し、産婦人科偶発事例報告事業（2004年より）、妊産婦死亡報告事業（2010年より）、産科医療補償制度（2019年より）、医療事故調査制度（2017年より）等から得られた情報の発信、および医療安全・医療の質向上に向けた事業に取り組んでいる。

再発防止および産婦人科医療の質の向上の観点から、医療事故が発生した場合、会員およびその医療機関が、まずは自ら、事例を検証した上で、医療上の改善策を検討して実施することで再発防止につなげることが重要である。しかし、小規模施設においては、それらの実施が難しい場合がある。

部会としては、事例の検証および改善策の策定および実施を支援することが、安全な医療の提供を確保・維持するために必要であると考えられる場合に、会員からの支援要請に対応している。また、この支援は産婦人科医療の専門職団体としての役割でもあると考え、会員支援事業を2017年に開始した。産科医療補償制度原因分析委員会（以下、原因分析委員会）、妊産婦死亡評価委員会、医賠責保険委員会・日医指導・改善委員会等からの報告を受け、同じ医療行為を繰り返す会員に対して、再発防止・医療の質の向上のための支援を行っている。原則、会員からの支援要請を受けて実施する。

医会は再研修制度を構築し、より安全な医療を行うための仕組みを確立する観点から、日本母体救命システム普及協議会（J-CIMELS）を設立し、全国で講習会を開催している。また、無痛分娩関係学会・団体連絡協議会（JALA）からの要請を受けJ-MELS硬膜外鎮痛急変対応コースを開設した。

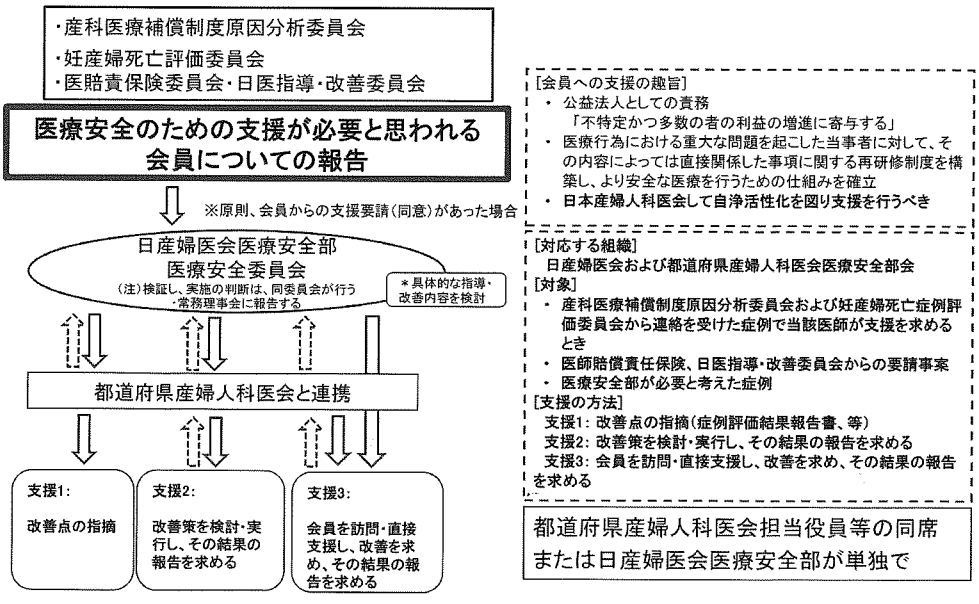
この度、医会と産科医療補償制度を運営する公益財団法人日本医療機能評価機構（以下、運営組織）との間で、原因分析委員会が原因分析を行った結果、再発防止および産科医療の質の向上の観点から改善取組みが必要とされた会員および当該機関に対して、医会と運営組織が協力して医療安全確保のための支援業務（以下、支援業務）を行う業務提携契約を締結した。2020年４月より、支援業務のための連携スキーム（以下、連携スキーム）を実施する。

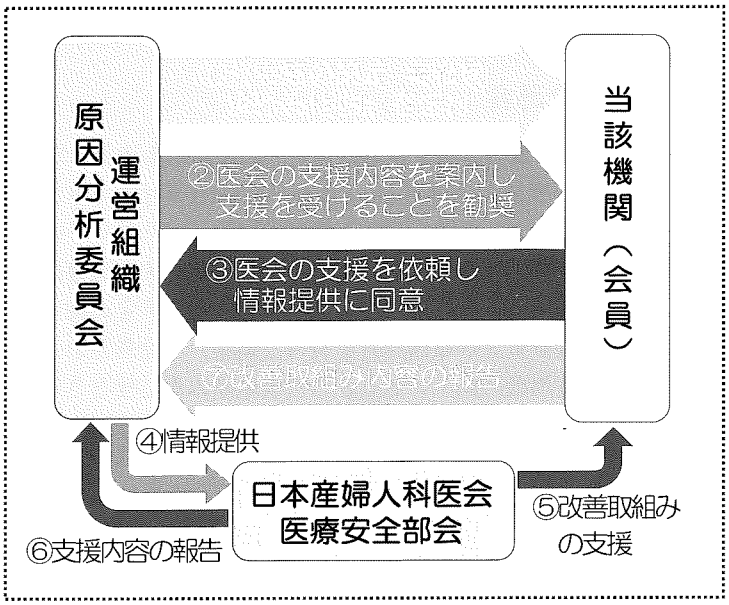
産科医療補償制度では、同一の分娩機関において複数の補償対象事案があり、複数事案目の原因分析を行った結果、これまでの原因分析報告書で指摘された事項について改善がみられず、同じような指摘が繰り返し行われることとなった場合、当該機関に対し原因分析報告書を送付する際に、指摘事項について一層の改善取組みを要請する「原因分析報告書の送付にあたり」という別紙（要望書）（以下、「別紙」）を送付し、その半年後を目途に当該機関から改善取組みの実施報告を求める対応を行っている。連携スキームは、この「別紙」対応に関して実施するものであり、概要は次のとおりである。

運営組織は、当該機関に「別紙」を送付する（①）際に、医会の行う支援業務についての案内書面を同封し、当該機関が医会の支援を受けるよう勧奨する（②）。当該機関は、医会の支援を受ける場合、医会に支援を依頼し、原因分析に関連する情報を運営組織が医会に提供することについて同意する旨の連絡を行う（③）。当該機関からの支援依頼を受け、運営組織は関連情報を医会に提供し（④）、医会は、当該機関に対して改善策の策定・実施等に関する支援を行う（⑤）。医会は、実施した支援内容について原因分析委員会に報告する（⑥）。当該機関は、「別紙」受領から半年後、原因分析委員会に対し改善取組みの実施報告を行う（⑦）。

産科医療補償制度開始から10年を過ぎた。この

医療安全に向けての会員支援事業





間92件の「別紙」が送付され、指摘事項に対して一層の改善取組みが提示された。その中で最も多い改善指摘事項が「胎児心拍数陣痛図の判読と対応」であった。

なお、医会による支援は、関係する各都道府県産婦人科医会と協力して実施する。情報管理については、運営組織から提供された情報および当該機関への支援を行う中で知り得た情報は、当該機関への支援業務の目的以外には使用しないこと、関係者以外への提供は行わないことを徹底する。

このように医会は産科医療補償制度の運営組織と連携して会員の支援要請に対応することになった。会員の皆様には、この支援業務についてご理解をいただきたい。

資料8

原因分析報告書要約版の公表を巡るこれまでの経緯

１．2018 年８月の「要約版」公表停止以前

○原因分析報告書「要約版」については、個人や分娩機関を特定できるような情報を記載していないことから、個人情報には該当しないものとして、制度運営に関する高い透明性の確保および同じような事例の再発防止や産科医療の質の向上を図ることを目的に、産科医療補償制度のホームページに掲載し、公表していた。

※2017 年 5 月 30 日：改正個人情報保護法改正

２．2018 年８月１日「要約版」公表の一旦停止

○2018 年に本制度の補償申請ならびに原因分析のために提出された診療録･助産録および検査データ等をデータベース化したもの（産科制度データ）の開示について検討を行うなかで、政府関係者や複数の法律専門家から、個人情報保護法の改正に伴い、情報提供元において個人を特定できる場合は個人情報の第三者提供に該当する「提供元基準」が明確に示されたことにより、当機構内において個人や分娩機関等を特定できる「要約版」の公表は、個人情報の第三者提供に該当するとの指摘を受けた。

このため、公表することについて同意を得ていない「要約版」の公表を一旦停止することとし、今後の「要約版」の公表については、公表の目的や効果、個人情報保護法に規定に照らして必要となる手続き等を踏まえ、幅広い視点で検討することとした。

※2018 年 7 月 20 日：本制度運営委員会で「要約版」公表停止を報告
※2018 年 8 月 1 日 ：本制度ホームページでの「要約版」掲載を停止

３．公表方針の見直しと 2019 年１月「要約版」公表の再開

○改めて法律専門家や政府関係者の見解も確認し、「要約版」の取り扱いについて検討した結果、以下の方針にて、2019 年１月以降、順次「要約版」の公表を再開することとした。

１）「要約版」の公表は、公益性が極めて高く、同じような事例の再発防止、産科医療の質の向上に広く寄与することから、『公衆衛生の向上』を目的とした個人情報の第三者提供にあたると考えられ、また、「要約版」公表のための同意取得には、保護者や分娩機関・関連医療機関など多様かつ多数の対象者が存在し、膨大な労力や費用が必要となることから、『同意を得ることが困難である』と考えられる。そのため、個人情報保護法第 23 条第１項第三号の例外規定に該当し、同意取得を必要とせずに「要約版」を公表できるとするのが原則である。

２）しかしながら、本制度の公益性や昨今の個人情報の管理にかかる社会的動向に鑑み、保護者および分娩機関・関連医療機関からの同意取得に努めたうえで、「要約版」の公表を再開することとした。

3）今後、保護者および分娩機関・関連医療機関から「要約版」の公表についての同意・不同意の意思を確認し、「要約版」の公表を行う。ただし、保護者または分娩機関・関連医療機関から「要約版」の公表を行うことについて同意しない旨の意思表示があった場合は、当該「要約版」は公表しない。

※2018 年 12 月～2019 年 1 月：
2018 年 11 月までに原因分析報告書送付済みの事案に関し、保護者、当該分娩機関等に対し、「要約版」公表についての同意・不同意の意思確認書を送付

※2018 年 12 月以降：保護者、当該分娩機関等への原因分析報告書の送付と併せ「要約版」公表についての同意確認書を送付

※2019 年 1 月以降　：本制度ホームページで順次「要約版」を掲載

4．2019 年 2 月「要約版」の公表に関するアンケート

○2019 年 2 月、「要約版」公表に関する意思確認において、「同意する」「同意しない」と回答した理由を把握するため、保護者および分娩機関に対して「要約版」公表に関するアンケートを実施した。（対象は、保護者および分娩機関それぞれについて、「同意する」との回答から 50 件、「同意しない」との回答から 50 件を無作為に抽出）

（回答者数 41 件、重複回答あり）

「同意しない」と回答した主な理由（保護者）	回答数	回答者数に対する割合
公表されることに何となく抵抗感があったため	20	48.8%
趣旨・目的には賛同するが、「要約版」の情報から個人や分娩機関が第三者に特定される不安があったため	19	46.3%
どのようなメリット（効果）やリスクが生じるのかよく分からなかったため	16	39.0%

（回答者数 35 件、重複回答あり）

「同意しない」と回答した主な理由（分娩機関）	回答数	回答者数に対する割合
どのようなメリット（効果）やリスクが生じるのかよく分からなかったため	18	51.4%
趣旨・目的には賛同するが、「要約版」の情報から個人や分娩機関が第三者に特定される不安があったため	12	34.3%
趣旨・目的に賛同できなかったため	9	25.7%

5．同意取得率向上に向けた取組み

○2019 年 7 月、「要約版」公表の同意確認のための保護者や分娩機関宛の案内文書について、「要約版」公表の主旨・目的や活用事例をより分かり易くする改定を行った。

○日本助産師会では、機関誌「助産師」2019 年 11 月号に「要約版」公表に関する記事を掲載し、会員に対して「要約版」の活用および公表への協力を求めた。日本産婦人科医会では、公表について理解をいただけるよう会員に対して働きかけを実施する。

６．2020 年 1 月に示された厚労省の見解及び個人情報保護委員会の大綱

○「要約版」の公表について、2018 年 7 月以前のように「要約版」を全件公表することについて、継続的に厚生労働省に相談しており、厚生労働省においては、個人情報保護委員会等とも連携のうえ、検討をすすめていた。

○2020 年 1 月に厚生労働省から、2019 年 12 月に個人情報保護委員会より公表された「個人情報保護法　いわゆる 3 年ごと見直し　制度改正大綱」（以下、「制度改正大綱」という）が示され、併せて「民間事業における個人情報の取扱いについては、各事業者が判断していくものであることから、評価機構ではこうした動きも踏まえ、公衆衛生の向上と個人情報保護とのバランスを勘案し、改めて方針を検討されることが望ましいものと考えられる。なお、以前のように要約版を全件公表することが社会から受け入れられるのであれば、厚生労働省は異論を唱えるものではない。一方で、要約版の公表がより広く社会から受け入れられるためにも、その記載内容については関係者がより安心できるものとなるように考慮することを提案する。」との見解を受けた。

○「制度改正大綱」においては、次のような記載がある。

> 現行の個人情報保護法において、「人の生命、身体又は財産の保護のために必要がある場合であって、本人の同意を得ることが困難であるとき」や「公衆衛生の向上又は児童の健全な育成の推進のために特に必要がある場合であって、本人の同意を得ることが困難であるとき」などの利用目的や第三者提供の制限の例外規定があり、個人情報の公益目的利用についても、一定の場合では許容されると考えられるところ、これまで当該例外規定が厳格に運用されている傾向があることから、想定されるニーズに応じ、ガイドラインやＱ＆Ａで具体的に示していくことで、社会的課題の解決といった国民全体に利益をもたらす個人情報の利活用を促進することとする。

○2020 年 2 月に開催された第 42 回運営委員会において、厚生労働省からの見解および「制度改正大綱」で示された内容を受けて、「要約版」公表の今後の対応方針について、公衆衛生の向上や個人情報保護とのバランスを勘案し、以前のように全件を一律公表していく方針について、あらためて原因分析委員会および運営委員会で議論していくと取りまとめられた。

○また、「要約版」の記載内容について、現行の医学的価値を毀損しない範囲で、個人を更に特定できないように見直し、工夫することを原因分析委員会において検討することとなった。

以上

(ここは空白のページです)

資料9

本書面は原因分析報告書要約版のサンプルであり、要約版に記載される情報の範囲・量がどのようなものかをご理解いただくためにお送りしています。

原 因 分 析 報 告 書 要 約 版《サンプル》

産 科 医 療 補 償 制 度

原因分析委員会第■部会

1. 「事例の概要」

1) 妊産婦等に関する情報

経産婦

現行の記載	変更後の記載
「初産婦」または 「●回経産婦」	「初産婦」または 「経産婦」（●回は記載しない）

2) 今回の妊娠経過

特記事項なし

3) 分娩のための入院時の状況

妊娠 36 週 5 日

15:00 頃 腹部緊満感あり

16:20 性器出血あり

16:50 入院、超音波断層法で胎児心拍数 60 拍/分の徐脈、胎盤の肥厚を認め、常位胎盤早期剥離と診断

4) 分娩経過

妊娠 36 週 5 日

16:57- 胎児心拍数陣痛図上、遅発一過性徐脈

17:06- 胎児心拍数陣痛図上、徐脈、基線細変動消失

17:30 常位胎盤早期剥離の診断で帝王切開により児娩出、子宮溢血所見あり

胎児付属物所見 胎盤面積の約 50%に凝血塊付着あり、血性羊水あり

5) 新生児期の経過

現行の記載	変更後の記載
1ｇ単位まで記載（例：2862g）	10 の位以下を切り捨て「XX00ｇ台」と記載（例：2800ｇ台）

⑴ 在胎週数:36 週 5 日

⑵ 出生時体重:2800g 台

⑶ 臍帯動脈血ｶﾞｽ分析: pH 6.60、BE -28.4mmol/L

⑷ ｱﾌﾟｶﾞｰｽｺｱ:生後 1 分 1 点、生後 5 分 1 点

⑸ 新生児蘇生:人工呼吸(ﾊﾞｯｸﾞ・ﾏｽｸ、ﾁｭｰﾌﾞ・ﾊﾞｯｸﾞ)、胸骨圧迫、気管挿管

⑹ 診断等:重症新生児仮死、低酸素性虚血性脳症(Sarnat 分類 stageⅢ)

⑺ 頭部画像所見:

生後 11 日 頭部 MRI で両側の基底核、大脳皮質に低酸素によるﾀﾞﾒｰｼﾞを受けたと考えられる部位を認め、低酸素性虚血性脳症の所見

現行の記載	変更後の記載
pH，PCO_2，PO_2，HCO_3^-，BE について記載	pH と BE について記載
pH は小数点第３位まで記載（例：6.602）	小数点第３位を切り捨て、小数点第２位まで記載（例：6.60）

6) 診療体制等に関する情報

(1) 施設区分:病院

(2) 関わった医療ｽﾀｯﾌの数

医師:産科医 2 名、小児科医 1 名、麻酔科医 1 名

看護ｽﾀｯﾌ:助産師 2 名、看護師 4 名

【継続審議】病院、診療所、助産所の区分表記については継続審議

これまでと同様に記載

2. 脳性麻痺発症の原因

(1) 脳性麻痺発症の原因は、常位胎盤早期剥離によって胎児低酸素・酸血症をきたし、低酸素性虚血性脳症を発症したことであると考える。

(2) 常位胎盤早期剥離の関連因子は認められない。

(3) 常位胎盤早期剥離の発症時期は特定できないが、妊娠 36 週 5 日の 15 時頃またはその少し前の可能性があると考える。

3. 臨床経過に関する医学的評価

1) 妊娠経過

妊娠中の管理は一般的である。

2) 分娩経過

(1) 入院時の対応(超音波断層法による胎児心拍数と胎盤の確認)は一般的である。

(2) 妊産婦の症状(腹部緊満感、性器出血)および超音波断層法所見(胎児徐脈、胎盤の肥厚)より、常位胎盤早期剥離と診断し、帝王切開を決定したことは適確である。

(3) 帝王切開決定から 40 分後に児を娩出したことは一般的である。

(4) 臍帯動脈血ｶﾞｽ分析を実施したことは一般的である。

(5) 胎盤病理組織学検査を実施したことは適確である。

3) 新生児経過

新生児蘇生(ﾊﾞｯｸﾞ・ﾏｽｸによる人工呼吸、気管挿管、胸骨圧迫、ﾁｭｰﾌﾞ・ﾊﾞｯｸﾞによる人工呼吸)は一般的である。

4. 今後の産科医療向上のために検討すべき事項

1) 当該分娩機関における診療行為について検討すべき事項

なし。

2) 当該分娩機関における設備や診療体制について検討すべき事項

なし。

3) わが国における産科医療について検討すべき事項

(1) 学会・職能団体に対して

常位胎盤早期剥離は、最近の周産期管理においても予知が極めて困難であるため、周産

期死亡や妊産婦死亡に密接に関与する。常位胎盤早期剥離の発生機序の解明、予防法、早期診断に関する研究を推進することが望まれる。

⑵ 国・地方自治体に対して

なし。

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資料10

内容は以下URLで閲覧できます。
http://www.sanka-hp.jcqhc.or.jp/documents/prevention/report/pdf/Saihatsu_Report_10_All.pdf

第10回
産科医療補償制度
再発防止に関する報告書

――――産科医療の質の向上に向けて

2020年3月

公益財団法人 日本医療機能評価機構
Japan Council for Quality Health Care

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資料11

産医補償第[redacted]号
2020年3月31日

〒[redacted]

公益財団法人日本医療機能評価機構
理事・産科医療補償制度事業管理者　鈴木　英明
産科医療補償制度再発防止委員会委員長　木村　正

「第10回　産科医療補償制度　再発防止に関する報告書」に記載されている「産科・小児科医療関係者に対する提言」について（依頼）

拝啓　時下ますますご清祥の段、お慶び申し上げます。平素は産科医療補償制度の運営に格別のご高配を賜り、厚くお礼申し上げます。

さて、2009年1月に発足した産科医療補償制度は、分娩に関連して発症した重度脳性麻痺児とそのご家族の経済的負担を速やかに補償するとともに、原因分析を行い、同じような事例の再発防止に資する情報を提供することなどにより、紛争の防止・早期解決および産科医療の質の向上を図ることを目的としております。

この度、再発防止委員会において、「第10回　産科医療補償制度　再発防止に関する報告書」を取りまとめ、先般送付させていただきました。

本報告書では、「第3章　テーマに沿った分析」において、「新生児管理について」および「「胎児心拍数陣痛図について」を取り上げ、産科・小児科医療関係者に対する提言を記載しております。

これら提言が記載されている「産科医療の質の向上に向けて」の項につきまして、本報告書の抜粋を同封いたしますので、貴会におかれましてもお取り組みいただきますようお願い申し上げます。

なお、本報告書は、本制度加入分娩機関、関係学会・団体、都道府県、政令指定都市、保健所設置市、および特別区宛にも送付しておりますことを申し添えます。

今後とも、産科医療補償制度につきまして、ご理解、ご協力賜りますようお願い申し上げます。末筆ながら、今後益々のご健勝をお祈り申し上げます。

敬具

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資料12

医政安発0324第9号
令和2年3月24日

公益財団法人
日本医療機能評価機構　理事長　殿

厚生労働省医政局総務課医療安全推進室長
（公印省略）

第10回産科医療補償制度再発防止に関する報告書の公表について

今般、貴団体においてとりまとめた標記報告書について、各都道府県、保健所設置市及び特別区並びに関係機関に対して、別添のとおり通知しましたのでお知らせいたします。

写

医政安発0324第6号
令和2年3月24日

各（都道府県／保健所設置市／特別区）衛生主管部（局）長　殿

厚生労働省医政局総務課医療安全推進室長
（公印省略）

第10回産科医療補償制度再発防止に関する報告書の公表について

医療行政の推進につきましては、平素から格別の御高配を賜り厚く御礼申し上げます。

産科医療補償制度につきましては、平成21年1月から、安心して産科医療を受けられる環境整備の一環として、①分娩に関連して発症した重度脳性麻痺児とその家族の経済的負担を速やかに補償し、②脳性麻痺発症の原因分析を行い、同じような事例の再発防止に資する情報を提供し、③これらにより、紛争の防止・早期解決および産科医療の質の向上を図ることを目的として公益財団法人日本医療機能評価機構において実施しているところです。

今般、同様の事例の再発防止のため、「第10回産科医療補償制度再発防止に関する報告書」が公表されましたので、貴職におかれましては、本報告書の内容を御確認の上、貴管内医療機関に対し、周知をお願いいたします。

なお、第10回報告書につきましては、別途、公益財団法人日本医療機能評価機構から各都道府県知事、保健所設置市長及び特別区長宛に送付されており、同機構のホームページ(http://www.sanka-hp.jcqhc.or.jp/index.html)にも掲載されていますことを申し添えます。

資料13

SCIENTIFIC REPORTS
nature research

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OPEN

Synergic interaction between ritodrine and magnesium sulfate on the occurrence of critical neonatal hyperkalemia: A Japanese nationwide retrospective cohort study

Yukari Yada[1], Akihide Ohkuchi[2]✉, Katsufumi Otsuki[3], Keiji Goishi[4], Mari Takahashi[5], Naohiro Yonemoto[6], Shigeru Saito[7], Satoshi Kusuda[8]✉ & The Survey Group Studying the Effects of Tocolytic Agents on Neonatal Adverse Events in Japan Society of Perinatal and Neonatal Medicine[5]*

Our aim was to evaluate the association between ritodrine and magnesium sulfate ($MgSO_4$) and the occurrence of neonatal hyperkalemia or hypoglycemia among late preterm infants in a retrospective cohort study. We used a nationwide obstetrical database from 2014. A total of 4,622 live preterm infants born at 32–36 gestational weeks participated. Fourteen risk factors based on both clinical relevance and univariate analysis were adjusted in multivariable logistic regression analyses. Neonatal hyperkalemia and hypoglycemia occurred in 7.6% (284/3,732) and 32.4% (1,458/4,501), respectively. Occurrence of hyperkalemia was associated with concomitant usage of ritodrine and $MgSO_4$ compared with no usage (adjusted odds ratio [aOR] 1.53, 95% confidence interval [CI] 1.09–2.15). Occurrence of hypoglycemia was associated with ritodrine alone (aOR 2.58 [CI 2.21–3.01]) and with concomitant usage of ritodrine and $MgSO_4$ (aOR 2.59 [CI 2.13–3.15]), compared with no usage, and was associated with long-term usage ($\geq$ 48 hours) of ritodrine and cessation directly before delivery. In conclusion, in late preterm infants, usage of ritodrine together with $MgSO_4$ was associated with occurrence of critical neonatal hyperkalemia, and long-term usage of ritodrine and cessation directly before delivery were associated with neonatal hypoglycemia.

The Cause Analysis Committee for Cerebral Palsy of the Japan Council for Quality Health Care (JCQHC) has suggested that of the nearly 1,000 cases of cerebral palsy, some may have occurred in neonates with hypoglycemia and/or hyperkalemia born to mothers receiving either ritodrine or magnesium sulfate ($MgSO_4$)[1]. In addition, 14 cases of unexpected neonatal hyperkalemia from mothers using tocolytic agents[2–14] –especially ritodrine and $MgSO_4$ concomitantly[2,3] – have been independently reported by neonatologists in Japan. At JCQHC request, the Japan Society of Perinatal and Neonatal Medicine (JSPNM) is evaluating the association between these agents and neonatal hyperkalemia or hypoglycemia occurrence. However, to the best of our knowledge, there have been no

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cohort studies in English suggesting a relationship between ritodrine administration and neonatal hyperkalemia. Regarding $MgSO_4$, there has only been one case reported of a very low birth weight infant with hyperkalemia accompanied by hypermagnesemia[15].

In 2013 the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommended against long-term tocolysis ≥48 hours with ritodrine and $MgSO_4$[16–18]. Following these restrictions, Kissei Pharmaceutical Co. Ltd. manufacturing ritodrine in Japan, published "A review of EU restrictions on short-acting beta-agonists, and guidelines regarding efficacy and safety of ritodrine hydrochloride (injection and tablet) in Japan" in Dec. 2014[19]. Accordingly, two leading societies for obstetrical decision-making in Japan, the Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG), have not prohibited long-term tocolysis using ritodrine[20,21]. Therefore, long-term tocolysis using ritodrine has often been performed[22].

Although $MgSO_4$ had been used for seizure prophylaxis in women with preeclampsia or eclampsia[23], its usage as a tocolytic agent became covered by insurance in Japan in 2006[24]. Generally, maintenance therapy with $MgSO_4$ is not recommended in the USA[25]; however, long-term $MgSO_4$ tocolysis is widely performed in Japan because the package insert does not prohibit usage at 22–36 gestational weeks[24]. In addition, long-term tocolysis with both ritodrine and $MgSO_4$ has been used in Japan when uterine contractions could not be controlled using ritodrine or $MgSO_4$ alone[26–29].

Ritodrine and $MgSO_4$ have been used widely as tocolytic agents in Japan[20,21]. Although hyperglycemia and hypokalemia are well-known adverse events of ritodrine in pregnant women[30], and hypoglycemia is a well-known adverse event in neonates born to mothers receiving ritodrine[30], whether ritodrine usage in preterm labor is associated with increased risk of neonatal hyperkalemia is unknown. Furthermore, although hyperkalemia has been reported as a rare adverse event of $MgSO_4$ in pregnant women[24], it is unknown whether $MgSO_4$ usage in women during preterm labor is also associated with increased neonatal hyperkalemia risk. To our best knowledge, association between ritodrine and/or $MgSO_4$ usage and neonatal hyperkalemia occurrence has not been documented in a large cohort study.

We hypothesized that long-term tocolysis with either ritodrine or $MgSO_4$ until 36 gestational weeks, or the combination of ritodrine and $MgSO_4$ may be associated with increased risks of neonatal hypoglycemia or hyperkalemia in Japan. Moreover, we also hypothesized neonatal hypoglycemia or hyperkalemia may be associated with increased risks of abnormal neurological findings including cerebral palsy. Therefore, our main aim was to investigate hyperkalemia and hypoglycemia incidence in neonates born to mothers receiving either ritodrine or $MgSO_4$ therapy for preterm labor. Our secondary aim was to investigate the association between neonatal hypoglycemia and hyperkalemia and later occurrence of abnormal neurological findings including cerebral palsy. Our study focused only on late preterm infants born after 32 gestational weeks. Such preterm infants are usually not severely ill at birth, and tend to be cared for in step down neonatal units or obstetrical wards without close examination, unlike neonatal intensive care units (NICUs).

Results

Maternal and infantile characteristics based on presence /absence of hypoglycemia. Hypoglycemia occurred in 32.4% at birth and at <3 hours after delivery in 94.3% of cases. Frequencies of the following were significantly higher in infants with hypoglycemia: Mother with PL/shortened CL/CI (preterm labor/shortened cervical length/cervical incompetency), placenta previa/low-lying placenta, cesarean section, twins/triplets, small-for-gestational-age (SGA) infants, and women with ritodrine alone or the concomitant usage of both ritodrine and $MgSO_4$. However, in infants with hypoglycemia, frequencies of women with preterm premature rupture of the membranes (pPROM), and GH/PE/eclampsia/ HELLP/AFLP (gestational hypertension/preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelets/acute fatty liver of pregnancy) were significantly lower (Table 1).

Effects of various risk factors on hypoglycemia occurrence. In multivariable logistic regression analyses using the "Hypoglycemia set", independent risk factors for hypoglycemia occurrence were cesarean section, SGA infants, and delivery to a mother with ritodrine alone or concomitant usage of ritodrine and $MgSO_4$ (Table 2). Interestingly, preterm premature rupture of the membranes (pPROM) was a negative independent risk factor for hypoglycemia occurrence.

Maternal and infantile characteristics based on presence/absence of hyperkalemia. Hyperkalemia occurred in 7.6% of cases at birth, and 24.0% at <3 hours, 9.2% at 3–5 hours, 53.0% at 6–23 hours, and 13.8% at ≥24 hours. Frequencies of hyperkalemia were significantly higher in infants born at <35 gestational weeks, with an Apgar score at 1 minute <3, and whose mother used ritodrine and $MgSO_4$ concomitantly (Table 3)

Effects of various risk factors on hyperkalemia occurrence. In multivariable logistic regression analyses using the "Hyperkalemia set", independent risk factors for hyperkalemia occurrence were delivery at <35 gestational weeks, an Apgar score at 1 minute <3, and delivery to a mother with concomitant usage of ritodrine and $MgSO_4$ (Table 4).

Maternal and infantile characteristics with the combination of $MgSO_4$ and ritodrine. Data from four usage groups – $MgSO_4$ alone, ritodrine alone, both $MgSO_4$ and ritodrine, and neither $MgSO_4$ nor ritodrine – are shown in Supplementary Table S1. $MgSO_4$ was the smallest group (n = 243, 5.3%), but frequency of GH/PE/eclampsia/ HELLP/AFLP was highest (67.1%), suggesting $MgSO_4$ alone was mainly used eclampsia prevention during pregnancy (Supplementary Table S1). On the contrary, frequencies of PL/shortened CL/CI were significantly higher in the ritodrine alone group (79.6%) and the combined $MgSO_4$ and ritodrine group (85.0%)

Characteristics	Non-hypoglycemia (N = 3,043)	Hypoglycemia (N = 1,458)	Missing value	*P*-value
Maternal characteristics				
Age (yr)	32.5 (29.5–36.5)	33.5 (29.5–37.5)	1	0.079
Nulliparity	1,509 (49.6)	704 (48.3)	0	0.426
Possible maternal risk factors for hypoglycemia				
Obstetrical complications				
TPL/shortened CL/CI	1,612 (53.0)	965 (66.2)	0	**<0.001**
pPROM	884 (29.1)	290 (19.9)	0	**<0.001**
GH/PE/eclampsia/HELLP/AFLP	483 (15.9)	198 (13.6)	0	**0.046**
Placental abruption	93 (3.1)	37 (2.5)	0	0.392
Placenta previa/Low-lying placenta	175 (5.8)	114 (7.8)	0	**0.009**
DM	29 (1.0)	16 (1.1)	0	0.634
GDM	159 (5.2)	77 (5.3)	0	0.943
Cesarean section	1,755/3,018 (58.2)	1,071/1,432 (74.8)	51	**<0.001**
$MgSO_4$ usage	606 (19.9)	362 (24.8)	0	**<0.001**
Ritodrine usage	1,371 (45.1)	988 (67.8)	0	**<0.001**
Combination of $MgSO_4$ and ritodrine[a]				
Neither $MgSO_4$ nor ritodrine	1,486 (48.8)	423 (29.0)	0	**<0.001**
$MgSO_4$ alone	186 (6.1)	47 (3.2)		
Ritodrine alone	951 (31.3)	673 (46.2)		
Both $MgSO_4$ and ritodrine	420 (13.8)	315 (21.6)		
Possible children's risk factors for hypoglycemia				
Gestational weeks at delivery	35.6 (34.2–36.4)	35.6 (34.2–36.4)	0	0.617
Delivery at <35 wk	1,169 (38.4)	563 (38.6)	0	0.922
Birthweight (g)	2,202 (1,916–2,464)	2,150 (1,820–2,432)	0	**<0.001**
Twins/Triplets	770 (25.3)	572 (39.2)	0	**<0.001**
Sex: male	1,732/3,042 (56.9)	788 (54.0)	1	0.072
SGA infants	342 (11.2)	196 (13.4)	0	**0.035**
Large-for-gestational-age infants	33 (1.1)	18 (1.2)	0	0.654
Apgar score at 1 min <3	93/3,040 (3.1)	43/1,456 (3.0)	5	0.926

Table 1. Maternal and infantile characteristics in 4,501 infants with data on hypoglycemia who were born at 32–36 gestational weeks. Abbreviations: yr, years old; TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using"Hypoglycemia set". Continuous variables are shown as median (interquartile range), and discrete variables are shown as n (%). The statistical differences between infants with vs. without hypoglycemia were tested using the Mann-Whitney test, Fisher's exact test, or χ^2 test. [a] The incidence of HG in women with "no usage of either $MgSO_4$ or ritodrine (Group 1: G1)", "$MgSO_4$ alone (Group 2: G2)", "ritodrine alone (Group 3: G3)", and "both $MgSO_4$ and ritodrine (Group 4: G4)" was 22.2, 20.2, 41.4, and 42.9%, respectively. Significant pairs by Bonferroni test were G1 vs. G3, G1 vs. G4, G2 vs. G3, and G2 vs. G4.

compared to the $MgSO_4$ alone group (35.8%) and the control group using neither $MgSO_4$ nor ritodrine (30.4%). This suggests ritodrine alone or both ritodrine and $MgSO_4$ in combination was mainly selected for PL therapy. Frequencies of hypoglycemia were significantly higher in women using ritodrine alone (41.4%) and using both $MgSO_4$ and ritodrine (42.9%) than in controls (22.2%). Frequency of hyperkalemia was significantly higher in women using both $MgSO_4$ and ritodrine (10.9%) than in controls (6.5%).

Duration- and dose-dependent effects of ritodrine on hypoglycemia occurrence. Next, we evaluated the association of the duration, maximum rate of administration, final rate of administration just before cessation, and time from cessation to delivery for ritodrine with the occurrence of hypoglycemia using the "Hypoglycemia: Ritodrine-alone plus control set" (Supplementary Table S2). The risk of hypoglycemia was associated with long-term tocolysis (total administration periods ≥2 days [48 hours]). However, short-term tocolysis (<2 days [48 hours]) was not a risk factor for hypoglycemia. The maximum rate of injection or final rate of injection just before cessation of ritodrine did not show dose-dependence. The risk of hypoglycemia was related to cessation just before delivery; if ritodrine was stopped ≥4 hours before delivery, the aOR of hypoglycemia was almost two thirds of when stopped <4 hours before delivery.

Risk factors[a]	Univariate analysis			Multivariable analysis[b]		
	Crude odds ratio (95% CI)		*P*-value	Adjusted odds ratio (95% CI)		*P*-value
Combination of $MgSO_4$ and ritodrine						
$MgSO_4$ alone vs. no usage	0.89	(0.63–1.24)	0.489	0.81	(0.56–1.16)	0.244
Ritodrine alone vs. no usage	2.49	(2.15–2.88)	<0.001	**2.58**	**(2.21–3.01)**	**<0.001**
Both $MgSO_4$ and ritodrine vs. no usage	2.64	(2.20–3.16)	<0.001	**2.59**	**(2.13–3.15)**	**<0.001**
Obstetrical complications						
pPROM	0.61	(0.52–0.71)	<0.001	**0.72**	**(0.61–0.85)**	**<0.001**
GH/PE/eclampsia/HELLP/AFLP	0.83	(0.70–0.996)	0.045	0.91	(0.74–1.12)	0.355
Placental abruption	0.83	(0.56–1.22)	0.332	0.91	(0.60–1.38)	0.670
Placenta previa/Low lying placenta	1.39	(1.09–1.78)	0.008	0.96	(0.74–1.26)	0.782
DM	1.15	(0.62–2.13)	0.649	1.62	(0.85–3.08)	0.145
GDM	1.01	(0.77–1.34)	0.937	1.14	(0.85–1.54)	0.372
Cesarean section	2.14	(1.86–2.46)	<0.001	**1.96**	**(1.67–2.31)**	**<0.001**
Delivery at <35 wk	1.01	(0.89–1.15)	0.898	0.95	(0.82–1.09)	0.646
Twins/triplets	1.91	(1.67–2.18)	<0.001	**1.23**	**(1.06–1.44)**	**0.009**
Sex: male	0.89	(0.79–1.01)	0.068	0.91	(0.80–1.04)	0.166
SGA infants	1.23	(1.02–1.48)	0.033	**1.35**	**(1.10–1.65)**	**0.004**
Large-for-gestational-age infants	1.14	(0.64–2.03)	0.656	1.58	(0.85–2.94)	0.146
Apgar score at 1 min <3	0.96	(0.67–1.39)	0.846	0.98	(0.66–1.45)	0.917

Table 2. Effects of various risk factors on hypoglycemia occurrence in 4,501 infants born at 32–36 gestational weeks. Abbreviations: CI, confidence interval; $MgSO_4$, magnesium sulfate; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using"Hypoglycemia set". [a]Risk factors were determined based on both clinical relevance and univariate analysis as follows: combination of $MgSO_4$ and ritodrine, obstetrical complications, cesarean section, delivery at <35 wk, twins/triplets, infantile sex, SGA infants, large-for-gestational-age infants, and Apgar score at 1 min <3. [b]Multivariable analyses were performed using the same risk factors as in univariate analyses. However, birthweight was not used as a risk factor due to the close relationship with gestational weeks. In addition, the obstetric complication of TPL/shortened CL/CI was not used as a risk factor because either ritodrine or $MgSO_4$ was commonly used under these conditions. Excluding 57 patients with missing data for 14 variables, a total of 4,444 patients underwent multivariable analysis. Abbreviations: TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency.

Duration- and dose-dependent effects of ritodrine or $MgSO_4$ on hyperkalemia occurrence. Incidence rate of hyperkalemia in women with ritodrine alone was not different from that in women with $MgSO_4$ alone. We then evaluated the association of tocolytic agents' duration, maximum rate of administration, final rate of administration just before cessation, and time from cessation to delivery with hyperkalemia occurrence, using the "Hyperkalemia: Both ritodrine and $MgSO_4$ plus control set" (Supplementary Table S3, S4). Hyperkalemia risk was associated with long-term tocolysis with ritodrine. In women in whom the maximum rate of injection or final rate of injection just before cessation of ritodrine was $\geq$170 μg/min, the risk was significantly higher than in those with no usage of ritodrine. Risk of hyperkalemia was related to the cessation of ritodrine just before delivery; if stopped $\geq$4 hours before delivery, hyperkalemia risk almost equaled no usage. As for $MgSO_4$, there was no relationship between duration of administration, maximum rate of injection, or final rate of injection before cessation. However, risk of hyperkalemia was related to $MgSO_4$ cessation just before delivery; hyperkalemia risk in women in whom $MgSO_4$ was stopped $\geq$4 hours before delivery was not significantly different from that in women with no usage of ritodrine.

Maternal and infantile characteristics based on presence/absence of cerebral palsy occurring 3 years after birth. Cerebral palsy occurred in 23 cases (0.5%) (Supplementary Table S5). Frequencies of placental abruption, delivery at <35 weeks of gestation, and Apgar score at 1 minute <3 were significantly higher in infants with cerebral palsy. Gestational weeks at delivery was earlier, and birth weight was also smaller. Due to this small sample size, we did not perform multivariable analysis.

Maternal and infantile characteristics based on presence/absence of any neurological impairments occurring 3 years after birth. Neurological impairments occurred in 193 cases (4.5%) (Supplementary Table S6). Cerebral palsy was only 12%. Other impairments included developmental language disorder alone, low score of developmental quotient, autism spectrum disorder (autism), attention-deficit/hyperactivity disorder (ADHD), auditory disorder, visual impairment, epilepsy, or developmental coordination disorder. Frequencies of nulliparous women, GH/PE/eclampsia/ HELLP/AFLP, placenta abruption, delivery at <35 weeks of gestation, male infants, SGA infants, Apgar score at 1 minute <3, and hypoglycemia were higher in infants with neurological impairments. In addition, frequencies of PL/shortened CL/CI, or cervical

Characteristics	Non-hyperkalemia (N = 3,448)	Hyperkalemia (N = 284)	Missing value	*P*-value
Maternal characteristics				
Age (yr)	33.5 (29.5–36.5)	33.5 (29.8–37.5)	2	0.221
Nulliparity	1,766 (51.2)	161 (56.7)	0	0.084
Possible maternal risk factors for hyperkalemia				
Obstetrical complications				
TPL/shortened CL/CI	1,973 (57.2)	175 (61.6)	0	0.152
pPROM	953 (27.6)	65 (22.9)	0	0.096
GH/PE/eclampsia/HELLP/AFLP	561 (16.3)	54 (19.0)	0	0.244
Placental abruption	119 (3.5)	6 (2.1)	0	0.302
Placenta previa/Low-lying placenta	214 (6.2)	23 (8.1)	0	0.206
DM	38 (1.1)	2 (0.7)	0	0.766
GDM	163 (4.7)	20 (7.0)	0	0.086
Cesarean section	2,229/3,417 (65.2)	191/281 (68.0)	34	0.362
$MgSO_4$ usage	770 (22.3)	82 (28.9)	0	**0.015**
Ritodrine usage	1,830 (53.1)	174 (61.3)	0	**0.008**
Combination of $MgSO_4$ and ritodrine[a]				
neither $MgSO_4$ nor ritodrine	1,418 (41.1)	98 (34.5)	0	**0.003**
$MgSO_4$ alone	200 (5.8)	12 (4.2)		
Ritodrine alone	1,260 (36.5)	104 (36.6)		
Both $MgSO_4$ and ritodrine	570 (16.5)	70 (24.6)		
Possible children's risk factors for hyperkalemia				
Gestational weeks at delivery	35.2 (34.1–36.2)	34.8 (33.4–36.1)	0	**<0.001**
Delivery at <35 wk	1,549 (44.9)	154 (54.2)	0	**0.003**
Birthweight (g)	2,126 (1,832–2,388)	2,056 (1,814–2,363)	0	**0.042**
Twins/Triplets	1,005 (29.1)	91 (32.0)	0	0.310
Sex: male	1,937/3,447 (56.2)	153 (53.9)	1	0.456
SGA infants	462 (13.4)	34 (12.0)	0	0.585
Large-for-gestational-age infants	33 (1.0)	1 (0.4)	0	0.513
Apgar score at 1 min < 3	112/3,443 (3.3)	18 (6.3)	5	0.011

Table 3. Maternal and infantile characteristics in 3,732 infants with data on hyperkalemia who were born at 32–36 gestational weeks. Abbreviations: yr, years old; GH, gestational hypertension; PE, preeclampsia; TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using "Hyperkalemia set". Continuous variables are shown as median (interquartile range), and discrete variables are shown as n (%). The statistical differences between infants with hypoglycemia vs. those without were tested using the Mann-Whitney test, Fisher's exact test, or χ^2 test. [a]The incidence of HK in women with "no usage of either $MgSO_4$ or ritodrine (Group 1: G1)", "$MgSO_4$ alone (Group 2: G2)", "ritodrine alone (Group 3: G3)", and "both $MgSO_4$ and ritodrine (Group 4: G4)" was 6.5, 5.7, 7.6, and 10.9%, respectively. Significant pair by Bonferroni test was G1 vs. G4.

incompetency, and twins/triplets were significantly lower in infants with neurological impairments. Median gestational weeks at delivery was earlier and birthweight was also smaller.

Effects of various risk factors on occurrence of any neurological impairments. Neurological impairments were evaluated in 4,279 infants (Supplementary Table S7). Excluding 989 patients with missing data for 16 variables, a total of 3,290 patients underwent multivariable analysis to assess effects on occurrence of any neurological impairments with the following 16 risk factors: combination of $MgSO_4$ and ritodrine, obstetrical complications, cesarean section, delivery at <35 wk, twins/triplets, infantile sex, SGA infants, large-for-gestational-age infants, Apgar score at 1 min <3, hypoglycemia at <48 h after birth, and hyperkalemia at <48 h after birth. Placental abruption, delivery at <35 weeks of gestation, male sex, SGA infants, and hypoglycemia were independent risk factors for the occurrence of any neurological impairments.

Discussion

Our current large cohort study yielded three novel findings. First, neonatal hyperkalemia within 48 hours after birth was associated with the concomitant usage of ritodrine and $MgSO_4$ among late preterm infants born at 32–36 gestational weeks. Second, neonatal hypoglycemia within 48 hours was associated with the usage of ritodrine alone or the concomitant usage of ritodrine and $MgSO_4$; incidence of hypoglycemia was markedly higher in

Risk factors[a]	Univariate analysis			Multivariable analysis[b]		
	Crude odds ratio (95% CI)		*P*-value	Adjusted odds ratio (95% CI)		*P*-value
Combination of $MgSO_4$ and ritodrine						
$MgSO_4$ alone vs. no usage	0.87	(0.47–1.61)	0.654	0.63	(0.33–1.20)	0.155
Ritodrine alone vs. no usage	1.19	(0.90–1.59)	0.224	1.20	(0.89–1.62)	0.231
Both $MgSO_4$ and ritodrine vs. no usage	1.78	(1.29–2.45)	<0.001	**1.53**	**(1.09–2.15)**	**0.015**
Obstetrical complications						
pPROM	0.78	(0.58–1.04)	0.085	0.78	(0.57–1.07)	0.118
GH/PE/eclampsia/HELLP/AFLP	1.21	(0.89–1.65)	0.232	1.37	(0.96–1.96)	0.085
Placental abruption	0.60	(0.26–1.38)	0.233	0.46	(0.19–1.09)	0.076
Placenta previa/Low lying placenta	1.33	(0.85–2.09)	0.210	1.24	(0.76–2.02)	0.389
DM	0.64	(0.15–2.65)	0.535	0.85	(0.20–3.56)	0.818
GDM	1.53	(0.94–2.47)	0.085	1.63	(0.998–2.67)	0.051
Cesarean section	1.13	(0.87–1.47)	0.354	0.96	(0.71–1.31)	0.798
Delivery at <35 wk	1.45	(1.14–1.85)	0.003	**1.46**	**(1.13–1.88)**	**0.004**
Twins/triplets	1.15	(0.88–1.49)	0.303	1.11	(0.82–1.50)	0.501
Sex: male	0.91	(0.71–1.16)	0.994	0.92	(0.72–1.18)	0.511
SGA infants	0.88	(0.61–1.27)	0.496	0.87	(0.59–1.28)	0.477
Large-for-gestational-age infants	0.37	(0.05–2.68)	0.323	0.35	(0.05–2.61)	0.306
Apgar score at 1 min < 3	2.01	(1.21–3.36)	0.008	**2.21**	**(1.29–3.81)**	**0.004**

Table 4. Effects of various risk factors on hyperkalemia occurrence in 3,732 infants who were born at 32–36 gestational weeks. Abbreviations: CI, confidence interval; $MgSO_4$, magnesium sulfate; pPROM, preterm premature rupture of the membranes; GH, gestational hypertension; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DM, diabetes mellitus; GDM, gestational diabetes mellitus; wk, gestational weeks; SGA, small-for-gestational-age; min, minute. This analysis was performed using "Hyperkalemia set". [a]Risk factors were determined based on both clinical relevance and univariate analysis as follows: combination of $MgSO_4$ and ritodrine, obstetrical complications, cesarean section, delivery at <35 wk, twins/triplets, infantile sex, SGA infants, large-for-gestational-age infants, and Apgar score at 1 min <3. [b]Multivariable analyses were performed using all the risk factors using the univariate analyses. However, birthweight was not used as a risk factor due to the close relationship with gestational weeks. In addition, the obstetric complication of TPL/shortened CL/CI was not used as a risk factor because either ritodrine or $MgSO_4$ was commonly used under these conditions. Excluding 40 patients with missing data for 14 variables, a total of 3,692 patients underwent multivariable analysis. abbreviations: TPL, threatened preterm labor; CL, cervical length; CI, cervical incompetency.

infants born to mothers with cessation of ritodrine just before delivery; in addition, incidence of hypoglycemia was higher in infants born to mothers with long-term tocolysis with ritodrine. Third, in infants born at 32–36 weeks of gestation, placental abruption, delivery at <35 weeks of gestation, male sex, SGA infants, and hypoglycemia within 48 hours after birth were independent risk factors for the occurrence of any neurological impairments.

In the current study, for the first time we have revealed concomitant usage of ritodrine and $MgSO_4$ is associated with incidence of neonatal hyperkalemia within 48 hours after birth in neonates born at 32–36 gestational weeks, although we could not show an association between neonatal hyperkalemia and cerebral palsy. Suzuki[2] analyzed data available in the Cause Analysis Report and demonstrated the relationship between delivery and cerebral palsy was unknown in 6.2% of nearly 800 cases of cerebral palsy. These infants showed marked characteristics: although considered normal, thereafter their condition changed suddenly and finally they developed severe cerebral palsy. Of these, 6 were cases of hypoglycemia and 3 of hyperkalemia, and in 2 cases of hyperkalemia with later occurrence of cerebral palsy, ritodrine and $MgSO_4$ were concomitantly used. In addition, in 11 of 14 cases of unexpected neonatal hyperkalemia soon after birth, ritodrine and $MgSO_4$ were also concomitantly used[3]. Our results further support the suggested association between concomitant usage of ritodrine and $MgSO_4$ and neonatal hyperkalemia. It is well known neonatal hyperkalemia can cause electrocardiographic abnormalities including ventricular tachycardia[31]. Therefore, our results serve as a warning about concomitant usage of ritodrine and $MgSO_4$ to prevent neonatal hyperkalemia. However, it is unknown why concomitant usage of ritodrine and $MgSO_4$, but not ritodrine alone or $MgSO_4$ alone, is associated with neonatal hyperkalemia. Hypermagnesemia might affect Na + /K + -ATPase[15,32]; however, to the best of our knowledge, there have been no cohort studies suggesting a relationship between ritodrine administration and neonatal hyperkalemia. Therefore, our clinical observations may suggest presence of synergy between ritodrine and hypermagnesemia to modify the Na + /K + -ATPase function.

Although we could not reveal the association between neonatal hypoglycemia and the later occurrence of cerebral palsy in this study, it is well-known that neonatal hypoglycemia increases the incidence of cerebral palsy[33,34]. Risk factors for cerebral palsy in infants with hypoglycemia are as follows: blood glucose levels <15 mg/dL, long duration of hypoglycemia, non-reassuring fetal status (NRFS), low Apgar score <5 at 1 min, neonatal seizure,

pathological jaundice, and hypertensive disorders of pregnancy for the mother[35]. Ritodrine is well-known to induce hyperglycemia in mothers which can cause hypoglycemia in neonates[36,37]. In the current study, incidence of hypoglycemia was markedly higher in infants born to mothers with either long-term tocolysis of ritodrine or cessation just before delivery. Therefore, ritodrine might be one of the risk factors for cerebral palsy. Hyperkalemia was not associated with the occurrence of cerebral palsy. In addition, we found placental abruption, delivery at <35 weeks of gestation, and Apgar score at 1 minute <3 were associated with later occurrence of cerebral palsy. Placental abruption and early delivery are well-known risk factors for cerebral palsy[38]. Although the contribution of asphyxia to the overall incidence of cerebral palsy is relatively small[39], metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery with both pH <7.00 and base deficit ≥12 mmol/L would have been sufficient to cause cerebral palsy[40].

In infants born at 32–36 weeks of gestation, placental abruption, delivery at <35 weeks of gestation, male sex, SGA infants, and hypoglycemia were independent risk factors for occurrence of any neurological impairments. Hyperkalemia was not an independent risk factor. Male sex is at higher risk of autism[41,42], and may be at high risk of ADHD[43]; however, the association between male sex and cerebral palsy is controversal[44]. An SGA infant is a risk factor for cerebral palsy in moderate to late preterm infants[45], and may be also associated with autism or ADHD[46,47]. Although our outcome of any neurological impairment was a composite outcome, and our data could be significantly biased due to a retrospective study design, our data support associations of male sex or an SGA infant on occurrence of neurological impairments including cerebral palsy, autism, or ADHD.

Our results warn about the concomitant usage of ritodrine and $MgSO_4$ to prevent neonatal hyperkalemia, and also warn about long-term usage of ritodrine and its cessation just before delivery to prevent neonatal hypoglycemia. Furthermore, because these adverse events occurring outside NICUs are not well-recognized among obstetricians and neonatologists, this study could have a marked impact on modifying current neonatal management for infants born to mothers with tocolytic agents. Accordingly, neonatal assessment of hyperkalemia can be suggested in women with concomitant usage of ritodrine and $MgSO_4$, and neonatal blood glucose monitoring can also be suggested in women with long-term tocolysis with ritodrine or cessation just before delivery.

The main strengths of our study include the following: (1) it is the first large cohort study evaluating associations between long-term tocolysis with both ritodrine and $MgSO_4$, and neonatal hypoglycemia and hyperkalemia; (2) it presents the first evidence of a synergic effect between ritodrine and $MgSO_4$ on occurrence of neonatal hyperkalemia; and (3) it is the first large cohort study investigating association of neonatal hyperkalemia and later occurrence of any neurodevelopmental impairments including cerebral palsy.

Our study has several limitations. First, it may be difficult to generalize results from this study with other countries. However, ritodrine hydrochloride and $MgSO_4$ have a long usage history in prenatal care, and $MgSO_4$ use is still widespread. The novel adverse events (neonatal hyperkalemia) due to concomitant use of ritodrine and magnesium sulfate should be added in the package insert of both $MgSO_4$ and ritodrine hydrochloride. Second, this was a retrospective cohort study possibly resulting in high risk of selection bias. Although we targeted infants born at 32–36 gestational weeks, 19% of infants did not have data for either hypoglycemia or hyperkalemia possibly leading to bias. In addition, we could not confirm presence/absence of neurodevelopmental impairments in almost 7% of infants, resulting in underestimation of the associations between hypoglycemia/hyperkalemia and subsequent occurrence of neurodevelopmental impairments. However, in this large retrospective cohort study, we attempted to decrease systematic bias through secondary investigation for ritodrine and magnesium sulfate usage, and attempted to adjust possible confounding factors using multivariable logistic regression analysis. In addition, before using the nationwide database, we checked for inappropriate values and transformed them to missing values. The main outcomes of hypoglycemia and hyperkalemia were newly investigated in the secondary inquiry, and diagnoses of hypoglycemia and hyperkalemia were validated by investigating levels of glucose and potassium within 48 hours after birth. Therefore, although this study is a retrospective study using a large database, we believe reducing selection bias risk is feasible as it adjusting for possible confounding factors in the relationship between ritodrine/magnesium sulfate usage and neonatal hypoglycemia/hyperkalemia occurrence. Third, we could not collect data on hypoglycemia/hyperkalemia from 277 hospitals (78%). However, the incidences of GH/PE/eclampsia/HELLP/AFLP, placenta previa/low-lying placenta, DM, GDM, and cesarean section in infants in the current study were almost the same as those in infants not involved in the current study (Supplementary Table S8), indicating current subjects may have been appropriately extracted from a nationwide obstetrical database. Fourth, inclusion criteria for pregnant women with only late preterm infants may limit generalizability of our results. However, since long-term tocolysis with ritodrine and $MgSO_4$ is often performed at 32–36 gestational weeks in Japan, and since tocolysis is not performed at ≥37 gestational weeks, we believe targeting at 32–36 gestational weeks may be appropriate for analyzing the relationship between tocolytic agents and occurrence of neonatal hypoglycemia and hyperkalemia.

Methods

Study design and participants. This was a retrospective cohort study of neonates born at 32–36 gestational weeks using a nationwide obstetrical database from 2014[48]. Because we needed to collect information on the infantile prognosis until almost 3 years old, it was followed by a secondary survey conducted in Japan in 2017–2018. In previous case series of hyperkalemia neonates, 50% (7/14) were born at 32–36 gestational weeks[3–14]. Neonates are usually managed on obstetrical wards in Japan if they have either ≥2,000 g birthweight or are at ≥35 gestational weeks at delivery. Therefore, we speculated such neonates might have developed cerebral palsy due to possible delay of the detection of hyperkalemia, because in neonates on obstetrical wards electrolyte abnormalities are not checked routinely unless they show symptoms. In addition, hyperkalemia often occurs in neonates born at <32 gestational weeks; therefore, exclusion of such early preterm infants may facilitate analysis of the association between tocolytic agents and hyperkalemia occurrence. Thus, we decided to investigate neonates born in a relatively late preterm period (32–36 gestational weeks), to evaluate the possible relationship

between tocolytic agents and neonatal hyperkalemia. For hypoglycemia, Suzuki[2] analyzed data available in the Cause Analysis Report, and determined 5 of 6 neonates (83%) who had hypoglycemia suspected associated with development of cerebral palsy were born at ≥37 gestational weeks. However, we did not include neonates born at ≥37 gestational weeks in our analysis since assessment of hypoglycemia was not part of our routine examinations.

We received approval from the JSOG Clinical Research Ethics Committee to use a nationwide obstetrical database from 2014 (No. JSOG2017–51), and also received approval from the JSPNM Clinical Research Ethics Committee for execution of the current study in the survey group to study the effects of tocolytic agents on neonatal adverse events (No. JSPNM2017–1). Then, we requested the directors of Departments of Obstetrics and Gynecology in 355 hospitals that had registered in the nationwide obstetrical database from 2014 (total stillbirths and infants: n = 220,052; those born at 32–36 gestational weeks: n = 24,943) to cooperate with the current study. Finally, 78 directors consented to this study, and kindly secured the cooperation of neonatologists in each hospital. A research investigator and research team members in each hospital gained approval for this study from each Clinical Research Ethics Review Committee. All methods in this retrospective study were performed in accordance with the relevant guidelines (Ethical Guidelines for Medical and Health Research Involving Human Subjects). Because this study is a retrospective study, it was very difficult to gain appropriate informed consents from each subject. Therefore, we gained consents using opt-out, which is a way for investigators to give subjects an opportunity to refuse to participate in this study by announcing the detail of this study in each participating institute. The Survey Committee constructed input pages for survey data on the Web system. Data were collected within 1 year after the approval of the current study.

We excluded the following infants from our survey: (1) born to women with unknown data on the usage of ritodrine or $MgSO_4$, (2) whose mothers were administered $MgSO_4$ only after birth or at an unknown time, (3) with a birthweight of either <500 or >4,000 g, or unknown birth weight, (4) with stillbirth or major anomalies (chromosomal anomalies, neonatal abnormalities, conditions probably contributing to impaired neurodevelopment, conditions requiring emergency surgery soon after delivery, and lethal conditions), and (5) with unknown data on both hypoglycemia and hyperkalemia (Fig. 1). The remaining 4,622 infants with data on either hypoglycemia or hyperkalemia at <48 hours after delivery were analyzed.

Collection of new variables by the secondary survey. The Survey Committee used a nationwide obstetrical database from 2014, which included 314 variables on maternal and neonatal information[48]. The input data in all variables were initially automatically checked using internalized data check scripts, and data input staff were informed of possible incorrect data. However, since the database was built using data from 355 institutes, there were inappropriate data in the database. Then, one author (A.O.) attempted to validate the database. The initial number of cases in the database was 24,960, but we found that 17 cases were duplicated; after exclusion the remaining 24,943 cases were used. Next, we determined inappropriate values for maternal height, pre-pregnancy maternal body weight, maternal body weight at delivery, maternal age, bleeding amounts, gestational weeks at premature rupture of the membranes, disseminated intravascular coagulation (DIC) score, neonatal birth weight, neonatal birth height, neonatal head circumference, Apgar score at 1 minute (min), Apgar score at 5 min, pH of umbilical artery, placental weight, and umbilical cord length. We finally transformed the inappropriate values to missing values.

The Survey Committee extracted the following 6 variables: facility name, anonymization number, date of birth, gestational weeks and days at delivery, birth weight, and neonatal sex. The committee members collaboratively decided survey items for the secondary survey. In the survey for ritodrine they were: presence/absence of injections, medical product name, total administration days (6 codes), maximum infusion speed (8 codes), final infusion speed (8 codes), and interval (hours) from cessation of ritodrine to delivery (6 codes). In the $MgSO_4$ survey they were: presence/absence of injections, medical product name, total administration days (6 codes), maximum infusion speed (8 codes), final infusion speed (8 codes), interval hours from cessation of $MgSO_4$ to delivery (6 codes), and administration period (pre-delivery alone, post-delivery alone, both pre- and post-delivery, unknown). In the survey for neonatologists they were: presence/absence of admission to NICU, causes for admission to NICU, presence/absence of measurements of magnesium concentrations in umbilical cord, concentration of magnesium in umbilical cord, presence/absence of measurements of blood sugar within 48 hours after delivery, blood sugar level at the nadir (mg/dL), presence/absence of hypoglycemia defined as <40 mg/dL[49], timing of the nadir blood sugar level (5 codes), presence/absence of measurements of potassium concentrations within 48 hours after delivery, potassium level at the maximum (mEq/L), presence/absence of hyperkalemia defined as >6.5 mEq/L[50], timing of the maximum potassium level (5 codes), three consecutive potassium levels just after the occurrence of hyperkalemia, infantile prognosis at almost 3 years (4 codes: death, presence of abnormal neurological findings, absence of abnormal neurological findings, unknown), detailed information on the disease or condition leading to abnormal neurological findings, and date of judgment of infantile prognosis.

Primary/secondary outcomes and risk factors. Primary outcomes were the occurrence of hyperkalemia and hypoglycemia. Secondary outcomes were cerebral palsy, and any neurodevelopmental impairments including cerebral palsy occurring 3 years after birth. Cerebral palsy was judged by the senior pediatrician (S. K.) who was involved neither in data acquisition nor in database construction. Cerebral palsy was defined as a non-progressive, non-transient central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture[51].

Based on both clinical relevance and univariate analysis, risk factors for occurrence of hypoglycemia or hyperkalemia were: obstetrical complications, cesarean section, $MgSO_4$ usage during pregnancy, ritodrine usage, gestational weeks at delivery, birth weight, multiple pregnancy, infantile sex, SGA and large-for-gestational-age defined as an infant with weight below the 10th percentile or ≥ the 90th percentile of gestational age[52], and Apgar score at 1 min <3. The above-mentioned 14 risk factors plus hypoglycemia and hyperkalemia were also determined risk factors for cerebral palsy or other neurological impairments.

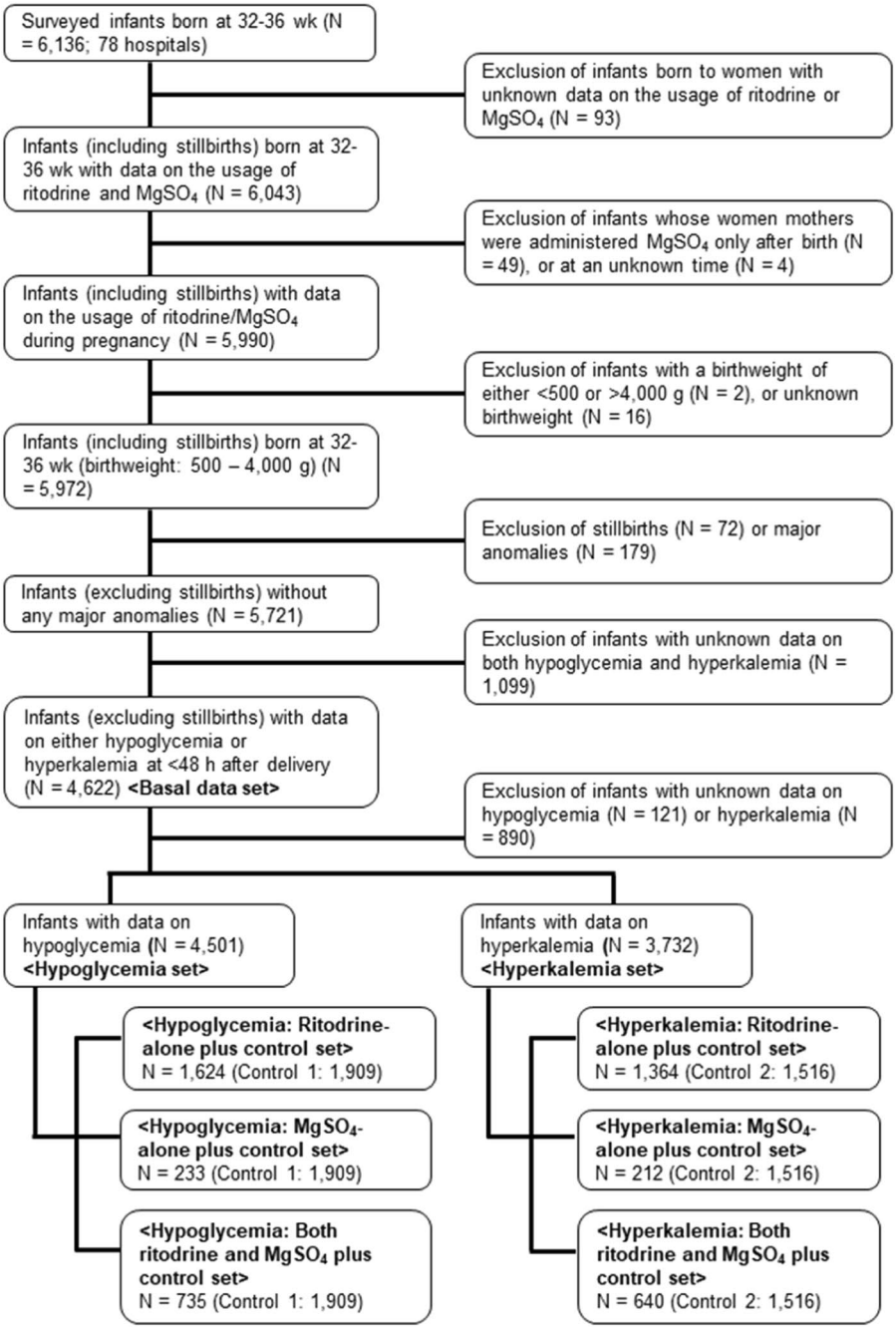

Figure 1. Patient Flowchart. "Basal data set" (N = 4,622) was created from 6,136 surveyed infants born at 32–36 gestational weeks. "Hypoglysemia set" (N = 4,501) was created from "Basal data set" after excluding 121 infants with unknown data on hypoglycemia; and "Hyperkalemia set" (N = 3,732) was created from "Basal data set" after excluding 890 infants with unknown data on hyperkalemia. "Hypoglycemia set" was divided into "Hypoglycemia: Ritodrine-alone plus control set" (Ritodrine-alone [N = 1,624] and control 1 without either ritodrine or $MgSO_4$ [N = 1,909]), "Hypoglycemia: $MgSO_4$-alone plus control set" ($MgSO_4$-alone [N = 233] and control 1), and "Hypoglycemia: Both ritodrine and $MgSO_4$ plus control set" (Both ritodrine and $MgSO_4$ [N = 735] and control 1). "Hyperkalemia set" was also divided into "Hyperkalemia: Ritodrine-alone plus control set" (Ritodrine-alone [N = 1,364] and control 2 without either ritodrine or $MgSO_4$ [N = 1,516]), "Hyperkalemia: $MgSO_4$-alone plus control set", ($MgSO_4$-alone [N = 212] and control 2), and "Hyperkalemia: Both ritodrine and $MgSO_4$ plus control set" (Both ritodrine and $MgSO_4$ [N = 640] and control 2).

Statistical analysis. Continuous variables are shown as the median (interquartile range) because of non-normal distributions of gestational weeks and birth weight at 32–36 gestational weeks, and binary and categorical variables are shown as n (%). The associations of ritodrine/$MgSO_4$ usage during pregnancy and the occurrence of infantile hypoglycemia/hyperkalemia within 48 hours after delivery were analyzed using Fisher's exact

test or the χ^2 test, followed by univariate logistic regression analyses. Then, multivariable regression analyses were performed while adjusting for confounding variables. Because the primary outcomes of hyperkalemia and hypoglycemia occurred in >200 cases, we judged we could use a maximum of 20 risk and/or confounding factors in the multivariable models. All analyses were performed using IBM SPSS Statistics (version 25 for Windows) and R (EZR ver. 1.37)[53]. Level of $p < 0.05$ was considered significant.

Data availability

Data and materials used in this study are available upon reasonable request to the corresponding author and under a collaboration agreement.

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References

1. Japan Council for Quality Health Care. Dai 7 kai Sanka Iryo Hosho Seido: Saihatsu boushi ni kansuru houkokusho [Japan Obstetrics Compensation System for Cerebral Palsy: Report for Preventive Measure] [in Japanese]. (ed. Japan Council for Quality Health Care) (Japan Council for Quality Health Care, 2017).
2. Suzuki, S. Shussei souki no shinseiji kyuuhen ni taiousuru [Strategy for the emergent serious condition of neonates] [in Japanese]. *Acta Obst. Gynaec. Jpn.* **68**, 133–136 (2016).
3. Itani, Y. Yokisenu shussyou go souki no shinseiji kou K kessyou [Unexpected neonatal hyperkalemia in early neonatal period] [in Japanese]. *JAOG news.* **67**, 10–11 (2015).
4. Takayanagi, T. *et al*. Seigo 24 jikan inai ni shoukousei no kou kariumu kessyou wo kitashita seijukuji no 2 rei [Occurrence of symptomatic hyperkalemia within 24 hours after birth in two term newborns] [in Japanese]. *Acta Neonatologica Japonica.* **38**, 833–836 (2002).
5. Hosoda, N., Uchida, T., kyoba, S. & Watanabe, M. Botai heno ryuusan magunesiumu touyo ni yori kou kariumu kessyou to kin kintyou teika wo kitashita soutai [Twins with hyperkalemia and hypotonia born from mother with administration of magnesium sulfate during pregnancy] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **44**, 654 (2008).
6. Yokozeki, Y. *et al*. Seigo 24 jikan de genin fumei no kou kariumu kessyou wo kitashita 2 syourei [A twin with hyperkalemia with unknown cause within 24 hours after birth] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **45**, 426 (2009).
7. Suzuki, M., Yoshio, H., Masaki, H., Yoshinare, R. & Ito, S. Botai ni ensan ritodorin to ryuusan maguneshiumu touyo ni yori kou kariumu kessyou wo kitashita 2 syourei [Two neonates with hyperkalemia born from mother with administration of both ritodrine hydrochloride and magnesium sulfate] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **21**, 727 (2009).
8. Yokota, S. *et al*. Botai he no ensan ritodorin to ryuusan magunesiumu no eikyou ni yori, kou K kessyou, shinshitsu sei hinpaku (VT) wo teishita shinseiji no 1 rei [Hyperkalemia followed by ventricular tachycardia affected by the administration of both ritodrine hydrochloride and magnesium sulfate to her mother] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **22**, 684 (2010).
9. Taniguchi, H. *et al*. Kou magunesiumu kessyou ni tomonai ikkasei kou kariumu kessyou wo teishita DD soutai rei [Transient hyperkalemia with hypermagnesemia in dichorionic diamniotic twins] [abstract] [in Japanese]. *Acta paediatrica Japonica.* **114**, 1949 (2010).
10. Uchida, N. *et al*. Kou maguneshiumu kessyou ni tomonau hi bounyou sei kou kariumu kessyou wo kurikaeshita souzan ji rei [Late preterm infant with repeated non-oligouretic hyperkalemia associated with hypermagnesemia] [in Japanese]. *Japanese Journal of Pediatrics.* **64**, 133–136 (2011).
11. Kaneko, T., Kobayashi, R., Usuda, T. & Wada, M. Kou kariumu (K) kessyou, shinshitsu hinpaku (VT) wo hassyoushita seikisan ji no ichi rei [Hyperkalemia followed by ventricular tachycardia in term neonate: a case report] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **48**, 467 (2012).
12. Nabeshima, K., Shigehara, K., Furukawa, N. & Tokuda, S. Kou K kesshou to RAA kei no koushin wo mitometa long-term tocolysis go no late preterm ji 2 rei [Two late preterm infants with hyperkalemia, increased levels of plasma renin and serum aldosterone born from mother with long-term tocolysis with both ritodrine hydrochloride and magnesium sulfate] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **48**, 516 (2012).
13. Tanaka, K. *et al*. Kou maguneshiumu kessyou ni tomonai syussei tyokugo kara kou kariumu kessyou wo hassyoushita goku teisyussyou taijuu ji no 1 rei [A very low birth weight infant with hyperkalemia just after birth accompanied by hypermagnesemia: a case report] [abstract] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **25**, 514 (2013).
14. Aoki, K., Matsuuchi, S. & Akaba, K. Souzan ji ni okeru botai ryuusan maguneshiumu shiyou to shinseiji kou kariumu kessyou tono kankei [Effects of antenatal magnesium sulfate on early neonatal hyperkalemia in preterm infants] [in Japanese]. *J. Jpn. Soc. Perin. Neon. Med.* **54**, 1037–1042 (2018).
15. Tanaka, K. *et al*. Early-onset neonatal hyperkalemia associated with maternal hypermagnesemia: a case report. *BMC Pediatr.* **18**, 55 (2018).
16. FDA Drug Safety Communication: New warnings against use of terbutaline to treat preterm labor. https://www.fda.gov/Drugs/DrugSafety/ucm243539.htm (2011).
17. FDA Drug Safety Communication: FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies. https://www.fda.gov/Drugs/DrugSafety/ucm353333.htm (2013).
18. Restrictions on use of short-acting beta-agonists in obstetric indications – CMDh endorses PRAC recommendations. https://www.ema.europa.eu/news/restrictions-use-short-acting-beta-agonists-obstetric-indications-cmdh-endorses-prac-recommendations (2013).
19. Oushu ni okeru tanjikan sayou gata beta shigeki yaku ni taisuru sochi oyobi nihon ni okeru utemerin (tyuu, jou) no yuukousei, anzensei ni tsuite [A review of EU restrictions on short-acting beta-agonists, and guidelines regarding efficacy and safety of ritodrine hydrochloride (injection and tablet) in Japan] [in Japanese]. http://di.kissei.co.jp/vcms_lf/re247001.pdf (2014).
20. Minakami, H. *et al*. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2014 edition. *J. Obstet. Gynaecol. Res.* **40**, 1469–1499 (2014).
21. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2017 edition [in Japanese]. http://www.jsog.or.jp/activity/pdf/gl_sanka_2017.pdf (2017).
22. Takagi, K. & Satoh, T. Is long-term tocolysis effective for threatened premature labour? *J. Int. Med. Res.* **37**, 227–239 (2009). Multicentre Premature Labour Study Group.
23. Witlin, A. G. & Sibai, B. M. Magnesium sulfate therapy in preeclampsia and eclampsia. *Obstet. Gynecol.* **92**, 883–889 (1998).
24. Magsent Injection Syringe 40 mL [Package insert]. https://pins.japic.or.jp/pdf/newPINS/00051281.pdf (2014).
25. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. *Obstet. Gynecol.* **128**, e155–e164 (2016).
26. Shinohara, S., Sunami, R., Uchida, Y., Hirata, S. & Suzuki, K. Association between total dose of ritodrine hydrochloride and pulmonary oedema in twin pregnancy: a retrospective cohort study in Japan. *BMJ Open.* **7**, e018118 (2017).

27. Nakamura, M. *et al*. Comparison of perinatal outcomes between long-term and short-term use of tocolytic agent: a historical cohort study in a single perinatal hospital. *J. Obstet. Gynaecol. Res.* **42**, 1680–1685 (2016).
28. Dudley, D., Gagnon, D. & Varner, M. Long-term tocolysis with intravenous magnesium sulfate. *Obstet. Gynecol.* **73**, 373–378 (1989).
29. Kawagoe, Y., Sameshima, H., Ikenoue, T., Yasuhi, I. & Kawarabayashi, T. Magnesium sulfate as a second-line tocolytic agent for preterm labor: a randomized controlled trial in Kyushu Island. *J. Pregnancy.* **2011**, 965060 (2011).
30. Utemerin injection 50 mg [Package insert]. https://di.kissei.co.jp/dst01/pdf/di_uti19.pdf (2019).
31. Emder, P. & Crawford, G. Ventricular tachycardia in a neonate secondary to hyperkalaemia. *Aust. Paediatr. J.* **19**, 112–113 (1983).
32. Bara, M., Guiet-Bara, A. & Durlach, J. Regulation of sodium and potassium pathways by magnesium in cell membranes. *Magnes. Res.* **6**, 167–177 (1993).
33. Mahajan, G., Mukhopadhyay, K., Attri, S. & Kumar, P. Neurodevelopmental outcome of asymptomatic hypoglycemia compared with symptomatic hypoglycemia and euglycemia in high-risk neonates. *Pediatr. Neurol.* **74**, 74–79 (2017).
34. McIntyre, S. *et al*. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. *Dev. Med. Child. Neurol.* **55**, 499–508 (2013).
35. Montassir, H. *et al*. Associated factors in neonatal hypoglycemic brain injury. *Brain Dev.* **31**, 649–656 (2009).
36. Seltzer, H. S. Drug-induced hypoglycemia. A review of 1418 cases. *Endocrinol. Metab. Clin. North. Am.* **18**, 163–183 (1989).
37. Musci, M. N. Jr., Abbasi, S., Otis, C. & Bolognese, R. J. Prolonged fetal ritodrine exposure and immediate neonatal outcome. *J. Perinatol.* **8**, 27–32 (1988).
38. Trønnes, H., Wilcox, A. J., Lie, R. T., Markestad, T. & Moster, D. Risk of cerebral palsy in relation to pregnancy disorders and preterm birth: a national cohort study. *Dev. Med. Child. Neurol.* **56**, 779–785 (2014).
39. Ellenberg, J. H. & Nelson, K. B. The association of cerebral palsy with birth asphyxia: a definitional quagmire. *Dev. Med. Child. Neurol.* **55**, 210–216 (2013).
40. Phelan, J. P., Korst, L. M. & Martin, G. I. Application of criteria developed by the Task Force on Neonatal Encephalopathy and Cerebral Palsy to acutely asphyxiated neonates. *Obstet. Gynecol.* **118**, 824–830 (2011).
41. May, T., Adesina, I., McGillivray, J. & Rinehart, N. J. Sex differences in neurodevelopmental disorders. *Curr. Opin. Neurol.* **32**, 622–626 (2019).
42. May, T., Sciberras, E., Brignell, A. & Williams, K. Autism spectrum disorder: updated prevalence and comparison of two birth cohorts in a nationally representative Australian sample. *BMJ Open.* **7**, e015549 (2017).
43. Wang, T. *et al*. Prevalence of attention deficit/hyperactivity disorder among children and adolescents in China: a systematic review and meta-analysis. *BMC Psychiatry.* **17**, 32 (2017).
44. Linsell, L., Malouf, R., Morris, J., Kurinczuk, J. J. & Marlow, N. Prognostic factors for cerebral palsy and motor impairment in children born very preterm or very low birthweight: a systematic review. *Dev. Med. Child. Neurol.* **58**, 554–569 (2016).
45. Zhao, M., Dai, H., Deng, Y. & Zhao, L. SGA as a risk factor for cerebral palsy in moderate to late preterm infants: a system review and meta-analysis. *Sci. Rep.* **6**, 38853 (2016).
46. Lampi, K. M. *et al*. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. *J. Pediatr.* **161**, 830–836 (2012).
47. Heinonen, K. *et al*. Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: a longitudinal study. *BMC Pediatr.* **10**, 91 (2010).
48. Takeda, S. *et al*. Houkoku: Syuusanki iinkai [Annual Report: Perinatal Medicine Committee] [in Japanese]. *Acta Obstet. Gynaecol. Jpn.* **68**, 1381–1403 (2016).
49. Committee on Fetus and Newborn. Adamkin D.H. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* **127**, 575–579 (2011).
50. Vemgal P., Ohlsson A. Interventions for non-oliguric hyperkalaemia in preterm neonates. *Cochrane Database Syst. Rev.* (**1**), CD005257 (2007).
51. Ishii, N., Kono, Y., Yonemoto, N., Kusuda, S. & Fujimura, M. Neonatal Research Network, Japan. Outcomes of infants born at 22 and 23 weeks' gestation. *Pediatrics.* **132**, 62–71 (2013).
52. Itabashi, K. *et al*. Atarashii zaitai kikan betsu shussei ji taikaku hyoujun ti no dounyuu ni tsuite [Introduction of new gestational age-specific standards for birth size] [in Japanese]. *Acta paediatrica Japonica.* **114**, 1271–1293 (2010).
53. Kanda, Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* **48**, 452–458 (2013).

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Author contributions

Yukari Yada (Y.Y.), Akihide Ohkuchi (A.O.), Katsufumi Otsuki (K.O.), Keiji Goishi (K.G.), Mari Takahashi (M.T.), Naohiro Yonemoto (N.Y.), Shigeru Saito (S.S.), and Satoshi Kusuda (S.K.) are main authors. A.O. wrote the main manuscript text and prepared figure and all tables. Y.Y., A.O., K.O., K.G., M.T., S.S., and S.K. designed this study. Y.Y., A.O., K.O., K.G., M.T., S.S., and all researchers listed in Consortia: Authors' list for the Survey Group Studying the Effects of Tocolytic Agents on Neonatal Adverse Events in Japan Society of Perinatal and Neonatal Medicine contributed acquisition of data. Y.Y., A.O., K.O., K.G., S.S., and S.K. firstly performed statistical analyses, N.Y. secondly checked the statistical results in view of a professional statistician, and A.O. performed the final statistical analysis using IBM SPSS Statistics version 25 and EZR version 1.37. All main authors assisted with analysis, and interpretation of data. All main authors reviewed the manuscript, and had an important role on critical revision of the manuscript. S.K. supervised this study.

Competing interests

The authors declare no competing interests.

Additional information

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