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Prostaglandins in biofluids in pregnancy and labour: A systematic review

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Abstract

Prostaglandins are thought to be important mediators in the initiation of human labour, however the evidence supporting this is not entirely clear. Determining how, and which, prostaglandins change during pregnancy and labour may provide insight into mechanisms governing labour initiation and the potential to predict timing of labour onset. The current study systematically searched the existing scientific literature to determine how biofluid levels of prostaglandins change throughout pregnancy before and during labour, and whether prostaglandins and/or their metabolites may be useful for prediction of labour. The databases EMBASE and MEDLINE were searched for English-language articles on prostaglandins measured in plasma, serum, amniotic fluid, or urine during pregnancy and/or spontaneous labour. Studies were assessed for quality and risk of bias and a qualitative summary of included studies was generated. Our review identified 83 studies published between 1968–2021 that met the inclusion criteria. As measured in amniotic fluid, levels of PGE_2, along with $PGF_{2\alpha}$ and its metabolite 13,14-dihydro-15-keto-$PGF_{2\alpha}$ were reported higher in labour compared to non-labour. In blood, only 13,14-dihydro-15-keto-$PGF_{2\alpha}$ was reported higher in labour. Additionally, $PGF_{2\alpha}$, $PGF_{1\alpha}$, and PGE_2 were reported to increase in amniotic fluid as pregnancy progressed, though this pattern was not consistent in plasma. Overall, the evidence supporting changes in prostaglandin levels in these biofluids remains unclear. An important limitation is the lack of data on the complexity of the prostaglandin pathway outside of the PGE and PGF families. Future studies using new methodologies capable of co-assessing multiple prostaglandins and metabolites, in large, well-defined populations, will help provide more insight as to the identification of exactly which prostaglandins and/or metabolites consistently change with labour. Revisiting and revising our understanding of the prostaglandins may provide better targets for clinical monitoring of pregnancies. This study was supported by the Canadian Institutes of Health Research.

Introduction

It is widely believed that prostaglandins are important in the initiation of human labour [1]. Multiple studies have documented increased expression of cyclooxygenases, key enzymes in

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prostaglandin synthesis, in gestational tissues with the onset of labour, however, this has not been consistently observed [2]. Additionally, prostaglandins are present in maternal blood, urine, and amniotic fluid during pregnancy [3], however, the evidence supporting or refuting their role in labour is conflicting. Prostaglandins are known to affect uterine contractility and cervical ripening [4] and have thus been successfully used for labour induction since the late 1960's, though the use of prostaglandin synthesis inhibitors for prevention of preterm birth has been minimally successful and is associated with various fetal side effects [5]. Since their discovery in the 1930s, prostaglandins and their synthesis and metabolism are now known to be highly complex, which may contribute to these inconsistent outcomes seen during clinical targeting of this pathway. Aside from providing insight into labour processes, the presence of prostaglandins in peripheral tissues offers the potential for minimally invasive early prediction of labour onset and the ability to distinguish between true and false labour, which remains an ongoing clinical challenge [6]. Additionally, it has been suggested that biomarkers predictive of term labour (>37 weeks gestation) may also be useful for prediction of preterm labour (<37 weeks gestation), as both processes share common physiological changes involving cervical ripening, uterine contractions, and membrane rupture [7]. In 2010, preterm birth was estimated to occur in approximately 11% of all pregnancies and remains the leading cause of neonatal mortality worldwide [8], yet there is a lack of objective measures available to assess risk of premature delivery. Accurate prediction of term and preterm labour would allow for more informed patient planning and more efficient use of healthcare resources, for example, by reducing unnecessary hospitalizations and interventions. Despite evidence to suggest a role for prostaglandins in pregnancy and labour, literature defining the complexities of the pathway remain inconclusive and inconsistent. Therefore, we have systematically reviewed the scientific literature with the aim of answering three main questions to find evidence that either supports or refutes a role for prostaglandins in the initiation of labour: 1) Are prostaglandins or their metabolites detectable in biofluids in higher amounts in labour vs not in labour? 2) Are prostaglandins or their metabolites detected in increasing amounts prior to the onset of labour? And 3) Are prostaglandins or their metabolites present in urine, blood, or amniotic fluid predictive of preterm labour?

Methods

This systematic review was conducted and reported following the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). The protocol is available upon request. This review was not registered.

Information sources

The databases MEDLINE and EMBASE were searched for records. Additionally, the reference lists of eligible studies and relevant review articles were manually searched.

Search strategy

The search strategy included the key words "prostaglandins" AND "obstetric labor" AND ("amniotic fluid" OR "blood" OR "urine") as well as synonyms, related alternatives, and Medical Subject Heading (MeSH) terms as relevant. The searches were limited to human studies. Full details of the search terms for each database are given in S1 and S2 Tables. Citations retrieved from the initial search were downloaded into a reference manager (EndNote X9) and duplicates were removed. Two reviewers (EW and SLW) independently reviewed abstracts and removed those not relevant to the research questions. Following retrieval of full-text articles, both reviewers assessed the remaining citations against the eligibility criteria. Studies

excluded at this level were sorted based on reason for exclusion. Disagreements were resolved by discussion until consensus was reached.

Inclusion/Exclusion criteria

Primary study journal articles examining endogenous prostaglandins in blood, amniotic fluid, and/or urine during pregnancy and spontaneous labour were included in this review. Studies were excluded if the study was on animals, the study was examining exogenous prostaglandins for induction of labour or if participants experienced spontaneous abortion (prior to 20 weeks). As well, studies which only had samples collected following delivery were excluded. Publications with incomplete information (i.e., conference abstracts) were excluded. Only studies written in English or with an available English translation were included. The search did not include a time restriction, however, the databases MEDLINE and EMBASE include literature published since 1946 and 1947 respectively. The search was initially conducted on May 19, 2020 and was repeated on August 20, 2021.

Selection process/Data extraction

The following information was extracted by one reviewer (EW) from each of the final selected studies: population examined, sample number, type of biofluid collected, method of testing and measurement, metabolites/prostaglandins measured, time of sample collection, country of study origin, available measures of central tendency and variance, and major findings of the study.

Quality assessment

Studies were assessed for quality and risk of bias using a quality assessment tool (Table 1) adapted from Hadley et al. [9] for assessment of basic science research. Full details of the rubric can be found in Table 1. Studies were scored between 0–9. All studies were scored independently by two investigators (EW and KH) and disagreements in scores were resolved by discussion.

Table 1. Quality assessment rubric.

Quality assessment	1 point	0 points	N/A
1) Question/objective sufficiently described?	Primary study question or objective is clearly stated	Unclear question/objective or no question/objective	
2) Design appropriate to answer study question?	Study design is clearly stated and makes sense according to the study question/objective	E.g. uses convenient samples or study does not give enough information to determine study design	
3) Methods described in sufficient detail to allow for study to be replicated?	Samples, reagents, assay used to measure prostaglandins are sufficiently described, methods for sample collection are clearly described	Some information missing or no information/ insufficient information is given on samples, reagents, assays, methods for sample collection	
4) Researchers used blinding?	Yes	No	
5) Sample number sufficient for internal validity?	Study has pre-planned sample size and/or power analysis or confidence intervals suggest sufficient sample size	No power analysis or confidence intervals suggest insufficient sample size	
6) Appropriate negative controls?	Control group is appropriate to answer study question	Controls are from a clearly different population	
7) Appropriate statistical analysis?	There is a comparison of means with appropriate transformations of data	No statistical analysis provided	
8) Results reported in sufficient detail?	Results match methods i.e. all prostaglandins measured are reported on	Some measurements missing from results	
9) Do the results support the conclusion?	Conclusion makes sense given results and answers primary study question/objective	Conclusion is overstated based on results or not related to main study question and main results	

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Data synthesis

A qualitative summary was generated, and tables were created with the main results from each study. No pooled analysis was performed.

Results

Studies identified

The electronic search returned 2257 unique records after removal of duplicates from 2688 records. 2101 records were removed at the title/abstract level, leaving 156 records for assessment at the full-text level. Hand search of reference lists yielded an additional 35 records for review, resulting in a total of 191 full text records. Of the records assessed at the full text level, 108 were excluded, leaving n = 83 studies for inclusion in this review (Fig 1).

Main characteristics of studies

Summaries of the main characteristics and relevant findings of the included studies can be found in Table 2 (presented in chronological order). Of the 83 studies, most assessed only one

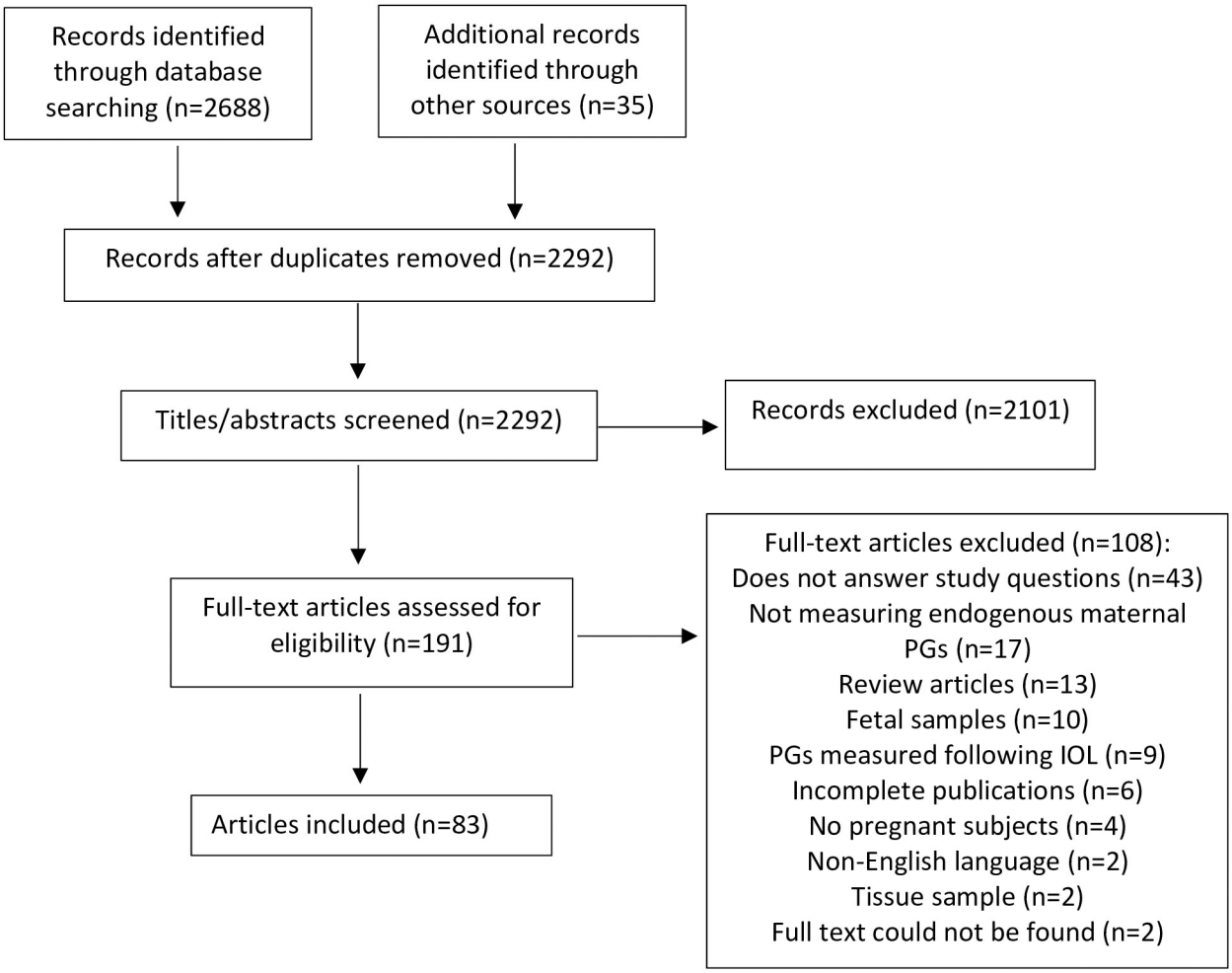

Fig 1. PRISMA diagram. Abbreviations: PG = prostaglandin, IOL = induction of labour.

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Table 2. Main characteristics of studies.

Study	Method	Sample Size	Biofluid	PG/Metabolite	Relevant Findings
Karim 1968 [10]	TLC and biological assay	n = 42 NL, n = 10 TL	plasma	$PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_1, PGE_2	NL < LOD
				$PGF_{2\alpha}$	higher at delivery than 1st stage labour
Brummer 1972 [11]	RIA	n = 40 NL, n = 46 L	serum	$PGF_{2\alpha}$	L>TNL
					late pregnancy similar to nonpregnant
					increased through 1st stage labour (early-late), then decreased in 2nd stage
Gutierrez-Cernosek & Levine 1972 [12]	RIA	n = 10 1st TM	serum	$PGF_{2\alpha}$	peaked at 2nd TM, decreased to nonpregnant levels at term
		n = 52 2nd TM			
		n = 54 3rd TM			
		n = 9 serial (14-40wks)			
Brummer 1973 [13]	unknown	n = 13 1st TM	serum	$PGF_{2\alpha}$	decreased in 2nd TM, plateaued in 3rd TM
		n = 40 2nd TM			
		n = 75 3rd TM			
Brummer & Craft 1973 [14]	RIA	n = 58 L	serum	$PGF_{2\alpha}$	highest in 1st stage labour, decreased in 2nd stage and remained low
		n = 7 serial L			
Hertelendy et al 1973 [15]	RIA	n = 8 PTNL	plasma	PGE	<32wks pregnant similar to nonpregnant
		n = 32 L			increased through 1st stage labour (early-late), then decreased in 2nd stage
Keirse & Turnbull 1973 [16]	GC	n = 12 TNL, n = 38 TL	AF	PGE_2	TL>TNL
					increased through 1st stage labour
				PGE_1	<LOD
Salmon & Army 1973 [17]	RIA	n = 57	AF	$PGF_{2\alpha}$	L>TNL
					constant through 2nd and 3rd TM, rise after 36wks
					spike during 1st stage labour
Challis et al 1974 [18]	RIA	n = 4 TNL, n = 9 TL	plasma	PGF	TL>TNL (nonsignificant)
Green et al 1974 [19]	GC-MS	n = 2 TL	plasma	$PGF_{2\alpha}$	no correlation with stage of labour
		n = 5 term serial		PGFM	TL>TNL
					increased through 1st stage labour
Hamberg 1974 [20]	RIA?	n = 3 serial (9-40wks)	urine	t-PGFM	increased with GA, peaked at term
		n = 8 TNL, n = 1TL			TL>TNL
Hennam et al 1974 [21]	RIA	n = 13 1st TM	plasma	$PGF_{2\alpha}$	levels lowest at 2nd TM compared to 1st and 3rd
		n = 10 2nd TM			L>3rd TM
		n = 20 3rd TM			
		n = 99 L			
Hibbard et al 1974 [22]	RIA	n = 42 TNL, n = 13 TL	AF	$PGF_{2\alpha}$	TL>TNL
					increased with GA after 36 weeks
		n = 22 PTNL			64% <LOD
Hillier et al 1974 [23]	RIA	n = 11 TNL, n = 5 TL	AF	$PGF_{2\alpha}$	TL>TNL
					increased with labour stage
			plasma		no correlation with labour stage

(*Continued*)

Table 2. (Continued)

Study	Method	Sample Size	Biofluid	PG/Metabolite	Relevant Findings
Keirse et al 1974 [24]	RIA and GC	n = 20 TNL, n = 26 TL	AF	PGF	TL>TNL
		n = 8 PTNL			TNL>PTNL
					increased through 1st stage labour
MacDonald et al 1974 [25]	RIA	n = 6 NL, n = 6 L	AF	$PGF_{2\alpha}$	L>NL
Singh & Zuspan 1974 [26]	PC and TD	n = 6	AF	$PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_1, PGE_2	constant from 24-36wks, increase in labour
Hillier et al 1975 [27]	RIA	n = 13 TNL, n =? TL	AF	PGF	increased with labour stage, peaked before delivery
		n = 8 PTNL			increased from 2nd TM to term
Johnson et al 1975 [28]	RIA	n = 38 NL, n = 8 L	AF	$PGF_{2\alpha}$	L>NL
		n = 11 PTNL			3rd TM > 2nd TM
		n = 33 NL, n = 99 L	plasma		no difference between NL and L
		n = 15 PTNL			no pattern with labour
Pokoly & Jordan 1975 [29]	RIA	n = 6 TNL, n = 2 TL (CS)	AF	PGF	TL>TNL for CS only
		n = 4 TNL, n = 13 TL	plasma		no difference between NL and L
			AF	PGE	TL>TNL (nonsignificant)
			plasma		no difference between NL and L
Dray & Frydman 1976 [30]	RIA	n = 24 NL, n = 37 L	AF	$PGF_{2\alpha}$	L>NL
		n = 19 PTNL			higher in late 3rd TM than early 3rd TM
					increased with labour stage
				PGE_2	L>TNL
					<LOD before 24wks, increased to 36wks, then remained constant to term
					increased with labour stage
				PGE_1	<LOD
Granstrom & Kindahl 1976 [31]	RIA	n = 1 term serial	urine	t-PGFM	TL>TNL
					late 3rd TM > nonpregnant
Keirse et al 1977 [32]	RIA	n = 40 TNL, n = 46 TL	AF	PGF, PGFM	TL>TNL
					increased through 1st stage labour
Kinoshita et al 1977 [33]	RIA	n = 7 TNL, n = 10 TL	AF	$PGF_{2\alpha}$	TL>TNL
				PGE_1	no difference between TNL and TL
		n = 10 TL, n = 10 TNL	plasma	$PGF_{2\alpha}$	no difference between TNL and TL
		n = 10 3rd TM serial			no pattern with gestation in 3rd TM
				PGE_1	no difference between TNL and TL
					no pattern with gestation in 3rd TM
					no correlation with labour stage
TambyRaja et al 1977 [34]	RIA	n = 27 PTL	AF	$PGF_{2\alpha}$	increased through 1st stage labour
Haning et al 1978 [35]	RIA	n = 4 TNL, n = 8 TL	plasma	PGFM	TL>TNL
Mitchell et al 1978 [36]	RIA	n = 13 NL, n = 10 L	plasma	PGF, PGE	L > NL
		n = 7 PTL			no correlation with stage of labour
				PGFM	L > NL
					no difference with PTL and NL
					increased with labour stage

(*Continued*)

Table 2. (Continued)

Study	Method	Sample Size	Biofluid	PG/Metabolite	Relevant Findings
Nieder & Augustin 1978 [37]	RIA	n = 34	AF	$PGF_{2\alpha}$, PGE	increased from 31wks to term, steeper after 36wks
			plasma		no correlation with GA
Zuckerman et al 1978 [38]	RIA	n = 5 L	plasma	$PGF_{2\alpha}$	lower in 1st stage labour than 2nd or 3rd
					peaked at delivery and at placental separation
Ghodaonkar et al 1979 [39]	RIA	n = 2 serial (20-40wks)	plasma	PGFM	no pattern with gestation
		n = 14 TL			increased in 2nd and 3rd stages of labour
Mitchell et al 1979 [40]	RIA	n = 24 NL, n = 31 TL	AF	6-keto-PGF_{1a}	TL>TNL
					no correlation with GA or cervical dilation
Satoh et al 1979 [41]	RIA	n = 17 serial (8-39wks)	AF	PGFM	TL>TNL
					no pattern with gestation in 3rd TM
		n = 8 TNL, n = 10 TL	plasma		TL>TNL
		n = 53 PTNL			no correlation with GA
					increased with labour stage, peaked at delivery
		n = 30 3rd TM serial	urine	t-PGFM	L>NL
Lewis et al 1980 [42]	GC-MS	n = 6 1st TM	plasma	6-keto-PGF_{1a}	2nd-3rd TM > nonpregnant
		n = 9 2nd-3rd TM			
Dubin et al 1981 [43]	RIA	n = 39 serial (16-40wks)	plasma	PGFM	TL>TNL
		n = 17 PTD			no correlation with GA
Sellers et al 1981 [44]	RIA	n = 13 TNL, n = 21 TL	plasma	PGFM	TL>TNL
		n = 12 PTNL, n = 22 PTL			PTL>PTNL
					no difference between PTNL and PTL
					no difference between PTL who delivered term and preterm
					increased with labour stage in PTL and TL
Ylikorkala et al 1981 [45]	RIA	n = 9 serial	plasma	6-keto-PGF_{1a}	TL>TNL
					increased with labour stage
Fuchs et al 1982 [46]	RIA	n = 14 TNL, n = 20 TL	plasma	PGFM	TL>TNL
Fuchs et al 1982 [47]	RIA	n = 10 TNL, n = 14 TL	plasma	PGFM	TNL>PTNL
		n = 10 PTNL, n = 15 PTL			PTL>PTNL
Mitchell et al 1982 [48]	RIA	n = 10 TNL, n = 10 TL	plasma	bicyclo-PGEM	TL>TNL
		n = 10 1st TM			1st TM > nonpregnant
		n = 10 2nd TM			decreased in 3rd TM until labour
		n = 10 3rd TM			
Sellers et al 1982 [49]	RIA	n = 10 TL	plasma	PGFM	increased with labour stage, peaked 5min after delivery
Sharma et al 1982 [50]	RIA	n = 92 NL, n = 6 TL	plasma	$PGF_{2\alpha}$	TL>NL
					remained unchanged until 2wks before delivery, then increased
				PGE_2	no difference between TL and NL
					remained unchanged until 2wks before delivery, then increased

(*Continued*)

Table 2. (Continued)

Study	Method	Sample Size	Biofluid	PG/Metabolite	Relevant Findings
Fuchs et al 1983 [51]	RIA?	n = 4 TNL, n = 17 L	plasma	PGFM	TL>TNL
					increased with labour stage
Nieder & Augustin 1983 [52]	RIA	n = 23 1st TM	AF	PGF, PGE	unchanged from 9-34wks, increase at 35wks
		n = 37 2nd TM			
		n = 103 3rd TM			
Spitz et al 1983 [53]	RIA	n = 12 serial (10-40wks)	plasma	6-keto-PGF_{1a}	decrease after 33wks
Husslein & Sinzinger 1984 [54]	RIA	n = 5 TNL, n = 5 TL	plasma	PGEM	TL>TNL
		n = 5 PTNL			no correlation with labour stage
Nagata et al 1984 [55]	RIA	n = 6 term serial	plasma	$PGF_{2\alpha}$	TL>TNL
				PGE_1, PGE_2	no difference between NL and L
					no correlation with labour stage
Reddi et al 1984 [56]	RIA	n = 10 TL	AF	PGF, PGFM	increased through 1st stage labour
Sellers et al 1984 [57]	RIA	n = 14 TNL, n = 9 TL	plasma	PGFM	TL>TNL
Yamaguchi & Mori 1984 [58]	RIA	n = 4 <20wks	plasma	PGFM	L>NL
		n = 3 20-30wks			no correlation with GA
		n = 16 30-40wks		6-keto-PGF_{1a}	L>NL (nonsignificant)
Brennecke et al 1985 [59]	RIA	n = 9 TNL, n = 27 TL	plasma	PGFM	TL>TNL
		n = 12 serial			increased with labour stage
				bicyclo-PGEM	no difference between TNL and TL
					no correlation with GA or labour stage
Ogino & Jimbo 1986 [60]	RIA	n = 5 24-28wks	plasma	$PGF_{2\alpha}$	peak at 32-36wks
		n = 4 28-32wks		PGE_2	lowest at 36-40wks
		n = 7 32-36wks			
		n = 8 36-40wks			
Weitz et al 1986 [61]	RIA	n = 6 PTL-TD	plasma	PGFM	PTL>PTNL
		n = 14 PTL-PTD			higher in PTL who delivered PT than those who delivered term
		n = 11 PTNL			
Ylikorkala et al 1986 [62]	RIA	n = 8 TNL, n = 13 TL	urine	6-keto-PGF_{1a}	increased with labour stage and with C-section
Berryman et al 1987 [63]	RIA	n = 23 L	AF	PGD_2	increased through 1st stage labour
Nagata et al 1987 [64]	RIA	n = 9 TL	plasma	PGFM	increased with labour stage (nonsignificant)
				PGE_1	low throughout labour
Nagata et al 1987 [65]	RIA	n = 7 serial	plasma	PGFM	TL>TNL
					decreased 2wks prior to labour
					increased with labour stage
Romero et al 1987 [66]	RIA	n = 23 PTNL, n = 30 PTL	AF	$PGF_{2\alpha}$, PGE_2	PTL>PTNL
Noort et al 1988 [67]	RIA	n = 12 1st TM	urine	6-keto-PGF_{1a}	L>NL (nonsignificant)
		n = 12 2nd TM			
		n = 12 3rd TM			
		n = 12 TL			
Romero et al 1988 [68]	RIA	n = 32 PTL-TD n = 22 PTL-PTD	AF	PGE_2	higher in PTL who did not respond to tocolysis than those who responded to tocolysis

(*Continued*)

Table 2. (Continued)

Study	Method	Sample Size	Biofluid	PG/Metabolite	Relevant Findings
Sahmay et al 1988 [69]	RIA	n = 8 TNL, n = 9 TL	AF	$PGF_{2\alpha}$	no difference between TNL and TL
			plasma		TL>TNL
			AF	PGE	no difference between TNL and TL
			plasma		TNL>TL
Noort et al 1989 [70]	RIA	n = 7 TL	plasma	PGFM	increased with labour stage
				6-keto-PGF1a	no correlation with labour stage
Romero et al 1989 [71]	RIA	n = 25 PTL-TD	AF	$PGF_{2\alpha}$	no difference between PTL who delivered term and preterm
		n = 16 PTL-PTD		PGFM, bicyclo-PGEM	higher in PTL who delivered PT than those who responded to tocolysis
Yamamoto & Kitao 1989 [72]	RIA	n = 76 term serial	plasma	$PGF_{2\alpha}$	TL>TNL
					increased with labour stage and delivery
Mazor et al 1990 [73]	RIA	n = 10 PTL-TD	AF	$PGF_{2\alpha}$	no difference between PTL who delivered term and preterm
		n = 10 PTL-PTD		PGE_2	higher in PTL who delivered PT than those who delivered at term
Norman & Reddi 1990 [74]	RIA	n = 54 TL	AF	$PGF_{2\alpha}$, PGFM, PGE_2	increased through 1st stage labour
Fairlie et al 1993 [75]	RIA	n = 20 TL	plasma	PGFM	increased with labour stage
				bicyclo-PGEM	in nulliparous: rose after amniotomy but did not change with labour
					in multiparous: rose with amniotomy then increased with labour stage
Hillier et al 1993 [76]	RIA	n = 50 PTL	AF	PGE_2	high levels associated with PTD and delivery within 1wk of amniocentesis
Johnston et al 1993 [77]	RIA	n = 18 TNL, n = 28 TL	plasma	PGFM	TL>TNL
					rose following amniotomy, then remained constant until delivery
				PGEM	TL>TNL only in primigravid
					rose 1–2 after amniotomy, then remained constant until delivery
MacDonald & Casey 1993 [78]	RIA	n = 50 TNL, n = 190 TL	AF	$PGF_{2\alpha}$	TL>TNL (forebag and upper compartment)
					increased with labour stage, then decreased at 3-5cm dilation
				PGFM	TL>TNL (forebag and upper compartment)
					increased with labour stage, then leveled out at 4–5.5cm dilation until delivery
				PGE_2	TL>TNL (forebag)
					no difference between TL and TNL in upper compartment
					increased with labour stage, then leveled out at 4–5.5cm dilation until delivery
Romero et al 1993 [79]	RIA	n = 24 NL, n = 16 TL	AF	$PGF_{2\alpha}$, PGFM, PGE_2, 6-keto-$PGF_{1\alpha}$	TL>NL
Romero et al 1994 [80]	RIA	n = 82 TNL, n = 168 TL	AF	$PGF_{2\alpha}$, PGFM, PGE_2, 6-keto-$PGF_{1\alpha}$	TL>TNL
					increased through 1st stage labour
Lindsay et al 1995 [81]	ELISA	n = 8 serial (1st-3rd TM)	urine	2,3-dinor-6-keto-$PGF_{1\alpha}$	no correlation with GA
					pregnant >> nonpregnant

(*Continued*)

Table 2. (Continued)

Study	Method	Sample Size	Biofluid	PG/Metabolite	Relevant Findings
Romero et al 1996 [82]	RIA	n = 28 serial (n = 17 L)	AF	$PGF_{2\alpha}$, PGE_2	TL>TNL
					increased with GA at term
Ichikawa & Minami 1999 [83]	RIA	n = 30 serial	urine	$PGF_{2\alpha}$	TL>NL
					increased from 28-36wks
				PGFM	TL>NL
					increased from 28-36wks and again at 2nd stage of labour
Mitchell et al 2005 [84]	ELISA	n = 24 TNL, n = 37 TL	AF	9α,11β-PGF_2	TL>TNL
		n = 13 PTNL, n = 56 PTL			PTNL>PTL
Lee et al 2008 [85]	ELISA	n = 68 TNL, n = 34 TL	AF	$PGF_{2\alpha}$	TL>TNL
		n = 65 PTNL			no correlation with GA until 36wks, 25-fold increase at TNL
					increased with labour stage
				PGE_2	no difference between TL and TNL
					no correlation with GA until 36wks, 2-fold increase at TNL
Lee et al 2009 [86]	ELISA	n = 140 PPROM (n = 126 PTD)	AF	$PGF_{2\alpha}$	high levels associated with low GA at delivery and PTD
Maddipati et al 2014 [87]	LC-MS	n = 10 TNL, n = 35 TL	AF	$PGF_{2\alpha}$, PGFM, PGE_2, bicyclo-PGEM, PGA_2, PGJ_2	TL>TNL
		n = 18 PTNL			
				19-OH-PGE_2	no difference between TL and TNL
					TNL>PTNL
Park et al 2016 [88]	ELISA	n = 132 PTL (n = 41 PTD)	AF	$PGF_{2\alpha}$	high levels associated with low GA at delivery and PTD
Rosen et al 2019 [89]	GC-NICI-MS	n = 740 (n = 41 sPTD)	urine	$PGF_{2\alpha}$	no difference in 3rd TM levels between term and preterm delivery
Eick et al 2020 [90]	GC-NICI-MS	n = 469 (n = 50 PTD)	urine	$PGF_{2\alpha}$	levels at 20-24wks and 24-28wks higher in preterm than term group
					associated with increased odds of PTB
Peiris et al 2020 [91]	LC-MS	n = 10 TNL, n = 28 TL	AF	$PGF_{2\alpha}$, PGFM, PGE_2	TL>TNL
Takahashi et al 2021 [92]	LC-MS	n = 11 TNL, n = 10 TL	AF	PGE_2, 15-keto-PGE_2, PGEM, 19-OH-PGE_2	TL>TNL

Abbreviations: TLC = thin layer chromatography, NL = no labour, TL = term labour, LOD = limit of detection, RIA = radioimmunoassay, L = labour, TM = trimester, PTNL = preterm no labour, GC = gas chromatography, AF = amniotic fluid, TNL = term no labour, GC-MS = gas chromatography-mass spectrometry, PGFM = 13,14-dihydro-15-keto-$PGF_{2\alpha}$, t-PGFM = 5α,7α-dihydroxy 11-keto tetranor-prostane 1,16-dioic acid, GA = gestational age, PC = paper chromatography, TD = transmission densitometry, CS = Caesarean section, PTL = preterm labour, PTD = preterm delivery, bicyclo-PGEM = 11-deoxy-13,14-dihydro-15-keto-11,16-bicyclo PGE_2, PGEM = 13,14-dihydro-15-keto-PGE_2, PTL-TD = preterm labour-term delivery, PTL-PTD = preterm labour-preterm delivery, PT = preterm, ELISA = enzyme-linked immunosorbent assay, PPROM = preterm premature rupture of membranes, LC-MS = liquid chromatography-mass spectrometry, NICI = negative ion chemical ionization, sPTD = spontaneous preterm delivery.

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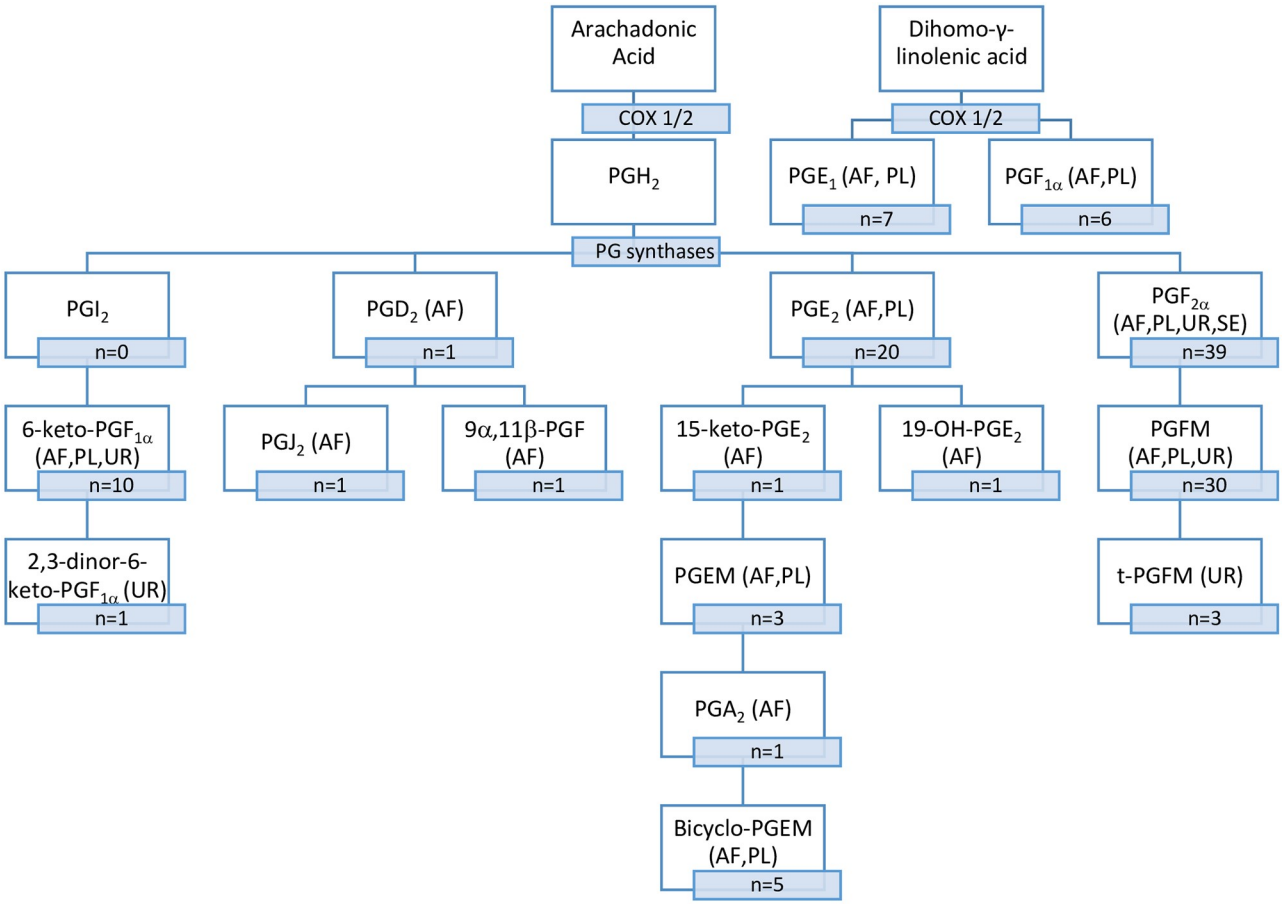

Fig 2. Prostaglandin metabolism pathway. n denotes the number of studies that measured the prostaglandin/metabolite. Abbreviations: AF = amniotic fluid, PL = plasma, UR = urine, SE = serum, COX 1/2 = cyclooxygenase 1/2, PGFM = 13,14-dihydro-15-keto-$PGF_{2\alpha}$, PGEM = 13,14-dihydro-15-keto-PGE_2, bicyclo-PGEM = 11-deoxy-13,14-dihydro-15-keto-11,16-bicyclo PGE_2, t-PGFM = 5α,7α-dihydroxy-11-keto tetranor-prostane-1,16-dioic acid.

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biofluid, (34 plasma, 32 amniotic fluid, 8 urine, 4 serum) while 6 studies assessed multiple biofluids. The range of prostaglandins and metabolites investigated included $PGF_{2\alpha}$, $PGF_{1\alpha}$, 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM), 5α,7α-dihydroxy-11-keto-tetranor-prostane-1,16-dioic acid (t-PGFM), PGE_1, PGE_2, 15-keto-PGE_2, 13,14-dihydro-15-keto-PGE_2 (PGEM), 11-deoxy-13,14-dihydro-15-keto-11,16-bicyclo-PGE_2 (bicyclo-PGEM), 6-keto-$PGF_{1\alpha}$, 2,3-dinor-6-keto-$PGF_{1\alpha}$, PGA_2, PGD_2, PGJ_2, 19-OH-PGE_2, and 9α,11β-PGF_2. Prostaglandins and the corresponding metabolites measured are described in Fig 2. In addition, many older studies used measurement techniques which were unable to differentiate between subcategories of prostaglandins and therefore reported levels of PGE or PGF. The range of prostaglandin concentrations reported using different measurement techniques are shown in Table 3.

Amniotic fluid

Labour and non-labour. In total, 25 studies compared amniotic fluid prostaglandins in labour vs non-labour. $PGF_{2\alpha}$ increased in labouring participants compared to non-labouring participants in most studies, (Table 2) however, one study found no difference [69]. Similarly, PGE_2 was reported to increase with labour in 11/12 studies [16, 26, 30, 66, 78–80, 82, 87, 91,

Table 3. Range of prostaglandin concentrations reported using different measurement techniques.

Biofluid	PG/Metabolite	Measurement Technique	Range
plasma	PGE	RIA	NL: 4.8 [36]–3641.2 [69] (pg/ml), L: 5.4 [36]–2429.1 [69] (pg/ml)
	PGF	RIA	NL: 6.2 [36]–480 [29] (pg/ml), L: 7.9 [36]–600 [29] (pg/ml)
	PGE_2	TLC and biological assay	NL: <200 pg/ml [10]
		RIA	NL: 4.6 [60]–15,600 [55] (pg/ml), L: 559 [50]–21,200 [55] (pg/ml)
	PGE_1	TLC and biological assay	<200 pg/ml [10]
		RIA	NL: 2600 [55]–10,000 [33] (pg/ml), L: 4500 [64]–6800 [33] (pg/ml)
	$PGF_{2\alpha}$	TLC and biological assay	NL: <200 pg/ml [10], L: <200 [10]– 18,000 [10] (pg/ml)
		GC-MS	NL: <70 [19]–600 [19] (pg/ml), L: <100 [19]–200 [19] (pg/ml)
		RIA	NL: 17 [37]–4600 [55] (pg/ml), L: 33.1 [21]–7900 [55] (pg/ml)
	$PGF_{1\alpha}$	TLC and biological assay	NL: <200 pg/ml [10]
	6-keto-$PGF_{1\alpha}$	GC-MS	NL: 131 [42]–244 [42] (pg/ml)
		RIA	NL: 18.7 [53]–318.6 [58] (pg/ml), L: 21 [70]–608 [70] (pg/ml)
	PGEM	RIA	NL: 58 [54]–554 [77] (pg/ml), L: 82 [54]–433 [77] (pg/ml)
	Bicyclo-PGEM	RIA	NL: 49 [48]–200 [59] (pg/ml), L: 62 [48]–500 [75] (pg/ml)
	PGFM	GC-MS	NL: 31 pg/ml [19], L: 267–942 [19] (pg/ml)
		RIA	NL: 32.1 [61]–490 [41] (pg/ml), L: 20 [75]–2880 [58] (pg/ml)
serum	$PGF_{2\alpha}$	RIA	NL: 200 [13]–1800 [12] (pg/ml), L: 100 [11]–3000 [11] (pg/ml)
AF	PGE	RIA	NL: 89 [37]–1400 [29] (pg/ml), L: 502.8 [69]–8800 [29] (pg/ml)
	PGF	RIA	NL: 50 [27]–1650 [24] (pg/ml), L: 500 [27]–75,000 [27] (pg/ml)
	PGE_2	GC	NL: <200 [16]–6200 [16] (pg/ml), L: 1200 [16]–17,000 [16] (pg/ml)
		PC and TD	NL: 250 [26]–300 [26] (pg/ml), L: 1700 pg/ml [26]
		RIA	NL: <10 [30]–11,177 [80] (pg/ml), L: 17.8 [76]–28,197 [74] (pg/ml)
		ELISA	NL: 24 [85]–4749 [85] (pg/ml), L: 62 [85]–36,651 [85] (pg/ml)
		LC-MS	NL: <10 [87]–70,493 [87] (pg/ml), L: <10 [87]–105,739 [87] (pg/ml)
	PGE_1	GC	NL: <500 pg/ml [16], L: <500 pg/ml [16]
		PC and TD	NL: 1000 [26]–1200 [26] (pg/ml), L: 1800 pg/ml [26]
		RIA	NL: <10 [30]–5000 [33] (pg/ml), L: 4400 pg/ml [33]
	$PGF_{2\alpha}$	RIA	NL: 29 [66]–4700 [26] (pg/ml), L: 27 [71]–44,270 [33] (pg/ml)
		ELISA	NL: 8 [85]–926 [85] (pg/ml), L: 78 [85]–15,326 [85] (pg/ml)
		LC-MS	NL: <10 [87]–127 [91] (pg/ml), L: <10 [87]–42,537 [87] (pg/ml)
	$PGF_{1\alpha}$	PC and TD	NL: 1500 [26]–2000 [26] (pg/ml), L: 12,000 pg/ml [26]
	6-keto-$PGF_{1\alpha}$	RIA	NL: 67 [79]–809 [80] (pg/ml), L: 68 [80]–1927 [80] (pg/ml)
	PGEM	LC-MS	NL: 71 pg/ml [92], L: 8425 pg/ml [92]
	Bicyclo-PGEM	RIA	L: 75 [71]- 4275 [71] (pg/ml)
		LC-MS	NL: <10 [87]–66,900 [87] (pg/ml), L: 8361 [87]–133,800 [87] (pg/ml)
	15-keto-PGE_2	LC-MS	NL: 0 pg/ml [92], L: 210.24 pg/ml [92]
	19-OH-PGE_2	LC-MS	NL: 0 [92]–221,100 [87] (pg/ml), L: 73.7 [92]–202,675 [87] (pg/ml)
	PGFM	RIA	NL: 80 [79]–1571 [79] (pg/ml), L: 105 [71]–25,028 [56] (pg/ml)
		LC-MS	NL: <10 [87]–114.79 [91] (pg/ml), L: <10 [87]–28,360 [87] (pg/ml)
	PGD_2	RIA	L: 900 [63]–1800 [63] (pg/ml)
	PGJ_2	LC-MS	L: 8542.8 pg/ml [87]
	9α,11β-PGF_2	ELISA	NL: 30 [84]–204 [84] (pg/ml), L: 10 [84]–396 [84] (pg/ml)
	PGA_2	LC-MS	NL: <10 [87]–16,722 [87] (pg/ml), L: <10 [87]–50,167 [87] (pg/ml)

(*Continued*)

Table 3. (Continued)

Biofluid	PG/Metabolite	Measurement Technique	Range
urine	$PGF_{2\alpha}$	RIA	NL: 0.99 [83]–1.85 [83] (pg/g creatinine), L: 2.03 [83]–3.14 [83] (pg/g creatinine)
		GC-NICI-MS	NL: 1840 [90]–2060 [89] (pg/ml)
	6-keto-$PGF_{1\alpha}$	RIA	NL: 114,000 [67]–571,000 [67] (pg/g creatinine), L: 426,980 [62]–1,219,000 [67] (pg/g creatinine)
	PGFM	RIA	NL: 1.82 [83]–4.87 [83] (pg/g creatinine), L: 7.93 [83]–12.70 [83] (pg/g creatinine)
	t-PGFM	RIA	NL: 0.46 [20]–2.32 [20] (μg/hr), L: 1.06 [41]–2.50 [31] (μg/hr)
	2,3-dinor-6-keto-$PGF_{1\alpha}$	ELISA	NL: 623,232 [81]–1,096,181 [81] (pg/ml)

Published data presented as ng/ml, nanomolars, or picomolars were converted to pg/ml and data presented as ng/g creatinine or ng/mmol creatinine were converted to pg/g creatinine. Data published in μg/hr were not converted and are presented as in the original article.

Abbreviations: RIA = radioimmunoassay, NL = non-labour, L = labour, TLC = thin layer chromatography, GC-MS = gas chromatography-mass spectrometry, PGEM = 13,14-dihydro-15-keto-PGE_2, bicyclo-PGEM = 11-deoxy-13,14-dihydro-15-keto-11,16-bicyclo PGE_2, PGFM = 13,14-dihydro-15-keto-$PGF_{2\alpha}$, PC = paper chromatography, TD = transmission densitometry, ELISA = enzyme-linked immunosorbent assay, LC-MS = liquid chromatography-mass spectrometry, GC-NICI-MS = gas chromatography-negative ion chemical ionization-mass spectrometry, t-PGFM = 5α,7α-dihydroxy 11-keto tetranor-prostane 1,16-dioic acid.

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92]. 6-keto-$PGF_{1\alpha}$ and PGFM and were reported to increase in labouring participants compared to non-labouring participants in three [40, 79, 80] and seven [32, 41, 78–80, 87, 91] studies, respectively. Results were mixed for PGE_1 [26, 33]. PGE was not found to increase with labour [29, 69].

Prior to labour onset. Of the included amniotic fluid studies, 15 measured prostaglandins at more than one time point throughout pregnancy. $PGF_{2\alpha}$, $PGF_{1\alpha}$, and PGF were generally found to increase around term or prior to labour [17, 22, 27, 28, 30, 37, 52, 82, 85], though two studies found no pattern throughout pregnancy [26, 33]. Among studies that measured PGE or PGE_2, most (4/6) reported increased levels around 35–36 weeks [30, 37, 52, 85]. PGE_1 was not found to change with gestational age [26, 30, 33].

Predicting preterm labour. Six amniotic fluid studies investigated prostaglandins as predictors of preterm labour. Some studies suggest that $PGF_{2\alpha}$ may be predictive of preterm delivery in those with threatened preterm labour [88] and PPROM [86] however, results are mixed [71, 73]. PGFM and bicyclo-PGEM were found in higher levels in participants with preterm labour leading to preterm delivery compared to those who eventually delivered at term [71]. Increased PGE_2 levels may be predictive of delivery before term [68, 73] and before 34 weeks [76].

Blood

Labour and non-labour. In total, 27 studies compared labour and non-labour groups. $PGF_{2\alpha}$ was reported to increase with labour compared to non-labour in most (6/8) studies [21, 41, 50, 55, 69, 72]. All 15 studies that measured PGFM reported higher levels in labour compared to non-labour (Table 2). Three studies measuring PGE reported varying results [29, 36, 69]. PGE_1, PGE_2, and PGF were all generally found to remain unchanged with labour [29, 33, 36, 50, 55].

Prior to labour onset. In total, 18 studies obtained measurements of plasma throughout pregnancy. Among those that measured $PGF_{2\alpha}$, some found increasing levels at or near term [37, 50, 60] however results were conflicting [21, 28, 33]. In 5/6 studies PGFM was not found to change with increasing gestational age [39, 41, 43, 44, 58]. Results for $PGF_{2\alpha}$ in serum were mixed [11–13].

Predicting preterm labour. Two studies investigated prostaglandins in plasma as predictors of preterm labour. One study found that PGFM levels were higher in participants in

preterm labour who delivered preterm compared to those who went on to deliver at term [61] though the other study reported no significant difference [44].

Urine

Labour and non-labour. Five studies compared labouring vs non-labouring groups. The metabolite t-PGFM was reported to increase with labour compared to non-labour [20, 31, 41].

Prior to labour onset. Four studies measured changes in prostaglandins in urine throughout pregnancy. $PGF_{2\alpha}$, PGFM, and t-PGFM were reported to increase around term, though this was only reported in one study for each prostaglandin/metabolite [20, 83]. The metabolite 2,3-dinor-6-keto-$PGF_{1\alpha}$ did not change throughout pregnancy [81].

Predicting preterm labour. Two urine studies investigated prostaglandins as predictors of preterm labour. One found that $PGF_{2\alpha}$ levels in urine samples collected at median 32.1 weeks were not significantly different between participants who delivered at term and those that delivered preterm [89]. In contrast, averaged levels of $PGF_{2\alpha}$ in urine were also found to be associated with increased odds of preterm birth (OR = 1.98) [90].

Serial prostaglandin measurement during spontaneous labour

Although not a primary study question of this review, we noted that n = 40 studies obtained serial samples during labour. In general, prostaglandins measured in amniotic fluid increased throughout labour. Results were mixed for those that measured plasma and serum.

Quality assessment

Scores from the quality assessment were distributed as follows: 17% scored between 0–3, 41% scored between 4–6, and 42% scored between 7–9. The areas with the lowest scores were researcher blinding and sufficiency of sample number for internal validity. Scores for each study can be found in S3 Table.

Discussion

We demonstrate, through a systematic review of the literature investigating prostaglandins and metabolites in peripheral biofluids during pregnancy and labour, that prostaglandins of the PGE and PGF families do exhibit changes through pregnancy and labour, though results are inconsistent and inconclusive. Changes in PGE_2, $PGF_{2\alpha}$, and PGFM levels with labour are most prominent in amniotic fluid, and to a lesser extent in blood. Similarly, our synthesis suggests that PGE_2, $PGF_{2\alpha}$ and $PGF_{1\alpha}$ increase in amniotic fluid as pregnancy progresses and peak around term, though in plasma, a consistent pattern is unclear. Patterns in urine prostaglandin levels were inconclusive due to a relatively small number of studies investigating this biofluid. An important limitation is a general lack of data on prostaglandins and metabolites outside the PGE and PGF families, and as such we are unable to comment on their potential role in pregnancy and labour. Further, few studies examined prostaglandins as biomarkers for preterm labour and more research is needed to provide conclusive evidence for which prostaglandins or metabolites examined could offer the best options for prediction.

Measurement techniques for prostaglandins

Inconsistent study designs and methods greatly limited our ability to compare findings across studies. Up to the late 1990's, researchers most commonly used radioimmunoassay techniques, which can be highly sensitive, but are often limited by the specificity of the antibody used and the potential of antibody cross-reactivity with similar molecules [87]. One study included in

this review developed and reported on a radioimmunoassay for $PGF_{2\alpha}$ with a cross-reactivity with $PGF_{1\alpha}$ of 12.2% [17], which may have obscured patterns in $PGF_{2\alpha}$ and made it difficult to ascertain fine-tuning of the prostaglandin pathway among similar molecules. Furthermore, multiple other studies using radioimmunoassay techniques were unable to differentiate between $PGF_{2\alpha}$ and $PGF_{1\alpha}$, and PGE_2 and PGE_1 and therefore could only report on levels of PGF and PGE, respectively, making it difficult to compare the results of these studies with others. Lack of specificity and accuracy in these radioimmunoassay techniques may have contributed to the discrepancies across results and highlights the importance of re-visiting dogma in light of novel evidence and technologies. In contrast, the high specificity and sensitivity of mass spectrometry for lipid identification suggests that this method may be more suitable and accurate for measurement of prostaglandins [87]. Additionally, the capability of mass spectrometry to co-assess multiple prostaglandins and metabolites can provide a quantitative profile of prostaglandins before and during labour, as well as identify prostaglandins and/or metabolites not previously measured that may play a role in pregnancy and/or labour [93].

Considerations among unique biofluids

Among the studies included in this review, the most assayed biofluid was maternal plasma. Although an appealing fluid due to its ability to be sampled relatively easily, results from measurements in plasma were often conflicting, especially among studies that measured primary prostaglandins. Accurate measurement of changes in primary prostaglandin levels in blood is complicated by their rapid metabolism and correspondingly short half-life [94, 95]. This difficulty is further compounded by the production of prostaglandins by platelets that occurs during isolation of plasma and storage of samples [36, 96, 97]. Measurement of plasma PGFM appears to be a good alternative for $PGF_{2\alpha}$, as there is no evidence that this metabolite is formed during sample collection or isolation and therefore may more accurately reflect endogenous prostaglandin production [19]. The primary metabolite of PGE_2, however, is chemically unstable [98], which necessitates the measurement of its degradation product, bicyclo-PGEM, for an accurate index of PGE_2 production [99]. Therefore, results from early studies measuring primary prostaglandins and/or PGEM in plasma and/or serum should be interpreted with these considerations in mind and future studies in blood should aim to measure PGFM or bicyclo-PGEM as indices of $PGF_{2\alpha}$ or PGE_2 production, respectively.

Amniotic fluid lacks prostaglandin metabolizing enzymes [100, 101], which suggests that measurement of the primary prostaglandins in this fluid may be more accurate than in serum or plasma. However, sampling amniotic fluid is more difficult and may introduce infections harmful to the developing fetus, making this fluid impractical as a predictive resource. Additionally, prostaglandin levels vary based on method of collection and region of the amniotic sac [102, 103] which complicates any interpretation of results from studies and limits the clinical utility of an amniotic fluid test for prediction of preterm labour.

Measurement of the main urinary metabolite of $PGF_{2\alpha}$ may be preferable to measuring PGFM in plasma or serum in some cases, as a significant portion of circulating $PGF_{2\alpha}$ is eventually excreted into the urine [104]. In the present investigation, we identified only nine studies that assayed urine, and we suggest that the presence of urinary metabolites of prostaglandins during pregnancy and labour merits further study.

Demographic and clinical information

Among the articles included in this review, we noted that very few provided complete demographic and clinical information on their participants. Factors including age, race/ethnicity, membrane status, and gravidity/parity may impact prostaglandins levels and a lack of

consideration for these variables may obscure patterns of prostaglandin levels throughout pregnancy and labour. Complete descriptions of gestational age groups and clearly defined outcomes for both term and preterm labour would additionally make studies more easily comparable. As well, preterm labour is generally defined as labour occurring before 37 weeks gestation, however the pathophysiological processes involved in extreme preterm birth (<28 weeks) may vary dramatically from those near term [105]. Therefore, stratification of outcome groups based on gestational age at delivery may be more informative, though would require larger sample sizes to maintain statistical power.

Role for other prostaglandins

While prostaglandins of the E and F series are most clinically targeted for labour management, there is evidence to suggest that other members of the prostaglandin family may play a role in pregnancy and labour. For example, PGD_2 has been shown to increase uterine contractility and blood flow in various mammals [106–108] and is associated with cervical dilation in humans [63]. Two metabolites of PGD_2, 9α,11β-PGF_2 and PGJ_2, were each identified only once among the articles included in this review and were both reported to increase with term labour [84, 87]. These metabolites may be of interest to future researchers, as the development of new methodologies such as mass spectrometry have allowed for more accurate and sensitive measurements of select members of the prostaglandin pathway.

Limitations

The main limitation of this review is that only studies in English or with an available English translation were included, which may have resulted in missing some relevant articles. However, current resources limited the feasibility of including non-English studies.

Conclusion

We have identified evidence to suggest that prostaglandin levels, particularly within the PGE and PGF families, do increase in some biofluids during pregnancy and labour. However, changing prostaglandin levels throughout pregnancy and labour are likely highly complex and warrant further investigation, including serial measurements with more precise methodologies in higher-powered studies. Two important limitations identified in this review are the lack of data on the complexity of the prostaglandin pathway outside of the PGE and PGF families and the inherent difficulty in measuring primary prostaglandins in blood, due to their short half-lives in this biofluid. With the advent of i) new methodologies that can assess multiple prostaglandins and metabolites together, ii) a more developed understanding of the range of prostaglandins and iii) a better understanding of the heterogeneous nature of term and preterm labour, future studies that take each of these parameters into account in their study design will help provide further insight into the changing levels of prostaglandins in pregnancy and labour.

Supporting information

S1 Table. EMBASE search terms.
(DOCX)

S2 Table. MEDLINE search terms.
(DOCX)

S3 Table. Quality assessment scores.
(DOCX)

S1 Checklist. PRISMA 2020 checklist.
(DOC)

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