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The mnemonic code of pregnancy: Comparative analyses of pregnancy success and complication risk in first and second human pregnancies

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ABSTRACT

Obstetrical complications such as spontaneous abortion/miscarriage, fetal growth restriction, preeclampsia or preterm birth occur in approx. 15% of human pregnancies. Clinical experts often state that a previous uncomplicated pregnancy reduces the risk for complications in subsequent pregnancies. *Vice versa*, a prior pregnancy affected by obstetrical complications increases the risk for reoccurrence. However, published evidence directly underpinning these clinical statements is sparse. Considering that the maternal immune adaptation may be causally involved in determining the outcome of subsequent pregnancies, a comprehensive analysis of clinical data was long overdue.

We here present a systematic analysis of clinical data using a PubMed-based approach to identify human studies with relevant information on birth weight and incidences of pregnancy complications in first and second pregnancies. From initially 18,592 publications, 37 studies were included in the quantitative data analysis.

Women with a previous pregnancy affected by complications where a derailed immune response can be inferred have a 2.2–3.2-fold increased risk to be affected again in a subsequent pregnancy. Conversely, a normally progressing primary pregnancy reduced the risk for complications in a subsequent pregnancy by 35–65%. Moreover, an uncomplicated primary pregnancy was associated with a 4.2% increased birth weight in a following pregnancy without a difference in gestational age at delivery.

In conclusion, the increased birth weight after previously uncomplicated pregnancies suggests that an immune memory is mounted during primary pregnancies. This immune memory may promote the successful outcome of subsequent pregnancies or – if missing or compromised – account for a risk perpetuation of pregnancy complications.

1. Introduction

The majority of pregnancies progresses normally and without complications. However, in approx. 15% of all pregnancies, obstetrical complications occur, some of which pose a lethal threat the life of the mother or the fetus. These complications include the onset of spontaneous abortion/ miscarriage, gestational hypertension, gestational diabetes, preeclampsia, intra-uterine growth restriction (IUGR), preterm birth or a small for gestational age (SGA) baby (WHO, 2017).

During pregnancy, the maternal immune system is in direct contact with allogeneic, paternally encoded Major Histocompatibility Complex (MHC) I molecules expressed on fetal trophoblast cells (Kovats, 1990; Madeja, 2011). A tailored maternal endocrine and immune adaptation to pregnancy has been proposed to be largely responsible for the tolerance of the allogeneic fetus, hereby promoting successful pregnancy outcome (Arck and Hecher, 2013; Erlebacher, 2013; Thiele et al., 2018). Consequently, the inability to mount this tailored maternal immune response has been associated with the pregnancy complications listed above (Cappelletti et al., 2016; Cotechini et al., 2014; Helmo et al., 2018; Jafri and Ormiston, 2017; Yang et al., 2010). There is a general consensus among clinicians with expertise in obstetrics that a previous successful pregnancy reduces the risk for complications in subsequent pregnancies, including the risk for spontaneous abortion/ miscarriage, preterm birth and preeclampsia. Considering that higher maternal age is a known risk factor for pregnancy complications (Sheen et al., 2018; Wu et al., 2019) and that women are naturally older during their second pregnancy, these observations are even more striking. However, published evidence supporting an improved pregnancy

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outcome in subsequent pregnancies are sparse and often concealed in publications primarily focussing on pregnancy complications. Similarly, insights into distinct immune mediators that may be functionally involved in ameliorating the course of secondary pregnancies are still enigmatic.

Moreover, women affected by obstetrical complications in their first pregnancy have a significantly enhanced risk for complications in subsequent pregnancies, e.g. spontaneous abortion/ miscarriage, small for gestation age (SGA) babies or preeclampsia (Malmström and Morken, 2018; Manzanares et al., 2017; Weintraub et al., 2011). In contrast to the sparse information of a mnemonic code for pregnancy success resulting from normal progressing pregnancies, there is a variety of epidemiological studies to support an increased risk for recurrent pregnancy complications. Also, pathophysiological features associated with pregnancy complications are well studied. In these studies, the focus generally lies on the current pregnancy, whereas comprehensive studies comparing e.g. altered immune markers in primary and secondary pregnancies overshadowed by recurrent complications are still missing.

Thus, it was the aim of the study to conduct a comprehensive analysis of the chances for a recurrent successful pregnancy outcome (including birth weight as a proxy for unchallenged or improved fetal development) as well as the risks for recurrent pregnancy complications. We discuss our findings in the context of maternal immune adaptation to pregnancy and the potential existence of an immune memory mounted during uncomplicated primary pregnancies.

2. Material and methods

2.1. Selection of publications

A systematic analysis of birth weight and obstetric complications in first and subsequent pregnancies was conducted by a thorough literature research on PubMed based on the PRISMA guidelines (Moher et al., 2015). The last search was performed on December, 16th 2018. This systematic analysis only includes journal articles on humans available in English language. The literature research was performed by one person and independently confirmed by two other persona in order to resolve disagreements and remove ambiguity.

The following keywords were chosen to identify studies that include data on consecutive pregnancies in humans: “(second pregnancy OR subsequent pregnancy OR consecutive pregnancy OR parity OR parous) AND women”. The option to restrict the search of keywords to [Title/ Abstract] was applied. This query resulted in 18,592 hits (Fig. 1). Subsequently, additional keywords were applied individually to identify studies dealing with distinct pregnancy complications and birth outcome hereby creating seven subgroups: “(spontaneous abortion OR miscarriage)”, “(gestational hypertension OR pregnancy induced hypertension)”, “gestational diabetes”, “(preeclampsia OR preeclampsia)”, “Preterm”, “(SGA OR IUGR)” and “(birth weight OR birthweight)”.

All resulting articles identified by these seven queries were screened by title and abstract, following strict inclusion criteria (subsequent human pregnancy, pregnancy outcome and the respective pregnancy complications) excluding all non-relevant articles. The following reasons resulted in exclusion from the analysis: only the first pregnancy was considered, twin or multiple pregnancies, interventional studies, birth by caesarean section, case control studies regarding alcohol, smoking or other drugs in pregnancy, specific maternal condition or diseases, e.g. cancer, malaria, HIV, IVF/ICSI, induced abortion, implications of cerclage or conisation of the cervix, primary rupture of membranes, perineal/sphincter injuries and grand multiparity (Fig. 1).

All studies identified in the respective subgroups (Fig. 1) were further evaluated by full text. Final inclusion criteria were defined as the presence of a complete data set on the incidence rate of the respective pregnancy complications in first and subsequent, secondary pregnancy or the presence of a complete data set on birth weight and gestational length for the primary and secondary pregnancies, respectively (Fig. 1).

A total of 37 observational studies, mostly conducted retrospectively, were finally included in an in-depth quantitative analysis. An overview is provided by Table 1 including the number of study participants and geographic location of recruitment. Studies containing data for more than one subgroup have been reapplied for analysis.

2.2. Data analysis of risk for pregnancy complications

Full text analysis revealed the following number of included articles (Fig. 1): spontaneous abortion/ miscarriage (n = 3), gestational hypertension (n = 2), gestational diabetes (n = 5), preeclampsia (n = 9), preterm birth (n = 8), and SGA/ IUGR (n = 5). We analysed the risk of reoccurrence of a respective obstetric complication after a primary pregnancy affected by the respective complication as well as the probability of the continuous absence of the same complication after an uncomplicated primary pregnancy. Therefore, we calculated the relative risk increase and the relative risk decrease for secondary pregnancy in relation to the first pregnancy as follows:

$$\text{relative risk} = \frac{\textit{Disease incidence in secondary pregnancy}}{\textit{Disease incidence in primary pregnancy}}$$

2.3. Analysis of birth weight data

We identified 13 publications providing complete information on birth weight und gestational age at delivery in normally progressing primary and secondary pregnancies (Fig. 1). In order to quantify weight differences of neonates born from primary and secondary pregnancy, we calculated the relative weight change of the second pregnancy in relation to the previous pregnancy:

$$\textit{relative weight change} = \frac{\textit{mean birth weight of second pregnancy}}{\textit{mean birth weight of primary pregnancy}}$$

2.4. Data presentation

Data are presented as scatter dot plots using GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. Uncomplicated primary pregnancies are associated with increased birth weight in secondary pregnancies

Data obtained from a total of 13 studies on birth weight and gestational length in primary and secondary pregnancies (see Fig. 2A for references) revealed that the mean birth weight reported for primary pregnancies was 3.204 g ± 243 g and 3.338 g ± 246 g in secondary pregnancies (Fig. 2B). Based on these data, the relative weight increase of newborns in secondary pregnancies is 4.2% (Fig. 2A). An increased gestational length as a potential confounder for the higher birth weight in secondary pregnancies could be excluded (Fig. 2C).

3.2. Previous pregnancy complications with an immune pathogenesis increase the risk to suffer from the same complications in a subsequent pregnancy

We first assessed the risk for spontaneous abortion/ miscarriage in primary and secondary pregnancies and calculated a mean incidence of 10.9% for nulliparous women in the respective studies assessed here (see Fig. 3A for references). If the previous pregnancy ended in a spontaneous abortion/ miscarriage, the risk for spontaneous abortion/ miscarriage in a subsequent pregnancy was further increased by 2.2-fold, now affecting 23.8% of all secondary pregnancies (Fig. 3A right).

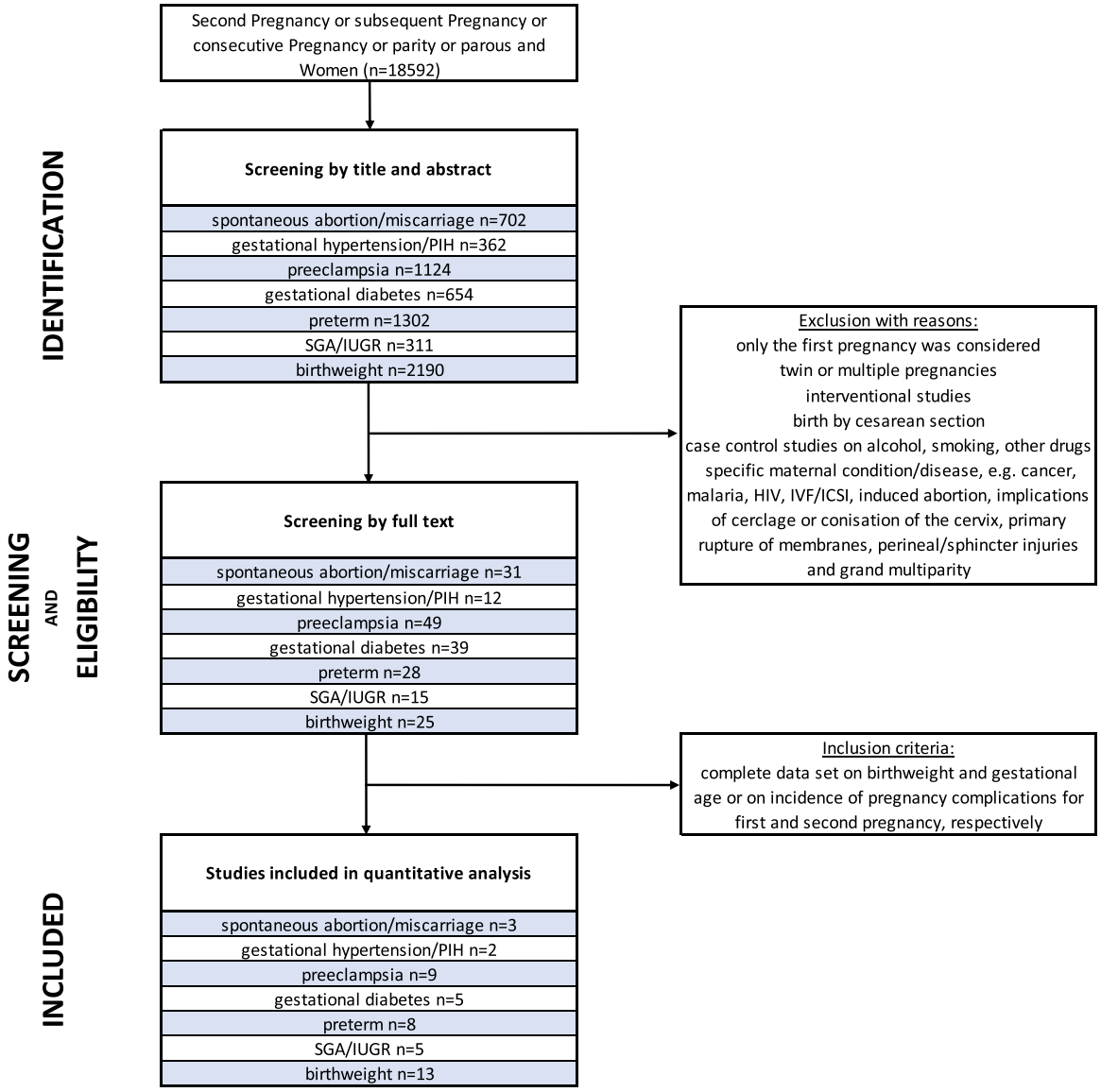

Fig. 1. Flow Diagram illustrating the way of identification and screening of the publications finally included in the quantitative data analysis. Abbreviations: PIH, pregnancy-induced hypertension; SGA, small for gestational age; IUGR, intra-uterine growth restriction; HIV, human immunodeficiency virus; IVF, in vitro fertilization; ICSI, intra-cytoplasmic sperm injection.

In contrast, a normal progressing previous pregnancy reduced the incidence rate of spontaneous abortion/ miscarriage by 54% (Fig. 3A left), now only affecting 4.9% compared to 10.9% observed in primary pregnancies.

Next, we assessed the mean incidence for preeclampsia in primary and secondary pregnancies, calculated from the nine articles included in our analysis (see Fig. 3B for references). Here, the onset of preeclampsia affected 4.8% of the nulliparous women. A previous pregnancy affected by preeclampsia increased the risk for its reoccurrence in secondary pregnancies by 3.0-fold (Fig. 3B right), now affecting up to 13.9% of all women. On the other hand, only 1.6% women developed preeclampsia in a secondary pregnancy if the primary pregnancy was unaffected by preeclampsia. This corresponds to a relative risk reduction of 65.0% (Fig. 3B left). Noteworthy, the recurrence risk for pregnancy-induced hypertension - which may develop to preeclampsia - could not be integrated in our analysis, as only two articles provided information on isolated hypertension in primary and secondary pregnancies (Boghossian et al., 2015; Wallace et al., 2016). The incidence for nulliparous women was 6.0% and 19,6%, respectively. A primary pregnancy affected by pregnancy-induced hypertension increased the recurrence rate in one study (Boghossian et al., 2015), whereas the recurrence rate was decreased in the other study (Wallace et al., 2016) (Table 2).

We then focused on the risk for preterm birth in primary and secondary pregnancies, including data from studies which defined preterm birth as live births before 37 completed weeks of pregnancy. We identified eight studies with complete data sets on primary and secondary pregnancies, some of which also included neonates born extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks) and moderate to late preterm (32 to 37 weeks, see Fig. 3C for references). We calculated a mean incidence of preterm birth for nulliparous women of 7.5%. A previous pregnancy with a preterm born baby enhanced the risk for a subsequent preterm birth by 3.0-fold (Fig. 3C right), affecting 21.3% of these secondary pregnancies. In contrast, a first child born at term reduced the risk for preterm birth in subsequent pregnancies by 36% (Fig. 3C left), affecting only 4.6% of secondary pregnancies.

Furthermore, we analysed the probability for SGA/IUGR in a primary pregnancy, which was 9.1% in the five studies we included in our analysis (see Fig. 3D for references). A previous birth of a SGA/ IUGR

Table 1
Overview of all cohort studies included in the analyses present herein.

Publication	Study population	n
(Ananth et al., 2007)	Missouri USA	154,810
(Bhattacharya et al., 2008)	Aberdeen UK	24,520
(Blankson et al., 1993)	Alabama USA	737
(Boghossian et al., 2014a)	Utah USA	62,013
(Boghossian et al., 2015)	Utah USA	26,787
(Boghossian et al., 2014b)	Utah USA	26,963
(Chiba et al., 2013)	Japan	560
(Cnattingius et al., 1999)	Sweden	243,858
(Ehrlich et al., 2011)	Northern California USA	22,351
(England et al., 2015)	Massachusetts USA	141,233
(Getahun et al., 2010)	Southern California, USA	65,132
(Ghaemmaghami et al., 2013)	Iran	858
(Grantz et al., 2015)	Utah USA	25,820
(Hathout et al., 1982)	Kuweit UAE	573
(Hernández-Díaz et al., 2009)	Sweden	763,795
(Hickey et al., 1992)	Alabama USA	152
(Hinkle et al., 2014)	Utah USA	25,241
(Hutcheon and Platt, 2008)	Montreal Canada	1,220
(Joshi et al., 2005)	Maharashtra India	770
(Khambalia et al., 2013)	New South Wales, Australia	142,843
(Lain et al., 2005)	Pennsylvania USA	6,148
(Lykke et al., 2009)	Denmark	536,419
(Mahande et al., 2013a)	Tanzania	3,909
(Mahande et al., 2013b)	Tanzania	3,359
(Majoko et al., 2004)	Zimbabwe	10,569
(Makkonen et al., 2000)	Finnland	8,842
(Manzanares et al., 2017)	Spain	7,896
(Merlino et al., 2006)	Ohio USA	1,241
(Mostello et al., 2008)	Missouri USA	103,860
(Ouh et al., 2018)	Korea	121,569
(Paterson and Saunders, 1991)	UK	75,974
(Räisänen et al., 2013)	Finnland	686,114
(Skjærven et al., 2002)	Norway	551,478
(Van Oostwaard et al., 2014)	Netherlands	503
(Voskamp et al., 2013)	Netherlands	259,481
(Wallace et al., 2016)	Aberdeen UK	24,520
(Wilcox et al., 1996)	UK	3,457

baby increased the risk for reoccurrence in a secondary pregnancy 2.9-fold (Fig. 3D right), thus affecting 24.1% of the women. A baby born with normal weight in a primary pregnancy reduced the risk for recurrence about 41% (Fig. 3D left), now only affecting 5.28% in secondary pregnancies.

3.3. Previous pregnancy complications with a metabolic phenotype dramatically augmented the recurrence risk

We evaluated the recurrence risk for gestational diabetes as a metabolic disorder affecting women during pregnancy and could identify five studies with relevant data. The mean incidence rate for gestational diabetes was 3.5% in nulliparous women (see Table 2). We could observe that an average of 49.6% pregnant women with previous gestational diabetes suffer from this disorder again. This corresponds to a 16.8-fold increase of risk (Table 2). An uncomplicated previous pregnancy only marginally reduced the relative risk for developing GDM in subsequent pregnancies, as the mean incidence was with 3.0% almost similar to first pregnancies, with a high variation between studies (Table 2).

4. Discussion

We here present a comprehensive and systematic analyses of pregnancy outcome in first and subsequent pregnancies, incorporating data provided by a number of observational studies. We now provide solid insights on the recurrence rates of uncomplicated pregnancies as well as the perpetuation of risks for pregnancy complications in secondary pregnancies upon previous complications. We identified a similar recurrence pattern with regard to spontaneous abortion/miscarriage, preeclampsia, preterm birth and SGA/IUGR. Women suffering from one of these complications in primary pregnancies showed an approx. three times higher risk to be affected again in a subsequent pregnancy. Conversely, the absence of a complication in a first pregnancy reduced the risk for complications in a consecutive pregnancy by 35–65%. We could also identify an increased birth weight in new-borns in secondary pregnancy, whilst the gestational length did not differ between first and second pregnancies. This equals the results from ultrasound assessments showing that parous women have heavier fetuses than nulliparous women (Kiserud et al., 2017). Interestingly, the results with regard to birth weight were very consistent between studies, although the 13 studies included show a great deal of heterogeneity in terms of ethnicity and maternal age. Further, number of participants in these studies were generally very high, which ensures equal distribution of potential confounder variables, such as rates of exercise, nutrition, or maternal weight gain.

The majority of the pregnancy complications we here assessed in primary and secondary pregnancies (spontaneous abortion/ miscarriage, preeclampsia, preterm birth and SGA/ IUGR) are attributable to distinct immunological pathophysiologies. (Cappelletti et al., 2016; Cotechini et al., 2014; Helmo et al., 2018; Jafri and Ormiston, 2017; Yang et al., 2010) This strongly underpins that the immune response mounted during a successful primary pregnancy may initiate a 'mnemonic code' in maternal immunity which spills over to a secondary pregnancy, accounting for the further reduction of pregnancy complications. *Vice versa*, if such mnemonic code is not mounted during primary pregnancy, complications may not only overshadow the ongoing, but also future pregnancies. Clearly, one should keep in mind that non-immune factors such as an abnormal karyotype of the embryo can account for spontaneous abortion/miscarriage. In fact, cytogenetic abnormalities have been detected in 61.5% of aborted fetuses, which – although to a lower extend - have also been observed in recurrent pregnancy losses (Boué et al., 1975; Coulam et al., 1996). Besides an abnormal karyotype of the embryo, recurrent pregnancy losses may result from congenital uterine abnormalities (Vaz et al., 2017).

In immunity, a 'mnemonic code' is generally referred to an immune memory. How could such immune memory during pregnancy be operational? It is well known that the first cells coming in contact with the maternal immune system are the fetal extravillous trophoblast cells (EVTs), which express a unique variety of HLA molecules (HLA-C, HLA-E, HLA-G) and constitute an allogenic challenge to the maternal immune system. The fetal antigens can interact with killer-cell immunoglobulin-like receptors (KIRs), that are expressed by maternal natural killer (NK) cells present in the uterus (Moffett-King, 2002; Moffett and Loke, 2006; Xiong et al., 2013). By binding to HLA molecules through their KIRs, uNK cells produce growth factors and initiate trophoblast migration into the decidua and the remodelling of the spiral arteries in order to ensure normal placenta development (Faas and De Vos, 2018; Xiong et al., 2013). These uNK cells are essentially involved in the pathogenesis of spontaneous abortion/ miscarriage, preeclampsia and IUGR/SGA, where decreased numbers have been described (Eide et al., 2006; Hill et al., 1995; Williams et al., 2009). This decrease is accompanied by an impaired remodelling of spiral arteries, placental hypoxia (Benton et al., 2016; Figueras and Gratacos, 2014; Kwiatkowski et al., 2016; Whitten et al., 2013), an inadequate formation of endovascular trophoblast plugs in maternal arterioles (Hempstock et al., 2003) and the generation of cytotoxic NK cells (Hambartsoumian, 1998; Piccinni and Romagnani, 1996) which leads to increased IL-2 and TNF-α production (Fukui et al., 2008; Hadinedoushan et al., 2007).

Interestingly, memory NK cells have been introduced very recently, a population with a unique transcriptome and epigenetic signature that can be exclusively detected in secondary pregnancies. It has been proposed that these cells might be associated with improved placentation observed in secondary pregnancies (Gamliel et al., 2018). Hence, these

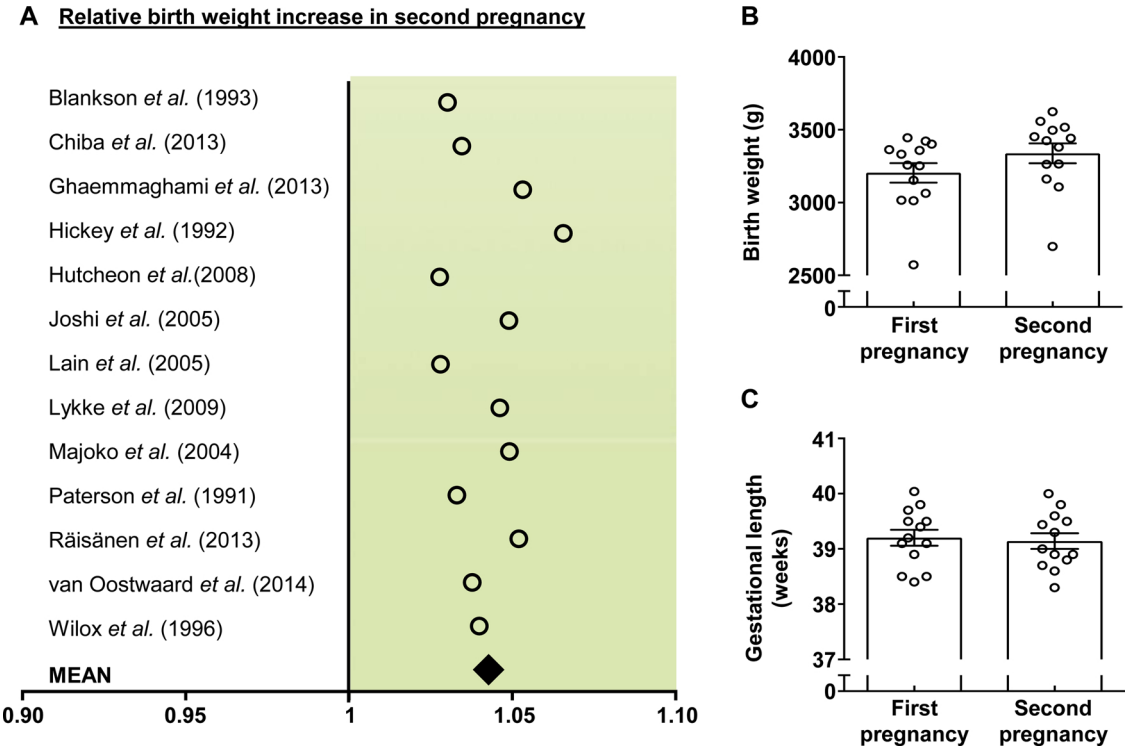

Fig. 2. Birth weight analysis of first and second pregnancy: (A) Relative birth weight increase in second pregnancy compared to first pregnancy presented as scatter plot. References of the 13 included original publications are indicated on the left. (B) Mean birth weight and (C) gestational age at delivery for first and second pregnancy obtain from the same studies presented as bar chart.

pregnancy-protective memory uNK cells might initiate proper placentation faster and more efficient, hereby accounting for the relative increase in birth weight we identified in secondary pregnancies. It can also be speculated that either the generation of memory NK cells may fail during primary pregnancies overshadowed with complications; or cytotoxic NK cells that developed during complications in primary pregnancies could acquire a memory phenotype, subsequently accounting for the recurrent risk for impaired remodelling of spiral arteries and placental hypoxia, both associated with pregnancy complications such as the faster progression of preeclampsia in secondary pregnancies (Li et al., 2014; Lain et al., 2005).

Besides uNK cells, $CD4^+CD25^+Foxp3^+$ regulatory T (T_{reg}) cells are essential for successful pregnancy progression, as they promote immune tolerance towards the semiallogenic conceptus. The generation of T_{reg} cells is induced by tolerogenic dendritic cells (tDCs) via progesterone-dependent pathways (Thiele et al., 2019). Moreover, the check-point inhibitor CD200 expressed on human and mouse trophoblast can act on immature dendritic cells to enhance Treg cell generation (Clark et al., 2017). In contrast, an increased number of mature DCs at the feto-maternal interface leads to the generation and activation of T effector (T_{eff}) cells, including pro-inflammatory T helper (TH) 17 cell subsets which mediate inflammation, as observed in women with preeclampsia (Zhang et al., 2017) or recurrent spontaneous abortion (Fu et al., 2014). This is accompanied by a reduced number of T_{reg} cells in the peripheral blood and also at the feto-maternal interface (Kwiatek et al., 2015; Sasaki et al., 2007).

Generally, at the end of an immune response to a specific antigen challenge, e.g. upon an infection, most T_{eff} cells die. However, a small percentage of T cells converts into memory cells (Lees and Farber, 2010). This acquisition of memory function has been predominately described for T_{eff} cells, and the re-exposure to the same antigen is characterised by a rapid immune response time and increased efficiency. In this context, a subsequent pregnancy constitutes - at least in most cases – also a re-exposure to the same paternal antigens.

The involvement of the adaptive immune system in the pathogenesis of obstetrical complications is generally accepted, for example mirrored by a T helper (Th)17/ T_{reg} imbalance in the context of preeclampsia (Eghbal-Fard et al., 2019) and miscarriage (Zhu et al., 2016). Whilst the frequency of $CD4^+$ T_{reg} cells during pregnancy and obstetrical complications have been extensively studied over the last decade, insights into the fate of $CD4^+$ T_{reg} cells after birth and in secondary pregnancies are still sparse. A subset of $CD4^+$ Treg memory cells with fetal antigen specificity could be detected after delivery of the litters in mice (Rowe et al., 2012). However, in this model, a non-physiological class II paternal MHC was over-expressed in the embryo, along with the overexpression of the corresponding T cell receptor in the mother, which may enable an anomalous T_{eff} response (Clark, 2016). Hence, the confirmation of $CD4^+$ T_{reg} memory cells persisting after birth and their potential to expand at an accelerated rate during subsequent pregnancies requires confirmation in more physiological models. Thus far, it is still unknown if and how $CD4^+$ T_{reg} cells develop memory function and identification of $CD4^+$ T_{reg} memory cells is challenging (Rosenblum et al., 2015).

However, considering that $CD4^+$ T_{reg} cells contribute to the course of normally progressing pregnancies and regulate T cell responses, $CD4^+$ T_{reg} memory cells may account for the improved pregnancy outcome, e.g. increased birth weight and reduced risk of pregnancy complications during secondary pregnancies. Fetal antigens already known by the maternal immune system from previous pregnancies could potentially enhance adaptational efficiency by improving placenta formation and subsequently fetal growth. Interestingly, an enhanced fetal growth has been also observed in mice immunized with a paternal MHC specific transplant (Wegmann, 1981), suggesting that alloantigen specific immunity might influence fetal growth in subsequent pregnancies. Conversely, a Th1 and Th17 cells rise during pregnancies has been linked to obstetric complications, presumably via the suppression of a $CD4^+$ T_{reg} response. Thus, it is conceivable that a predominance of T_{eff} cells during first pregnancies overshadowed by

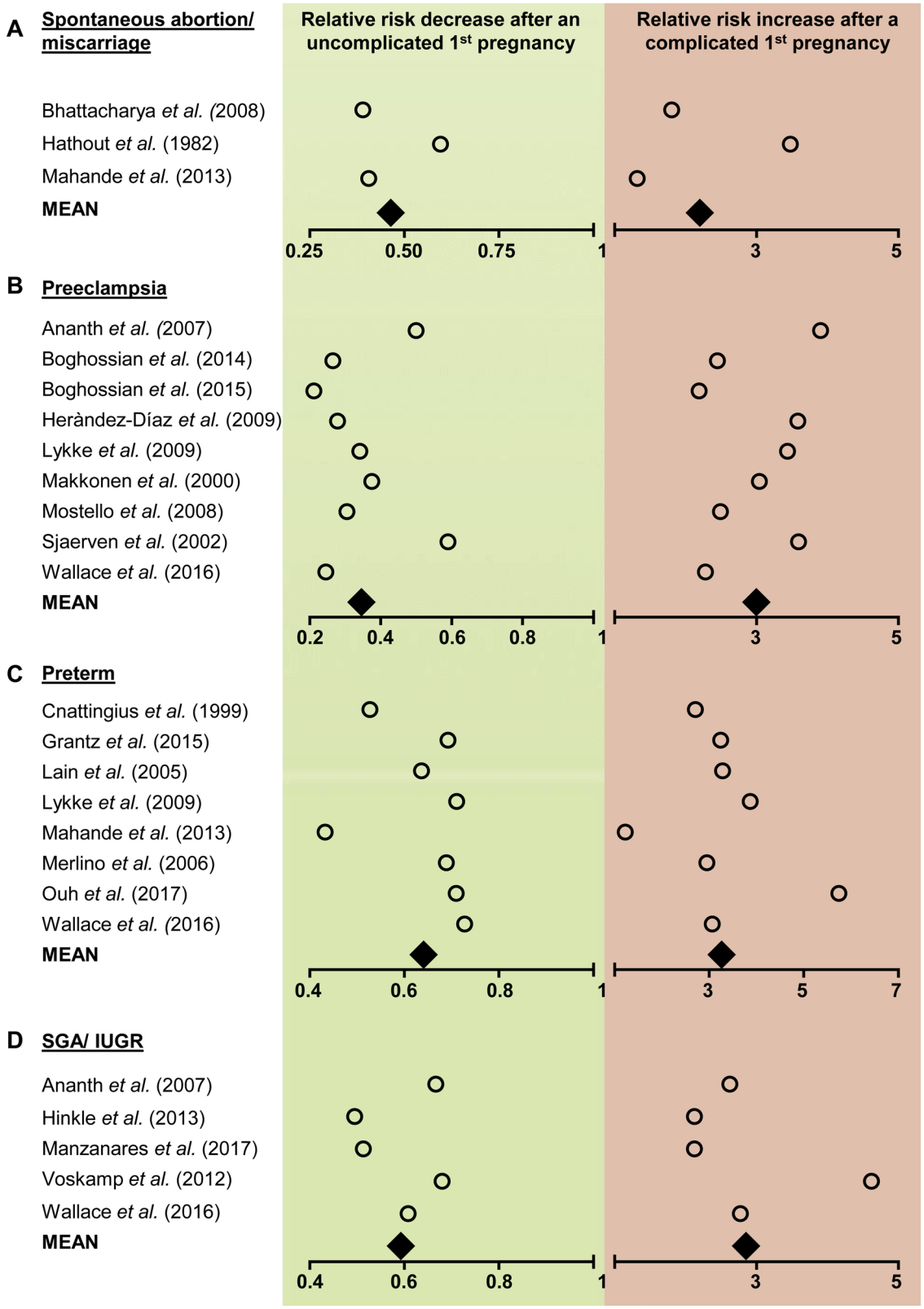

Fig. 3. Risk for obstetrical complications in second pregnancy: (A–D) Relative risk decrease after an uncomplicated first pregnancy (left) and relative risk increase after a first pregnancy affected by the respective complications (right) shown for (A) spontaneous abortion/ miscarriage, (B) preeclampsia, (C) preterm birth and (D) small for gestational age (SGA)/ intra-uterine growth restriction (IUGR) presented as scatter plot.

complications result in a higher frequency of T_{eff} memory cell and fewer $CD4^+T_{reg}$ memory cells, hereby accounting for the increased risk for recurrent complications in subsequent pregnancies. In this context, it would be interesting to know if the gestational period until the onset of a fetal loss is decreasing with increasing number of abortions.

Another immune cell population with emerging interest in various areas on immunology are innate lymphoid cells (ILCs) mirroring the phenotypes and functions of T cells. Whilst NK cells can be considered

Table 2
Risk for selected pregnancy complications in primary and secondary pregnancies.

	Relative risk decrease after an uncomplicated primary pregnancy	Relative risk increase after a complicated primary pregnancy
Gestational diabetes mellitus		
(Boghossian et al., 2014a)	1.05	37.95
(Ehrlich et al., 2011)	0.77	8.30
(England et al., 2015)	0.87	15.90
(Getahun et al., 2010)	1.08	10.59
(Khambalia et al., 2013)	0.73	11.14
MEAN	**0.90**	**16.78**
Gestational Hypertension		
(Boghossian et al., 2015)	0.20	2.17
(Wallace et al., 2016)	0.27	0.89
MEAN	**0.24**	**1.53**

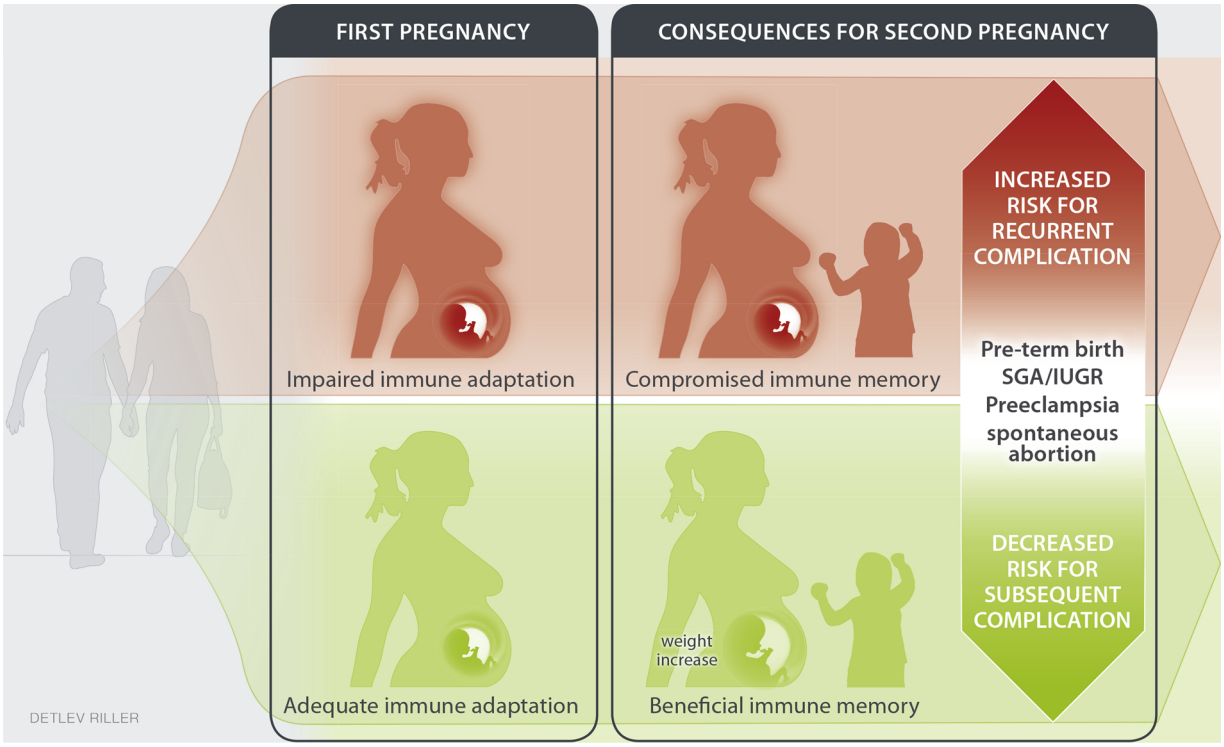

Fig. 4. Graphical summary: A previously uncomplicated pregnancy enabled by an adequate maternal immune adaptation to pregnancy promotes the generation of immune memory accounting for the successful outcome of subsequent pregnancies. *Vice versa*, a prior pregnancy affected by obstetrical complications with an immune pathogenesis impairs the generation of immune memory leading to an increased risk for recurrent pregnancy complications.

the innate counterparts of cytotoxic $CD8^+$ T cells, ILC1s, ILC2s, and ILC3s may represent the innate counterparts of $CD4^+$ TH1, TH2, and TH17 cells (Eberl et al., 2015). Although their relevance for reproduction has not been clarified yet, the presence of ILCs in the decidua has already been shown (Montaldo et al., 2016; Vacca et al., 2014) and also an association with the occurrence of preterm labor (Xu et al., 2018). In addition, $Eomes^{neg}CD49a^+$ ILC1s were demonstrated to specifically expand in second pregnancies in mice when the expression of the memory cell marker CXCR6 is upregulated (Filipovic et al., 2018). Here, further intensive research is necessary in order to reveal potential impact of ILCs memory on recurrent pregnancy outcome.

The concept of memory immune cells mounted during a first pregnancy is based on the presumption that the paternal antigen is equal in subsequent pregnancies. Hence, a different father and related altered fetal antigen repertoire should jeopardize any beneficial (or detrimental) effect conveyed by immune memory mounted during previous pregnancies. Indeed, a seminal study from 1996 reported that the risks of preeclampsia is 3.2% in nulliparous women, 1.9% for women with no change of partner and 3.0% for multiparous women with changed paternity (Trupin et al., 1996). Similar observations were made in the context of SGA (Bandoli et al., 2012; Hercus et al., 2018). In this regard, also the duration of sexual cohabitation with a new partner may be of relevance (Robillard et al., 1994).

Another important issue affecting the impact of memory immune cells on the outcome of secondary pregnancies may be the inter-pregnancy interval. The risk for preterm birth or a SGA infant is increased if the secondary pregnancy occurs within 12 month after delivery, possibly due to an incomplete involution of the uterus accompanied by the hormonal situation due to breast feeding. An interval of 12–24 month yields to the lowest risk for pregnancy complications in secondary pregnancies (Hanley et al., 2017; Hegelund et al., 2018; Zhang et al., 2018). Subsequently, the risk for obstetric complications rise again with increasing inter-pregnancy interval. An explanation for these clinical observations might be that the number of memory cells decrease over time, similar to a vaccination response which requires boosting. Underlying mechanisms are still elusive, but may be due to the limited capacity for self-renewal of $CD4^+$ T_{reg} memory cells. Interestingly, $CD4^+$ T_{reg} memory cells could be maintained by fetal microchimeric

cells which are present in the mother until long after birth (Boddy et al., 2015; Kinder et al., 2017).

In summary, we here propose that immune cell subsets may account for the increased recurrence risk of obstetric complications observed in secondary pregnancies. *Vice versa*, memory immune cells could also yield to an improved pregnancy outcome after uncomplicated first pregnancies. A graphical summary is provided in Fig. 4. We are aware that this concept is still speculative, and it is our intention and hope to sparkle research to provide the missing evidences and causations. The identification of cell subsets or mediators involved in determining the success of pregnancy and their use as diagnostic or therapeutic tools would be of pivotal value to predict and modulate the risk of pregnancy complications.

Author contributions

Conceptualization: KT; Literature Research: LSA, KT; Data presentation: KT; Writing – Original Draft: KT, PCA; Comments on manuscript: all authors.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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