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Maternal-foetal Conflict and Genetic Conditioning of Intrauterine Competition in sibling Pairs: A systematic Review

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ABSTRACT

The traditionalview of pregnancy as a harmonious collaboration is ill-conceived. For any conception, a parental tug-of-war for nutritional resources ensues at the biological rheostat between inherited matrigenes, patrigenes and rest of uniheritened maternal genome. This quantitative systematic review is an objective forwarded to translate maternal-foetal conflict as driven by genomic imprinting to obstetric complications of preeclampsia and gestational diabetes mellitus. Adverse maternal outcomes owing to duplication of the conflict in presence of two placentae link up to higher incidence of preeclampsia and gestational diabetes mellitus seen with twin pregnancies (pooled summary effect=3.5, and 2.27 respectively). A weak positive association was established betweendichorionicityand preeclampsia (pooled summary effect=1.46).Dizygosityin contradiction to previous literature displayed a small negative association for preeclampsia (pooled summary effect=0.47). No significant contribution of chorionicity was noted in risk of occurrences for gestational diabetes mellitus in terms of marked heterogeneity of the included studies (I^2=80.2%). These results warrant further research into differential prioritization of dichorionic and dizygotic pregnancies in respect to adverse maternal

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outcomes of preeclampsia and gestational diabetes mellitus.

Keywords:- Maternal-FoetalConflict, Genomic Imprinting, Preeclampsia, Gestational Diabetes, Chorionicity, Zygosity.

Introduction

The inherent instability of pregnancy delineates the conceptual distinction between gestational physiology and obstetric pathology. This narrowly harmonious collaboration between two beings is construed over individualized interests of the mother, the father, and the foetus (Haig et al., 2015). As half of a mother's genome is absent in each and every offspring, maternal-foetal genetic dissimilarity creates a resource allocation challenge over the biological rheostat; placenta. Offspring genes in the trophoblast are exclusively programmed to select for increased transfer of nutrients and oxygen, but this effect is opposed by limitation of transfers in the decidua as to exclusively serve maternal interests by minimizing the cost of pregnancy on the actor's body (Haig et al., 1993, Moore et al., 2012). The amounts of resources available for reproduction to any parent is finite. The increase in provision of resources to an offspring is associated with greater likelihood of survival and future reproduction for the offspring, but an exaggerated investment in the current gestation is likely to leave fewer resources for the future offspring. This leaves the mother two choices, either to invest a small amount and produce a large number of inexpensive offspring or foster great investment with cost of low fecundity (Haig, 1996). With exception of strict monogamy, the differential levels of maternal investment are a product of a parental tug-of-war within an embryo, a conflict which is likely to accentuate in mixed paternity between siblings (Fowden & Moore, 2012).

Maternal-foetal unit is a triploid entity comprised of three haploid genomes; non-inherited maternal genome, an inherited maternal genome, and a paternal genome (Haig, 2019). This situates the basis for three potential sources of conflict in a pregnancy; parent-offspring conflict (between maternal and foetal/placental genes), genomic imprinting (between madumnal and padumnal alleles), and gestational drive (between matrigenes that recognize themselves in offspring and the rest of the maternal genome; Haig, 1996). The conspiratorial behaviour of un-inherited maternal genome against the embryo lacking its copies (absent in the current offspring,

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50% probability of inheritance in the next offspring) should hypothetically eradicate that conception. This is circumvented by a meiotic veil of ignorance, an inability of maternal alleles to discriminate between embryos with and without their copies. However, nepotistic favouritism at the maternal–foetal interface has been described for major histocompatibility complex on chromosome 6 and the killer-cell inhibitory receptor complex on chromosome 19. Having evolved to distinguish self from other, they may mark an embryo as a foreign intruder lacking its copies, elimination of which would benefit the haplotype in such a way that a future offspring would have a ½ chance of carrying the self-haplotype (Haig, 2019). A placental function that's beneficial to the interacting parties like resistance to infection or homeostasis does not involve counteraction between mother and the embryo, differentiating it from a host-parasite relationship where cost outweighs any benefit to the host (Haig, 1996); suggesting that pregnancy is subject to multiple selection pressures at once, some that favour cooperation and some that foster conflict.

Genomic imprinting or hemizygous expression in a parent-of-origin manner (monoallelic with transcriptional silencing of counterpart) is unique to eutherian mammals (Wolf & Hager, 2006). Genes of paternal origin are postulated to strive for increased metabolic demand on mothers during gestation, whereas maternally-derived genes attempt to lower reproductive cost, ensuring not only mother's survival, but equal nutritional provision across multiple gestations (Haig, 2010). These predictions are strongly supported by foetal overgrowth seen in paternally expressed Beckwith–Wiedemann syndrome, and intrauterine growth retardation observed with maternally expressed Silver–Russell, Prader-Willi, and Temple syndrome. The remodelling of maternal physiology in gestation is accompanied by conversion of maternal endometrial supply to a low-resistance, wide-bore, amyotic circulation system. This haemochorial arrangement is absent of the efficiency offered by renal counter-current multipliers, limiting maternal ability to control the inflowing blood volume (Haig et al, 2019). The mechanism by which paternally-inherited genome in the embryo aims for unparalleled access to maternal circulation, thus accounting for increased resource allocation during gestational growth, could be explained by developmental fates of parthenogenetic (PG) and androgenetic (AG) mouse embryos. While the viability of uniparental embryos is averaged less than 9.5 days, the structural differentiation of

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extraembryonic tissue in PG embryos is poorly contested with giant trophoblast cells seen in AG embryos. The paternal genome codes for renewal and differentiation of trophoblast stem cells into giant cells, establishing maternal optima for investment, whereas maternal genome allows spongiotrophoblasts to form, thus limiting the outflow of nutrients from mother to the offspring (Ogawa et al, 2009). Lacking a direct inference; teratoma and hydatiform moles could be designated as human equivalent of uniparental embryos. In a complete mole, all 46 chromosomes are of paternal origin, arising from fertilisation of an enucleated oocyte by two sperm cells or a single sperm followed by duplication. The failure to form an embryoblast is accompanied by extensive trophoblastic proliferation, a characteristic of androgenetic embryos (Devriendt, 2005). Teratoma is a gonadal tumour of totipotent cells; diploid XX ova arrested prior to second meiotic division. The cells develop into somatic tissues like hairs, nails and teeth in absence of any extra-embryonic structures, comparatively alike to gynogenetic embryo development (Mikhail, 2019).

The influence of imprinted genes on viviparity in relation to mating strategy can be observed across dramatic phenotypic variations obtained in inter- and intra-specific crosses. Interbreeding between lions and tigers creates two morphologically distinct hybrids, liger or tigon (Kaur, Allahbadia & Singh, 2020). A female lion tends to inhibit intrauterine growth for an equal probability of survival among multiple cubs due to a competitive breeding strategy. However, a female tiger demonstrates no compensation need in regard to a monogamous heat cycle. In mating between a male lion and a female tiger, gestational growth goes uninhibited producing a liger weighing as large as >400kg. This occurs in a response to the lack of inhibition towards growth promotor genes of the lion, which would normally be compensated against by the female lion. For a cross between a male tiger and female lion, a tigon is unable to exceed growth size of his parents due to biparental expression of growth-inhibitory genes (McKinell & Wessel, 2012). This could be inferentially translated to polyandrous mating systems in human females.

The genetic conflicts between mothers and foetus may manifest phenotypically as gestational pathologies of diabetes and pre-eclampsia, originating from differential optima over maternal investment in the offspring (Forbes, 2018). If the contribution of genetic dissimilarity to

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causation of mentioned maternal pathologies and phenotypic discordance is to be followed down, its the likely inference that singleton pregnancy will offer less conflict than twin gestation, whereas dizygosity, and atypical twining will be subject to greater disagreement over resource allocation and in-utero competition than monozygotic twins. It is of inference that with perinatal risks likely higher in monochorionic pregnancies, maternal risks will be significantly higher in dichorionic gestations due to twin placentae, when contrasted against singleton pregnancy.

Methods

This quantitative systematic review derives its main theoretical background from works of evolutionary biologists, David Haig on kinship theory of genomic imprinting, and parent-offspring conflict. A total of 81 articles were selected through years 2000-2022, hosted by CINAHL, MEDLINE and EBSCO databases. The relevant keywords for search included preeclampsia, gestational diabetes, twin, chorionicity, zygosity, and singleton. The initial scrutiny excluded 33 articles with insufficiency reflected on abstracted text or dependent outcomes more focused on perinatal parameters than maternal complications. Data sets including anomalous gestations incompatible to life (conditions unique to monochorionicity/TTAP) or any other maternal morbidity with exception of dependent outcomes were not selected. For remaining studies, retrospective cohort studies were given preference over surveys, and statistical evidence was constrained under odds ratio and/or relative risk. Further scrutiny of full text allowed inclusion of only 25 studies, to yield reliable data adjusted for parity, maternal age, BMI and ethnicity.

Data Analysis

The results from individual studies were subjected to random effects model (DerSimonian & Laird, 1986) for calculation of pooled summary effect by incorporation of heterogeneity statistic. Despite the virtual homogeneity between included studies, the results reported high statistical heterogeneity making metanalysis an insufficient approach to adopt. To visually display the variability encountered, odds ratios for both the dependent variables (preeclampsia and gestational diabetes mellitus) with 95% confidence intervals were plotted on a logarithmic scale against chorionicity, zygosity and singleton/twin pregnancy.

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Results

For preeclampsia, the odds of occurrence in twin pregnancies were uniformly higher across all the studies when contrasted with singleton conception, amounting to a pooled summary effect of OR=3.5, CI=3.01-4.08.With relation to chorionicity, 03 out of 06 studies reported weakly positiveexposure risk in dichorionic (DCP) pregnancies than monochorionic pregnancies (MCP), while the remaining 03 yieldedsubstantially positive odds cumulating at a summary effect of OR=1.46, CI=0.97-2.2. For zygosity, the chance of preeclampsia developing was positively related to dizygotic twining across 02 studies, while one demonstrated a slight protective effect in dizygotic twining against preeclampsia, adding to a pooled effect of OR=0.47, CI=0.29-0.76.

Table. 1

Preeclampsia in Singleton vs Twin gestation

Authors	Study type	Duration	Patient source	Singleton n/N	Twin n/N	Odds ratio	95% CI
Sibai et al, 2000	Secondary analysis of prospective data	Not specified	National Institute of Child Health and Human Development	143/2946	87/684	2.48	1.82-3.38
Suzuki et al, 2008	Retrospective cohort	2001 to 2007	Japanese Red Cross Katsushika Maternity Hospital	196/11311	45/593	4.7	3.3-6.5
Foo et al, 2013	Analysis of prospectively recorded database	January 1987 to March 2011	St. George Hospital, Sydney	1559/3942	153/214	3.8	2.8-5.2
Laine et al, 2019	Population-based cohort study	1999 to 2014	Medical Birth Registry of Norway and Statistics Norway	31247/913789	1903/16174	4.07	3.65-4.54
Proctor et al, 2019	Retrospective cohort	October 2003 to	Sunny-brook Health Sciences Centre,	1992/48943	170/1520	2.96	2.5-3.5

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	February 2015	Toronto				
Pooled summary effect			35137/980931	2358/19185	3.5	3.01-4.08

I^2=67.83%

Table. 2

Preeclampsia in Monochorionic vs Dichorionic Pregnancy

Authors	Study type	Duration	Patient source	MCP n/N	DCP n/N	Odds ratio	95% CI
Savvidou et al, 2001	Retrospective cohort	September 1996 to September 1999	King's College Hospital	16/171	36/495	1.19	0.61-2.3
Suzuki et al, 2008	Retrospective cohort	2001 to 2007	Japanese Red Cross Katsushika Maternity Hospital	20/224	25/369	1.4	0.73-2.5
Sparks et al, 2013	Retrospective cohort	January 2002 to December 2007	University of California at San Francisco	22/203	104/492	5.85	1.31-26.13
Sarno et al, 2014	Retrospective cohort	January 2010 to December 2012	Department of Obstetrics & Gynaecology of University	6/47	48/158	2.7	1.1-6.7

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			Federico II of Naples				
Bartnik et al, 2016	Retrospective cohort	January 2009 to December 2014	1st Department of Obstetrics and Gynaecology, Medical University of Warsaw	7/79	46/233	2.53	1.04-6.45
Che et al, 2021	Retrospective single-centre	January 2016 to December 2019	Shanghai Maternity and Infant Hospital	74/499	330/1661	1.42	1.08-1.87
Pooled summary effect				145/1223	589/3408	1.46	0.97-2.2

$I^2 = 68.19\%$

Table 3.

Preeclampsia in Monozygosity and Dizygosity

Authors	Study type	Duration	Patient source	Monozygotic n/N	Dizygotic n/N	Odds ratio	95% CI
Savvidou et al, 2001	Retrospective cohort	September 1996 to September 1999	King's College Hospital	17/171	24/223	1.29	0.62-2.71

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Maxwell et al, 2001	Retrospective cohort	1994 to 1999	Abstracted from unspecified medical records	15/75	25/170	1.4	0.5-3.9
Lučovnik et al, 2016	Registry-based survey	2003 to 2012	Slovenian National Perinatal Information System	15/442	56/1255	0.9	0.4-2.0
Pooled summary effect				47/688	47/1648	0.47	0.29-0.76

I^2=23.84%

Note. As zygosity can't be determined by clinical assessment in same-sex dichorionic twins, the analysis is made under the assumption that all monochorionic twins are monozygotic, and all unlike-sex pairs are dizygotic twins.

For gestational diabetes mellitus, 04 out of 05 studies depicted a positive association between number of foeti and risk of developing GDM, whereas one study demonstrated a negative association, adding to a pooled effect of RR=2.27, CI= 1.19-4.3. Chorionicity was positively associated for 02 studies and negatively for the other two, amounting to OR=0.22, CI=0.1-0.44.

Table 4.

Relative Risk of Gestational Diabetes (GDM) in Singleton vs Twin Gestation

Authors	Study type	Duration	Patient source	Singleton n/N	Twin n/N	Relative Risk	95% CI

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Buhling et al, 2003	Population-based cohort	September 1994 to October 1997	Prenatal care centre	14/178	6/89	0.85	0.34-2.15
Rauh-Hain et al, 2008	Retrospective cohort	September 1998 to December 2006	Massachusetts General Hospital obstetric service. database	521/22503	22/553	1.7	1.13-2.61
Hiersch et al, 2018	Retrospective cohort	2012 to 2016	BORN Ontario	16731/266942	326/3901	1.13	1.01-1.28
Eshwal et al, 2021	Retrospective cohort	January 2011 to April 2020	Sunny-brook Health Sciences Centre, Toronto	1893/24770	180/1881	1.25	1.08-1.44
Pooled summary effect				18690/314393	534/6424	2.27	1.19-4.3

I^2=97.15%

Table 5.

Gestational Diabetes in Monochorionic vs Dichorionic pregnancy

Authors	Study type	Duration	Patient source	MCP n/N	DCP n/N	OR	95% CI

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Carter et al, 2015	Retrospective cohort	1990 to 2010	Tertiary care centre	29/411	85/1445	1.26	0.78-2.05
Feng et al, 2018	Retrospective cohort	January 2011 to December 2015	Capital Medical University	33/198	56/361	0.92	0.57-1.46
Anwar et al, 2021	Retrospective cohort	January 2019 to December 2020	Aziz Fatima Teaching hospital, Faisalabad	9/28	21/180	0.27	0.11-0.69
Cowherd et al, 2022	Retrospective cohort	2000 to 2016	Tertiary care centre	24/352	163/2627	1.06	0.60-1.86
Pooled summary effect				95/989	95/4613	0.22	0.11-0.44

I^2=80.2%

Discussions

The genetic conditioning of intrauterine conflict in sibling pairs could be evidenced by substantial differences in birth weights documented for twin births. This ties into the inference that dissimilarity in genetic makeup influences the ability of resource extraction from maternal supply by the sibling and its partner. Monochorionicity faces the most intimate of all intraspecific relationships through unequal sharing and intrauterine crowding (Heinesen, Imai & Maruyama, 2015). Further substance could be gathered through sex-specific discordance in growth, with male twins having higher birth weights than their female partner indicating an in-utero competition for maternal resources with female foetus being served a selective disadvantage (James, 2002). The contribution of genetic dissimilarity to gestational outcome if accounted for discordance in age and sex could be calculated through antenatal assessment of foetal biometrics (CRL, FL, HC, AC), and natal

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parameters such as birthweight, placental weight and head circumference.

Monozygotic twining is a consequence of a single fertilisation event and subsequent post-zygotic division. Being genetically similar, monozygotic gestations also possess identical gross prenatal environment such as parity, maternal age and maternal health. The competitive forces in play such as unequal partition (postzygotic splitting [3:1] occurs at a 4-cell stage, giving one member of the pair an early advantage) and chorionicity (single-chorion and double chorion pairs) may subject the monozygotic pair to non-likeness.

$$Xi1 = Gi + Mi + Pi + Zi + Ui + ei1$$

$$Xi2 = Gi + Mi + Pi - Zi - Ui - ei2$$

Where G represents genetic similarity, M denotes foetal development in the same uterus, and P defines the shared prenatal environment; with these forces being additive and similar in a monozygotic pregnancy. In competitive forces directed at benefit of one member over cost of the other in pair, Z describes equality of partition, U is for intrauterine conflict and e is the contribution specific to the individual. The subscript i designates the particular effect for the i-th pair.

Uo, the competing force between single-chorion pairs is absent in dizygotic twins, having been replaced by Ut between double-chorion pairs. The competitive force Zi is eliminated and genetic dissimilarity is represented by Gi' (Kempthorne & Osborne, 1961). The monochorionicpregnancies in this review weren't associated with adverse maternal outcomes, however counter evidence by a single study(Feng et al, 2018) documented higher predisposition of MCP to gestational diabetes than DCP. A stronger association was noted between eclampsia and DCP. Twin pregnancies were weighed more likely to be followed by maternal complicationsthan singleton conceptions.

$$Xi1 = Gi + Mi + Pi + Ui + ei1$$

$$Xi2 = Gi' + Mi + Pi - Ui - ei1$$

Superfecundation (SFC) arises from dual fertilizationevents over a single menstrual cycle in polyovulatory period. SFC can be monopaternal or heteropaternal and it differs from

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superfetation by timing of the second conceptionover a different menstrual cycle. Mothers can selectively produce offspring genotypes through abortion or implantation (Wolf & Hager, 2009). In presence of a second father, paternally derived genes may maximize resource allocation to the current child, but maternally derived genes are likely to force deposition for the future child by selecting against paternal genes (Haig & Westoby, 1989). In a polyandrous mating system, all offspring of a female are equally related to her and one another though maternally-derived alleles (r=1/2). However, shared paternity for full-siblings approximates r near ½ while this value for half-siblings is 0. This implies that under polyandry, offspring relatedness is more matrilineal, warranting higher level of maternal investment for selection on paternally-derived alleles under Hamilton's rule (Moore, 2012). The parent-offspring conflict is potentially more pronounced in this case as the differing paternal contributions to the foetal genomes of half-sibs are less constrained in demanding resources from the mother to the detriment of half-sibs (Moore, 2009).

Gene probability of inheritance by recent common descententails foetus gaining benefit and sibs experiencing cost at 1/2 for the uninherited maternal genome, the benefit lies at 01 for the inherited maternal genome,whereas cost to sibling amounts to 1/2. For inherited paternal genome, the current foetus gaining benefit approximates 01 whereas cost to sibling is a dividend of shared paternity, f/2 (Haig, 1991). This is of acute importance in heteropaternal superfecundation.

The weight differences documented for two cases of homopaternal superfecundation (Amsalem et al, 2001, Twin1=2390g, Twin2=2170g, Difference= 220g; Peigne et al, 2011, Twin1=124, Twin2=780g, Difference=460g), and one case of monopaternal superfetation (Ciebiera & Jakiel, 2017, Twin1=2180g, Twin2=1550g, Difference=630g)revealed substantial weight differences atypical of week discordance, and higher propensity of the smaller twin to congenital anomalies like left superior vena cava (Ciebiera & Jakiel, 2017) and tracheoesophageal fistula (Tuppen et al, 2019). The presence of anomalies is a subject that warrants further research as to how sibling conflict can alter development fate of the partner at disadvantage.

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Pre-eclampsia

Incidence of preeclampsia in twin pregnancy is 2 to 3 times higher in contrast to single gestation (Grantz et al, 2019), whereas relative risk for preeclampsia in dizygotic pregnancies nears 3.50 above the risk for monozygotic conception (Kotz et al, 2002). The failure of second wave of trophoblastic invasion could be seen under kinship theory of genomic imprinting as a loss in initial immunological conflict over the depth of implantation, followed by foetal countermeasures to attain more than the mother can afford to provide by endocrine spamming and biochemical persuasion of maternal physiology (increasing maternal blood pressure; Forbes, 2018). Paternally imprinted genes show upregulation in preeclampsia with downregulation of maternally expressed genes (Christians et al., 2017) and are more likely to undergo changes in expression than non-imprinted genes. This supports the data obtained by grouping of various twin cohort studies with singleton as non-exposure groups. If the contesting contribution of parent-offspring conflict is abated, the remaining evidence points to pathogenicity of the placental tissue as larger sizes placentae expose the maternal-foetal interface to greater perfusion damage (Ros et al, 1998), which in turn is a follow-through of an inflammatory response or foreign identification of placentae by matrigenes.

Gestational diabetes

Being similar to Diabetes Mellitus type II, GDM is characterised by insulin resistance and glucose intolerance. Functioning as a foetal tactic to force endowment of maternal resources by increasing access to glucose (Haig 1993, 1996), GDM can transition past the partum period. Roach et al estimates that for every additional foetus, the risk to develop GDM rises up by 1.80-fold. Placental hormones such as human placental lactogen have been known to exert diabetogenic effects on maternal endocrine system, a manipulative attempt which is opposed by high maternal production of insulin (Haig 1993).

The results for pooled relative risk of GDM in twin pregnancy were significantly conclusive of higher predisposition to maternal-foetal disagreement in twin pregnancy when contested with single gestation, but the effect of chorionicity in sum proved to be insignificant in drawing a relevance.

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Conclusion

Twin pregnancy is a high-risk event, and it is of inference that tripartite cooperation and conflict at maternal-foetal interface is the main driving force behind obstetric complications of preeclampsia and gestational diabetes mellitus. With two placentae, the risk is subject to duplication and warrants that DCP, and dizygotic pregnancies be treated with more caution for adverse maternal outcomes than MCP and monozygotic gestations.

Limitations and Future Studies

The study's main limitation was a small cut-off value for sample size inclusion (>200 pregnancies)taking note of incidence of MCP. 02 out of 04

studies that reported a positive association had sample sizes aggregating near 200. The inclusion criterion set at a single outcome per study also narrowed the data gathered,causing expansion of collection years to 02 more than a decade, where the diagnostic criterion of preeclampsia may have been vastly different. Though, adjusting for parity, maternal age, BMI and ethnicity were taken in consideration when including any study, the exclusion of same-sex pairs to clinically estimate zygosity, not incorporating the effect of a shared amniotic chamber in DCP and MCP whether monochorionic diamniotic, monochorionic monoamniotic, or dichorionic diamniotic, and the rarity of cases with superfecundation and superfetation; all tailored the application of parent-offspring conflict to association, not by weight contribution to causation.

Further research is needed to establish if DCP and dizygotic events should be considered preferentially to MCP and monozygotic pregnancies for maternal outcomes of GDM and preeclampsia. The intimacy of monochorionicity offers conditions unique to MCP such as TTAP, often linking to unhealthy perinataloutcomes, though genetic similarity between the siblings lowers maternal-foetal conflict as to presence of a single placentae.

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